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Review Article

Cancer Biology and Therapeutics: Navigating Recent Advances and Charting Future Directions

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ABSTRACT

Cancer, a multifaceted and heterogeneous ailment, persists as a substantial global public health concern. Recent strides in cancer biology have profoundly augmented our comprehension of the intricate genetic and molecular mechanisms underlying the inception and advancement of cancer. This headway has propelled the formulation of innovative therapeutic strategies, embracing targeted interventions and immunotherapies, which have showcased promising outcomes in clinical assessments. However, a multitude of obstacles continue to challenge the creation of efficacious and individualized cancer treatments. This systematic review encapsulates an extensive vista of contemporary advancements in cancer biology and therapeutics, accentuating pivotal breakthroughs in our grasp of cancer's intricacies, while illuminating the latest therapeutic avenues for cancer management. Moreover, the paper elaborates on the quest's upcoming trajectories in cancer research and treatment, encompassing burgeoning technologies and uncharted domains of inquiry that might pave the way for more efficacious and personalized interventions for individuals afflicted by cancer.

***Keywords*:** Cancer biology, cancer therapeutics, targeted therapies, immunotherapies, personalized medicine, emerging technologies

Introduction

Cancer is a heterogeneous group of disease which ranges from benign to malignant tumors and are classified based on their site of origin. The heterogeneity of cancers occur between different types of cancer, between persons with the same type of cancer, and certainly between primary and metastasized cancer in an individual.[1,2] This has led to the need for a progressive and in-depth understanding of tumor biology. Tumor biology describes the complex interplay between a multitude of cellular genes and regulatory genetic components in the development of cancer phenotypes. [3] A vast understanding of tumor biology which includes cancer initiation, proliferation, metastasis, and response to treatment is critical in reducing the burden of cancer. This has led to the unraveling of the hallmarks of cancer, tumor microenvironment, cancer cell metabolism and cancer stem cell biology. A vast understanding of tumor biology has led to advances in cancer therapeutics.[4] The traditional cancer treatments which includes chemotherapy, radiation therapy, and surgery is faced with nonspecific target of tumor cells and normal cells.

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This has created the quest to find a treatment that exhibits a high response rate while causing minimal side effects with focus on targeted therapy; the treatment is specific to cancer cells while sparing normal body cells. [5] In the last decade, there has been a tremendous progress made in understanding cancer biology and therapeutics. These advances have led to a substantial decrease in the number of cancer deaths in the western world with more than a million survivors in the last few months.[6] Novel contributions in cancer research include improving diagnosis, targeting tumor microenvironment, identifying novel drug targets, promoting efficacy of treatment while reducing toxicity.

Immune evasion is a major characteristic of cancer cells as the tumor microenvironment has been identified to be immunosuppressive. [7] Immunosuppressant effect of tumor microenvironment is positively correlated with tumor aggressiveness and reduced response to treatment. [7] Immunotherapy is therefore a fast growing field of cancer therapeutics. Immunotherapy has been classified into immune checkpoint inhibitor therapy, adoptive cell therapy, cytokine therapy. Immunotherapy though promising, has been met with toxicity challenge and idiosyncratic response hence the need for recent advances which will be discussed in this article. The immune checkpoints act as a brake on immune response which is a normal physiological response to prevent autoimmunity, and also regulate the immune cells. The immune checkpoints though physiologically important can mediate immune evasion [8], hence the need for inhibitors of this physiological process. The major inhibitors are anti-CTLA4, anti-PDL-1, anti-PD-1; and their use though effective has been correlated with immune related toxicities and more importantly low response rate [9]. There is consequently a need to develop biomarkers that can predict patient's response to this therapy. [10] Immunotherapy is therefore not a blanket treatment option but stems towards personalized medicine. Also, it is important to understand the

underlying biology across responders and non-responders. The development of more effective forms of immunotherapy has been discovered, which includes adoptive cell immunotherapy, natural killer cell therapy, combinatorial immunotherapy and more [11,12] , which are designed to cover up for the defect of other forms of immunotherapy. For instance, adoptive cell immunotherapy such as CAR-T cells effectively targets tumor surface proteins as opposed to MHC which is not magnanimously expressed by cancer cells as a survival mechanism. [7] Nanotechnology is also a thriving field in cancer therapeutics and has been effective in the delivery of drug to target site while eliminating the risk of non-specific target. [13] Nanoparticles are usually accepted to be less than or equal to 100nm although those of biological origin are often larger to allow a reasonable volume for packing of drugs. [14] Nanoparticles can either be of biological (polypeptides) or chemical (metals) origin. A drug made of nanoparticle named doxil, containing doxorubicin attached with PEG (polyethylene glycol), is associated with an immensely reduced side effects as compared with same medication without a nanostructure. [15] This drug has been approved by the FDA for the treatment of metastatic ovary and breast cancer. [16] Other novel achievements including artificial intelligence and machine learning, are further explored in this article.

This review seeks to establish recent advances made in understanding tumor biology which further translates to advances in therapeutics. We therefore thoroughly present latest cancer research advances, placing emphasis on novel therapeutics which researchers are exploring to improve cancer prevention, diagnosis, and treatment. We also took a look at the future directions in cancer research and its therapeutics.

Materials and Methods

The methodology for this systematic review involved a comprehensive search of relevant literature to identify recent advances and future directions in cancer biology and therapeutic approaches. To ensure a comprehensive search, several key databases including PubMed, Scopus, Web of Science, and Embase were selected. The search strategy employed a combination of relevant terms and concepts, such as "cancer," "biology," "therapeutics," "novel therapies," "targeted therapies," "immunotherapies," "emerging technologies," and "future directions." Boolean operators "AND" and "OR" were utilized to effectively combine search terms and expand the scope of literature retrieval. This section outlines the systematic approach utilized for conducting the review, encompassing the criteria for study inclusion and exclusion.

Inclusion Criteria

The study selection process adhered to specific inclusion criteria to ensure the relevance and quality of the chosen literature. Firstly, studies focusing on recent developments and future directions within the domains of cancer biology and therapeutic approaches were considered. The selected literature spanned a publication period of the last 5 years (from 2018 to 2023) to capture the most current advancements. Only peer-reviewed articles from reputable journals and academic sources written in English were included to guarantee rigorous scrutiny and accessibility. The chosen study types included original research articles, systematic reviews, meta-analyses, clinical trials, and expert reviews, ensuring a comprehensive representation of the field.

Exclusion Criteria

Complementing the inclusion criteria, specific exclusion criteria were implemented to refine the selection process. Studies deviating from the focal point of cancer biology or therapeutic advancements were excluded to maintain the thematic relevance of the review. Literature published outside the predefined time frame, prior to 2018 or after 2023, was omitted to ensure the spotlight on contemporary developments. Non-peer-reviewed sources, like conference abstracts and unpublished theses, were excluded to uphold the standard of credibility. Additionally, studies in languages other than English were omitted due to linguistic limitations. To eliminate redundancy, duplicate articles found across various databases were also excluded. Lastly, studies lacking a distinct emphasis on cancer biology or therapeutic strategies were omitted to uphold the thematic focus. By rigorously applying these inclusion and exclusion criteria, the review process ensured the selection of pertinent, high-quality literature that contributed to a comprehensive overview of recent strides and emerging directions in the realms of cancer biology and therapeutics.

Article Selection and Extraction

The retrieved articles were screened based on their relevance to the topic and alignment with the study's objectives. The screening process involved assessing titles, abstracts, and full texts to determine their suitability for inclusion. Data extraction encompassed critical information such as study objectives, methodologies, findings, and implications related to cancer biology and therapeutic advancements. The synthesized findings from the selected articles were subsequently analyzed and discussed in the context of recent progress and future directions in cancer research and treatment.

Results and Discussion

After analyzing a total of 211 relevant literature sources, this systematic review presents a comprehensive overview of recent advances and future directions in the field of cancer biology and therapeutics. The synthesized findings encompass a broad spectrum of topics, including molecular mechanisms underlying cancer development, novel therapeutic strategies such as targeted therapies and immunotherapies, as well as emerging technologies poised to reshape cancer treatment paradigms. The review highlights the growing understanding of cancer heterogeneity, genetic mutations, and signaling pathways that contribute to tumor initiation, progression, and metastasis. Moreover, it sheds light on the promising results of innovative treatments like immunotherapies and targeted agents, showcasing their potential to improve patient outcomes across various cancer types. The analysis also underscores the role of precision medicine in tailoring therapies to individual patients and emphasizes the significance of multidisciplinary collaborations in advancing cancer research. The integration of advanced technologies such as genomics, proteomics, and artificial intelligence in cancer research and treatment is discussed, showcasing their transformative potential. Overall, this review serves as a comprehensive synthesis of the latest advancements in cancer biology and therapeutic interventions, offering insights into the ongoing efforts to enhance cancer care and improve patient prognosis.

Overview of Cancer biology

Cancer as a multifaceted cluster of genetic diseases, is hallmarked by the uncontrolled growth and spread of abnormal cells in the body. Normally, cells grow and divide to form new cells as the body needs them in order to facilitate life continuity from one generation to the next. When cells grow old or become damaged, they die, and new cells take their place. However, cancer cells don't die when they should and instead continue to grow and divide uncontrollably, forming a mass of abnormal cells called a tumor. Cancer can develop in almost any part of the body and can spread to other parts of the body through the bloodstream or lymphatic system. There are many different types of cancer, each with its own set of causes, risk factors, symptoms, and treatments. [17]

Hallmarks of cancer

Human cells gain a set of skilled functionality known as cancer hallmarks as they advance from normal to neoplastic states, providing them with important skills required for tumor malignancy creation. [1] The concept of cancer hallmarks is an intuitive way for condensing cancer's vast phenotypic and genotypic complexity into a preliminary compilation of basic principles. As our understanding of cancer pathways has grown, other features of the disease have emerged as possible advancements. The eight hallmarks currently encompass the acquired abilities for sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing/accessing vasculature, activating invasion and metastasis, reprogramming cellular metabolism, and avoiding immune destruction. [2,3] Initially classified as "emerging hallmarks," evading immune destruction and deregulating cellular metabolism are now considered fundamental cancer hallmarks. These hallmarks of cancers

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are schematically depicted in Figure 1 below and are explicitly explained in this review. [20]

These distinguishing features fail to tackle the intricacies of cancer etiology, that is, the precise molecular and cellular mechanisms that allow developing preneoplastic cells to grow and gain these abnormal phenotypic abilities throughout tumor growth and progression. As a result, a new concept known as "enabling characteristics" was presented. These enabling qualities occur as a result of the neoplasia aberrant situation, which provides cancer cells and tumors with a way to acquire these useful characteristics. As a result, the enabling characteristics focused on the mechanism at the molecular and cellular levels through which hallmarks are adopted rather than the 8 hallmarks themselves. The two enabling pathways were genome instability and tumor-promoting inflammation. The Figure 2 below represents the additional four prospective emerging hallmarks and enabling traits, which may eventually be integrated as essential components of cancer conception hallmarks. They are "unlocking phenotypic plasticity," **"**nonmutational epigenetic reprogramming," "polymorphic microbiomes," and "senescent cells". [17,19]

Sustaining proliferative signalling

A vital part of cancer formation and progression is proliferation. Variations in the expression and functions of proteins involved with the cell cycle demonstrate this. Activation of many signaling pathways triggers the development of cell. Cancer benefits from mutated cells in terms of proliferation and survival.[4]

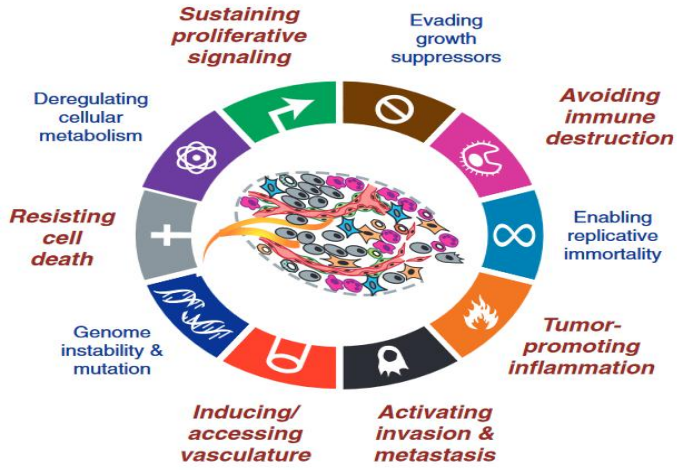

Figure 1: A schematic illustration of cancer's hallmarks. [20]

Figure 2: A graphical illustration of the evolving traits and hallmarks. [19]

Cancer cells transcend normal obstacles to proliferation as they adapt to continuous evolving hazardous milieu with limited oxygen tension, reduced glucose levels, and an acidic extracellular pH, all of which exacerbate instability in genes. [5] Tumor-suppressor proteins play an important role in cell-cycle progression by integrating internal and external cues to determine if the cell ought to stay latent or begin the active growth and division cycle. Retinoblastoma protein (RB) and TP53 are two regulatory proteins that are implicated in this hallmark of cancer. Many cancer cells cause these proteins to be mutated, resulting in their inactivation, exacerbating cancer formation and abnormal cell growth. RB protein plays a major role in the G1/S checkpoints regulation, serving as a checkpoint for the progression of cell cycles. When the RB is active, it commences the triggering of growth inhibition signals, which suppresses the transcription factor E2F, which is involved in the regulation of gene expression throughout the cell cycle. As regulators, cyclinD/cyclin-dependent kinase (CDK) 4/6 and cyclin-E/CDK2 complexes limit RB activity by phosphorylation, making it inactive and resulting in the release of E2Fs. Deregulation of the cycle cycle and alterations in the RB signaling pathway result in continual cell growth, as shown in Figure 3. [23]

The TP53 directly binds to the regulatory sites of genes involved in DNA repair and cell proliferation in response to damage to DNA and other cellular stresses. At high levels of DNA damage, or changes in the amount of nucleotide pools, and growth factor stimulation, TP53 can block cell cycle progression or induce apoptosis. Cancer cells cause TP53 function loss or gain, or TP53 inactivation, which results in the deletion of G1 checkpoints, impacting the regulation of cell growth and proliferation. Some growth factors activate several signaling pathways that have been linked to cancer, resulting in excessive cell proliferation. Growth factor activation of tyrosine kinase receptors (TKR) initiates transductions of the downstream signaling pathways ERK/MAPK, PI(3)K/Akt, STAT, PLCg, STAT (figure 4). [6,7] These implicated pathways in tumorigenesis are clearly depicted Figure 4. [23] Alteration in TGF-b signaling pathway results in high expression of EGF. Furthermore, TGF-b deficiency, an effective inhibitor of growth of cells, leads to uncontrolled proliferation, resulting in tumor development. [8]

Resisting cell death

Cancer cells use a variety of ways to avoid apoptosis. The mitochondrial apoptotic pathway is been implicated in cancer. Humans maintain tissue homeostasis by balancing proliferative and apoptotic stimuli. [9,10] Cancer pathogenicity is related to a surge in cells that avoided apoptosis or their partial engagement in the apoptotic machinery as a result of apoptosis dysregulation. Apoptosis is triggered by either internal or external stimuli, and the process necessitates energy. [11] Caspases, the final effectors of apoptosis, are activated by extrinsic or intrinsic pathways, cleaving numerous proteins and inducing apoptosis in cells. Death receptor ligands of tumor necrosis factor (TNF) such as fas, TRAIL, and TNF receptor 1 (TNFR1) found on the cell's surface interact with extrinsic pathway cues, causing its activation. The BCL-2 protein family regulates the mitochondrial apoptotic pathway, which is initiated by internal stresses caused by cellular challenges. Some members of the BCL-2 family interact with mitochondrial proteins, preventing them from generating pores, resulting in the suppression of apoptogenic factors as well as the degradation of anti-apoptotic proteins. The interplay of pro- and anti-apoptotic proteins can also influence cell survival and death. The alteration of regulatory proteins is an important element in cancer cell survival. Apoptosis inhibitors (IAPs) prevent cell death by controlling the caspase cascade and may regulate mechanisms of both the intrinsic and extrinsic in cells. [12,13] Cell dissociation from the extracellular matrix results in a sort of apoptotic cell death known as 'anoikis,' which modulates cell development and re-attachment to a new matrix. Cancer cells with the propensity to spread exhibit resistance to anoikis. Anoikis can trigger both the extrinsic and mitochondrial apoptotic pathways. Anti-apoptotic BCL-2 proteins are upregulated in many malignancies, while pro-apoptotic BH3 proteins are downregulated. According to research, increased levels of BCL-xL and MCL-1 induce cancer. Many cancers use strategies to stabilize

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MCL-1, a very unstable protein that degrades rapidly owing to proteasomal breakdown.

Downregulation of pro-apoptotic proteins, on the other hand, is another method of averting apoptosis onset. In different cancers, p53 tumor suppressor loss has been documented, which upregulates pro-apoptotic BH3-only proteins such as PUMA, BID, and NOXA. BAX and BAK, two pro-apoptotic effectors, have also been reported to be downregulated in a variety of cancers. So, cells that are unable to self-destruct, such as those overexpressing the apoptosis inhibitor BCL-2 or those with p53 mutation, may accrue additional genetic damage that promotes neoplastic development. Loss-of-function mutations in p53 would not only prohibit it from inducing apoptosis, but would also have an impact on its other tumor-suppressive properties, such as its capacity to activate DNA repair pathways, cause cell cycle arrest, and cell senescence. Figure 5 depicts an overview of the incidence that occurs when a cell that fails to enter apoptosis acquires an additional mutation that promotes abnormal proliferation of cells, resulting in increased progression of new malignant clone. [31] This occurrence demonstrates a tremendous synergy in the establishment of aberrations in apoptosis produced by excessive BCL-2 expression as well as unregulated cell proliferation caused by c-MYC overexpression. [14]

Invasion and metastasis

The majority of cancer-related deaths are the result of cancer cells metastasizing. The most perplexing part of cancer biology is metastasis.[15] The invasion-metastasis cascade is a complicated sequential and interrelated process that results in the formation of distant secondary cancers. Cell migration and local invasion into the surrounding extracellular matrix initiate the cycle of events. Cancer cells adapt to a new microenvironment and live in it, creating dormant macroscopic metastatic cells that are clinically identifiable by entering the vasculature, surviving rigorously bloodstream conditions, arresting at distant places, and extravasating into organ parenchyma. [16]

Thus, the complicated biological processes are orchestrated sequentially via: (1) tumor cell separation from its near neighbors and stroma at the local site; (2) Extracellular matrix enzymatic breakdown followed by directed motility; (3) Intravasation of blood or lymphatic arteries, as well as tumor embolization; (4) Survival in the circulation till arrival at a potentially deadly metastatic location; (5) Extravasation from the vessel and attachment to the endothelium of the blood artery at its destination; and (6) The spread and invasion of its new area, as well as the acquisition of a new blood supply. The aforementioned steps involved in tumor cells invasion and metastasis is illustration is diagrammatically using breast cancer in Figure 6. [35]

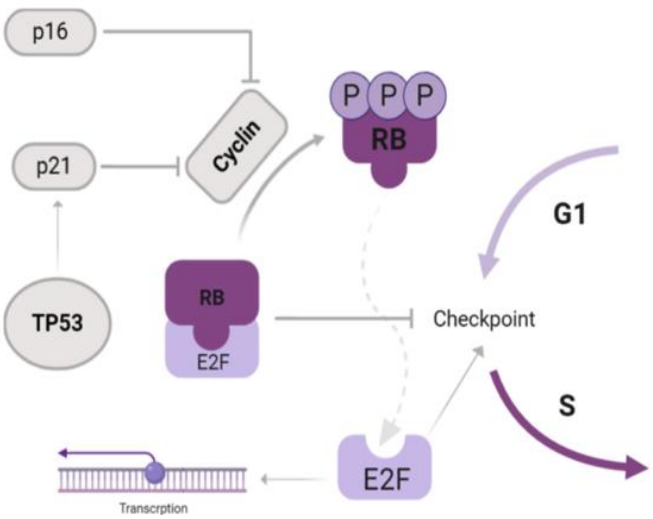

Figure 3: The routes involved in TP53 and RB are depicted schematically. [23]

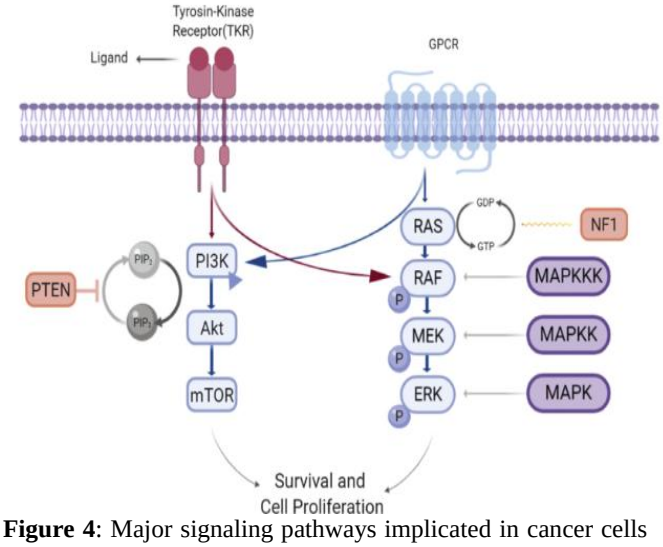

Figure 4: Major signaling pathways implicated in cancer cells proliferation

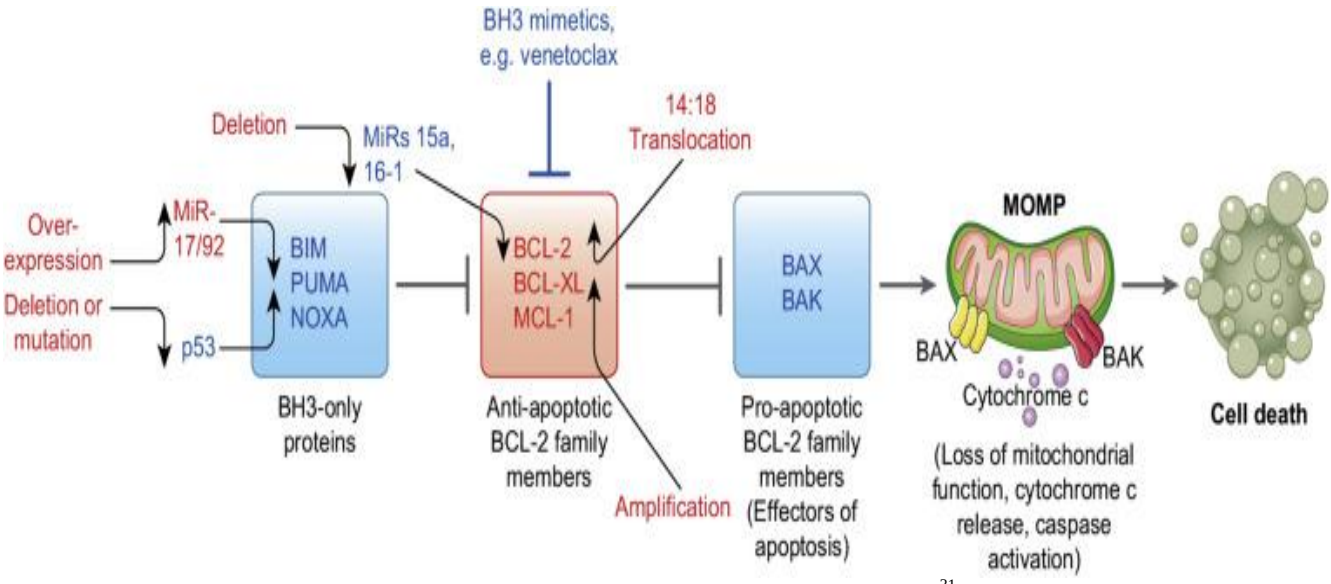

Figure 5: BCL-2 protein family interaction model. [31]

The epithelial-to-mesenchymal transition is a vital mechanism driving the invasion and metastasis of epithelial malignancies. [17] Invading cancer cells can activate this complex program either temporarily or permanently. When a tumor reaches the final organ site where it will form a metastatic deposit, it often undergoes mesenchymal-to-epithelial transition. An enzymatic alteration of collagen and inward migration of bone marrow-derived myeloid cells commonly prepare the niche in which cancer cells first get established in a new metastatic location. Different malignancies' metastatic patterns to various organs are not random, but occur preferentially in specific tissues, such as breast cancer to liver, bone, and brain, and lung cancer to brain and adrenal gland. [18] Early descriptions of metastases' "seed and soil hypothesis" relied on such patterns. At least some of these patterns appear to be influenced by tumor cells' production of chemokine receptors, which allows them to seek a suitable environment in order to create a colony.

Another mechanism is through the action of a mammalian enzyme heparanase which alone breaks heparan sulphate, an essential part of the ECM. As a result, the extracellular matrix is altered, and growth factors and cytokines bound to heparan sulphate are released. Angiogenesis, immune cell migration, and metastasis are subsequently enhanced. Heparanase expression has been found to be high in all cancers tested thus far, which promotes tumor formation while decreasing patient survival rates.[19] Heparanase regulates these differentiating traits within the tumor microenvironment, underscoring the importance of heparanase-targeted therapies.

Avoiding immune destruction

Cancer is characterized by the avoidance of immune destruction.[20] According to immune surveillance theory, the immune system maintains a continual vigilance against the formation of premalignant and, in certain cases, malignant cells. The discovery that persistent immunosuppression, as seen in organ transplant patients, is linked to an elevated incidence of various malignancies, particularly those of viral origin, provides supporting evidence. In immunocompetent people, there is further evidence that the immune system works as a crucial barrier to malignancies that are not induced by viruses. Cancer is caused by the immune system's failure to identify, reject, and remove tumor cells with defective self-antigen presentation. [18] Cancer cells use immunoediting strategies to avoid immune system detection. Cancer immunoediting is a technique in which the body's immune system can regulate and accelerate the development of tumors. Tumor growth is divided into three stages: elimination, equilibrium, and escape. During these stages, tumor immunogenicity is edited, and immunosuppressive mechanisms that favor disease progression are acquired.[21] TME, activated immune cells release cytokines and chemokines that promote inflammation and promote the growth of tumor cells. Through cytokines, chemokines, and adipocytokines, immune responses from innate cells like macrophages, mast cells, and neutrophils as well as adaptive cells like lymphocytes interact with epithelial cancer cells, fibroblasts, and endothelial cells in the TME. The molecular structure of cytokines and chemokines reveals the immune system's function in tumor genesis and growth. The key players in the immune response engaged in eradicating cancer cells which immunosurveillance identify particular antigens released by cancer cells. [22,23] Tumors can weaken the host immune cells within the TME and evade their surveillance by attracting immunosuppressive cells, lowering the tumor immunogenicity, or via other immunosuppressive mechanisms. [24] In the case of prostate cancer dyscrasias, all stages including asymptomatic conditions known as monoclonal gammopathy of uncertain significance and smoldering myeloma are implicated in the interaction between the immune system and malignant prostate cancer. Malignant prostate tumors eventually escape immune detection, progressing to active MM, where dysfunctional effectors lymphocytes, tumor-educated immunosuppressive cells, and mediators that are soluble work together to act as an inhibitor for antimyeloma immunity. Despite the fact that the immune system successfully removes malignant PCs and causes their dormancy at an early stage, malignant PCs manage to elude detection by the immune system. [25] Some tumor cells, such as cancer stem cells (CSCs), escape immune elimination and allow for the production of immunesuppressive TME by interaction with and recruiting of different immune cells such as natural killer (NK) cells, MDSCs, and regulatory Tcells. [26] Further understanding of CSC interactions with immune cells and their fundamental signaling processes will lead to new cancer immunotherapy. [27]

Inducing/ accessing vasculature

One of the most important features of cancer is a cell's ability to create angiogenesis. Angiogenesis is a biological process that regulates new blood vessels formation from pre-existing ones. This is a critical step in both embryonic development and wound healing, and it is heavily regulated by several mechanisms. A malignancy requires oxygen, nourishment, growth hormones, and the ability to disseminate to distant organs, which it can do through generating vasculature. [28] In cancer, angiogenesis becomes dysfunctional and hyperactivated. Because of the discovery of numerous proangiogenic factors in 1968, the association between angiogenesis and cancer was elucidated. Tumor angiogenesis is triggered by hypoxia, which develops in tumor cells as a result of insufficient blood flow. Cancer cells produce vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiogenin, transforming growth factor (TGF), and TNF, which are angiogenetic factors that attach to endothelial cell receptors of arteries and initiate vasculature. [25] When endothelial cells are activated, matrix metalloproteinases (MMPs) are secreted, resulting in basal membrane degradation. Endothelial cells penetrate surrounding tissues and produce new vessels as a result of this process. Angiotensin (TIE1/2) is required for the stability of newly formed vasculature. [26] Angiogenesis is important in cancer, and several studies have found that the level of angiogenetic factors is linked to tumor aggressiveness and has a high prognostic impact. Cancers also attract pericytes cells that enable vasculature as shown in Figure 7. [24,31] According to studies, B7-H3 (B7 homolog 3 protein) increased VEGFA expression and angiogenesis by stimulating the NF-B pathway. The B7-H3/NF-B/VEGFA axis has been shown to promote colorectal cancer angiogenesis, making it a prospective option for colorectal cancer treatment. [29]

Deregulating cellular metabolism

The process through which cancer cells meet their survival needs, such as nutrition acquisition, metabolism, redox homeostasis, and bioenergetics, is defective. When specific metabolites are altered, it affects gene and protein expression as well as their function. Cancer cells absorb a lot of glucose and glutamine. A transporter of glucose GLUT1, which permits glucose uptake, is extensively implicated in numerous cancer cell types and has been linked to poor prognosis and survival. The proximal rate-limiting stage in glucose metabolism is controlled by GLUT1. Glycolysis is the first main mechanism involved in breakdown of glucose, allowing glucose to be retained within the cell. Following glycolysis, the synthesis of NADH, ATP, and pyruvate anaerobically is possible. The Pentose phosphate pathway's irreversible oxidative arm adds to cellular NADPH reserves, whilst the reversible non-oxidative arm generates nucleotide precursor ribose-5-phosphate and glycolysis intermediates. Cancer cells use PPP to drive cell growth and proliferation as well as for antioxidant defense by producing NADPH. Depending on the physiological demands, the oxidative or non-oxidative arm of PPP may be activated in the synthesis of NAPDH and ribose-5-phosphate. In normal condition, Pyruvate is then carried into mitochondria and converted to acetyl-CoA, which feeds the TCA cycle, creating numerous TCA cycle intermediates as well as reduced NADH and FADH2. NADH and FADH2 provide energy for oxidative phosphorylation (OXPHOS), which produces ATP. Cancer cells convert glucose to lactate regardless of oxygen levels, requiring extra energy. The 'Warburg effect' refers to this occurrence of aerobic glycolysis. Cancer cells rely entirely on aerobic glycolysis even when mitochondria are functional, and the clear requirement for mitochondrial metabolism in tumor growth indicates that glucose produced by glycolysis/PPP vs. mitochondrial pathways supports a separate biology. Cancer cells rely heavily on glutamine as a source of carbon and nitrogen for the production of nucleotides, amino acids like glutamate and aspartate, and hexosamines, as well as the anaplerotic

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renewal of TCA cycle metabolites and OXPHOS. In cancer cells, glutamine plays a vital role in redox homeostasis. Pathways that promote carcinogenesis are boosted by low ROS levels, whereas apoptotic pathways are stimulated by high ROS levels. [34] Cancer cells are exposed to increased amounts of endogenous ROS as a result of their increase metabolic activity. To maintain redox equilibrium, antioxidants such as GSH must be synthesized, as a result cancer cells may increase the influx of nutrients and metabolic enzymes associated with antioxidant defense. [34,35] Furthermore, the activation of oncogenes like RAS, AKT, and MYC, as well as the loss of tumor suppressor genes like p53, drives aerobic glycolysis in cancer cells. [26] RAS increases glycolysis by activating mTOR and increasing the expression of hypoxia inducible factors (HIFs). HIF1 in turn promotes glycolysis by upregulating many genes, including glucose transporters such as GLUT1 and GLUT3.

Tumor promoting inflammation

Tumor-promoting inflammation is recognized as a characteristic of cancer in both etiology and ongoing tumor growth. [30] A number of inflammatory diseases linked to an elevated cancer risk exemplify the function of chronic inflammation as a cause of carcinogenesis. The unifying mechanism is the stimulation of a cytokine response or direct mutagenesis to promote carcinogenesis.[31] According to research, Helicobacter pylori infection causes 90% of gastric cancer occurrences. [29] In gastric organoids, H. pylori infection causes the production of a variety of inflammatory cytokines. H. pylori generates virulence factors like chronic active gastritis A (CagA) and stimulates multiple pathways such as the EGFR, S6 kinase, and cell cycle progression pathways, encouraging cancer formation. [32]

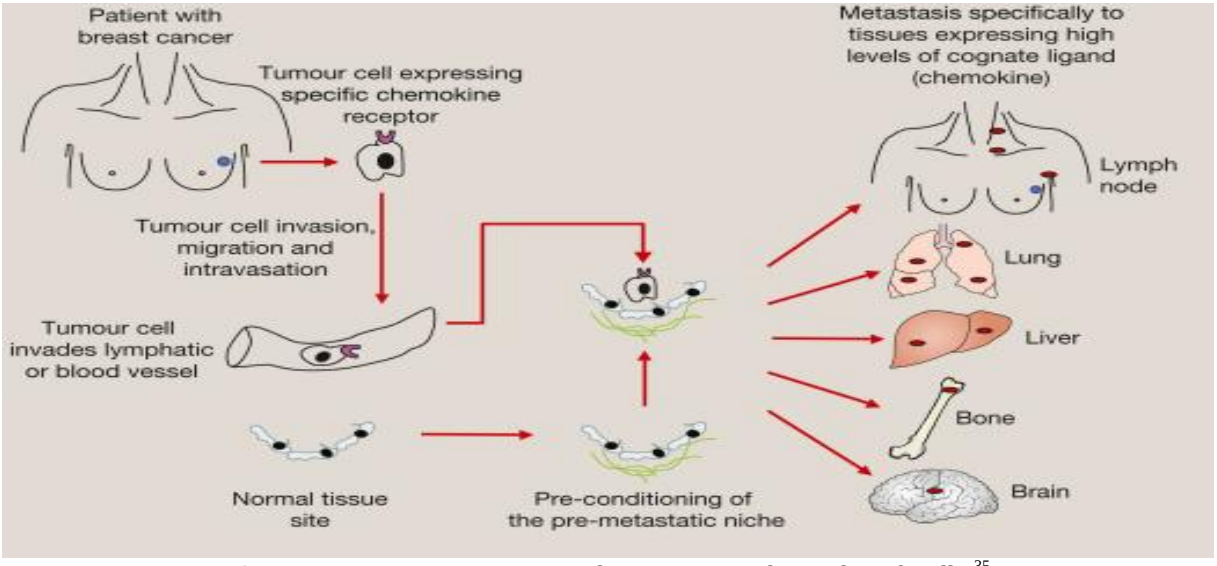

Figure 6: Breast cancer invasion and metastases are depicted graphically.[35]

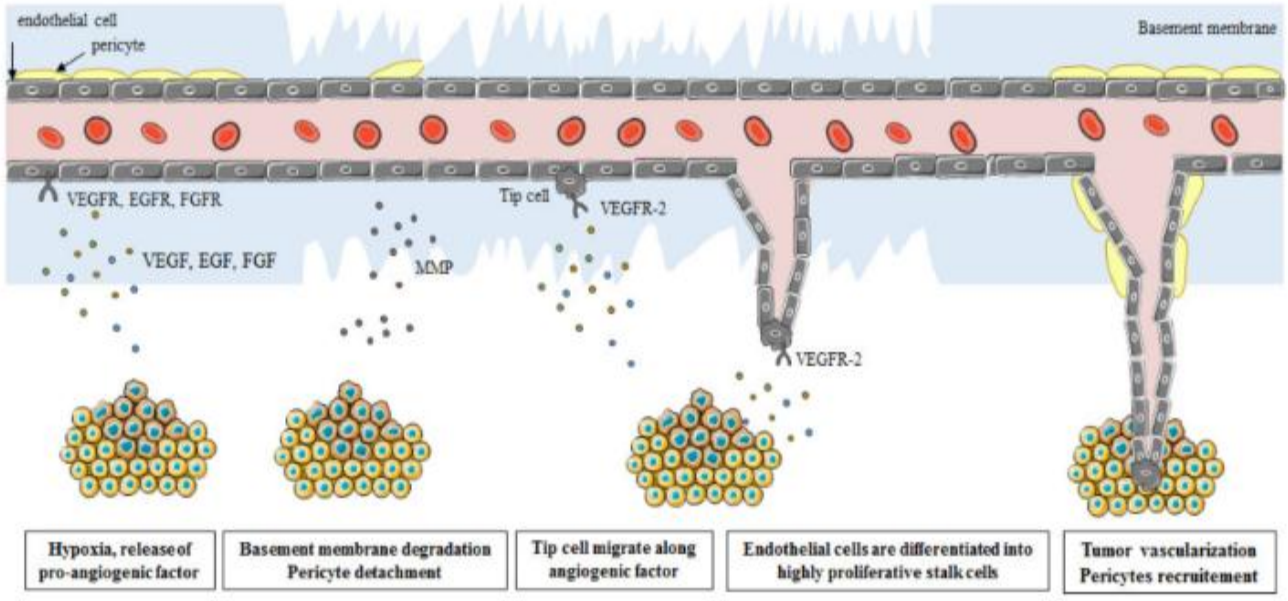

Figure 7: schematic processes involved in tumor neo-angiogenesis.[31]

Aflatoxin, asbestos, nitrosamines, alcohol, and tobacco are examples of environmental and chemical human carcinogens that cause tumor-promoting inflammation and can impair inflammation resolution, resulting to a severe worldwide cancer burden. Cancer is considered as an unhealed wound, drawing cell types and mechanisms related to injury repair and regeneration of tissue. Pathological inflammation is caused by constant stimulation of inflammatory signals, as well as the inability to utilize pro-resolving processes such as cell death "debris"

removal and the inhibition of pro-inflammatory cytokines. [33] Some innate immune cells, such as neutrophils, monocytes, and macrophages, are inflammatory mediators and disrupt normal myelopoiesis. This disruption results in the production of myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs). Immunosuppressive myeloid cells operate as a primary obstacle to cancer treatment as a result of their robust repressive effects on effector lymphocytes and their presence in the TME. [25] DNA demethylation promotes transcription of inflammation-related genes such as chemokine receptor 4 (CXCR4) and serum amyloid A (SAA) in advanced clear cell renal cell carcinoma (ccRCC), resulting in tumor promoting cancer cell-intrinsic inflammation via epigenetic remodeling. [34]

Enabling replicative immortality

Cancer is distinguished by its ability to achieve replicative immortality and enable macroscopic proliferation. [53] Telomeres serve an important function in the normal aging process of cells. The progressive shortening of telomeres that occurs after repeated cell divisions modulates cell longevity and replication capability. After 50 to 60 cell cycles, telomeres decrease to a critical length, resulting in cell senescence. As a result, the p53, p21, and Rb/p16 INK4A genes are activated, which are linked to cell growth inhibition and death. When the cell cycle arrest checkpoint fails to recognize shortened telomeres, DNA damage proteins are triggered, resulting in the formation of aberrant chromosomes. A cell with altered DNA is classified as being in the crisis stage and will generally suffer apoptosis. The telomere shortening process, which causes senescence or apoptosis in healthy cells, is thought to be a natural mechanism that suppresses tumor. Cells in carcinogenesis can engage maintenance systems of telomere to avoid cell senescence or apoptosis induced by shortening of telomere. Telomere maintenance mechanisms have been uncovered, including telomerase gene hTERT promoter alterations, reactivation of telomerase, oncogenes and mutation of tumor suppressor gene, and alternative telomere lengthening (ALT) telomerase independent process. According to statistics, telomerase activation achieves telomere stabilization in 85%-90% of cancer cells, but only 5%-15% display an ALT route. Despite the fact that most malignant cells have increased telomere reverse transcriptase (TERT) production through promoter mutation and telomerase activation, telomeres in Cancer cells have shorter telomeres and higher levels of telomerase activity than normal tissues. Indeed, it appears that the smaller the telomere, the more aggressive the malignancy and the worse the outcome. Telomerase activity has been detected in oral carcinomas, lung cancers, prostate cancers, liver cancers, breast cancers, neuroblastomas, colorectal cancers, and bladder cancers, among others. TERT over-expression lengthens telomeres in some cancer cell lines that have significantly short telomeres. In fact, chromosomal instability induced by the telomeric DNA damage response followed by end-to-end fusions enhances neoplastic transformation. Due to malignant transformation is a complex process, activating telomerase confers immortality but not neoplastic properties to cancer cells. However, if the precise moment of telomere shortening that causes telomerase activation is discovered, it could have a significant impact on tumor suppression. This will continue to be a challenge for future researchers.

Genome instability

Genomic instability is described as a grouping of mutations in DNA in the genome that contribute to heterogeneity of tumour. It is also a cumulative effect of genome modification that adds to the deterioration of genes that control division of cell and suppression of tumour. The majority of cancer cells have genome instability, which develops as a result of defects in the DNA damage sensor and repair circuitry, as well as an error in mitotic checkpoints which eventually leads to cell malignancy. [35] One of the distinctive features of tumour cells is genetic instability. The inability of cells to repair harmful double-strand breaks (DSBs) is the main underlying cause of genomic instability. Genomic instability promotes the generation of survival-promoting mutations, enhancing the probability that such alteration may proliferate into daughter cells (mitotic catastrophy) and have a significant role in progression of cancer. [36] DNA replication is a critical biological function, and faults in its execution or regulation can result in significant human illnesses such as cancer. Although DNA replication in eukaryotic cells is tightly controlled to ensure accurate DNA duplication before entering mitosis, it is constantly under attack from endogenous and exogenous factors that can disrupt fork progression. [37] Stalled forks can collapse or break into potentially hazardous and unstable structures. [36] Under normal conditions, cell cycle checkpoints inhibit the passage of damaged DNA into mitosis; however, mitotic DNA lesions are common in cancer cells. [38] In human malignancies, the two most common kinds of genomic instability are chromosomal instability (CIN) and microsatellite instability (MSI). [3,39] ROS-induced DNA damage has been linked to different cancers. Cancer cells produce more ROS as a result of alterations in the ROS scavenging system and important signaling pathways linked to cell metabolism. Furthermore, ROS production has been shown to be important in development and progression of cancer in a variety of settings. [40] Also, Hypoxia causes alternative splicing in both normal and malignant tumor components. 3059 alternative splicing events in 2005 genes are induced in liver cancer cells, contributing to dedifferentiation and genomic instability. [51,56]

Evading growth suppressor

To drive cell development, growth factor receptors must be activated by their linked proteins. Growth factor receptor activation is often highly modulated, as well as the production and secretion of the proteins that activate them. To thrive, tumour cells must dodge antigrowth signals. Cancer cells nearly always deactivate normal growth factor signaling pathways and exploit them to drive uncontrolled cell division. tumour cells gain growth factor self-sufficiency through three basic mechanisms: (1) generating and releasing growth factors to activate their own (autocrine) and nearby (paracrine) receptors, such as TGF and epidermal growth factor (EGF) binding to EGFR; (2) Increasing the quantity, form, or activity of growth factor receptors on their surface, such as HER2, such that they are able to convey a growth impulse to the nucleus even in the absence of corresponding ligand interaction; (3) Deactivating signaling pathways downstream of the receptor to permanently activate growth for example RAS mutation. [18] Growth suppression is centered on pRb and p53, which function as part of a broad network interconnected in a way that promotes redundancy and more efficient management. Tumor cells escape these antiproliferative controls through gene loss or mutations in their modulators such as TGF, or direct downstream targets of its activity, such as CDK4 and its inhibitory proteins, and cell growth contact inhibition, such as NF2 / Merlin and LKB1 epithelial soluble protein, which can cause abnormal growth when distorted when disrupted as observed in cancer tissues. Many more strategies have developed in recent years, whether directly or indirectly linked to the pRb and p53 pathways, and whether positively or negatively associated to antiproliferative control, confirming the evasion of growth suppressors a as a true cancer characteristic, aiding in the broad understanding of the complexities of this system, which may be a viable treatment target in many malignancies. [12] Cyclin-dependent kinase inhibitor 2A (CDKN2A) encodes the tumor suppressor p16INK4a, which binds to CDK4/6, causing an allosteric conformational shift that inhibits the development of the cyclin D-CDK4/6 complex. Because of the absence of this combination, Rb protein remains hypophosphorylated, favoring the development of the Rb/E2F repressive complex. As a result of the cell cycle arrest in G1, growth is suppressed. Epigenetic silencing of tumor suppressors like p16INK4a through hypermethylation of promoters enhances growth suppression escape. In addition, the hyperactivity of enhancer of Zeste homologue 2 (EZH2), a catalytic subunit of polycomb repressive complex 2 (PRC2), is linked to growth suppression evasion. Its suppression by CDKN2A demonstrates the significance of epigenetic instability in enabling the hallmarks. [34]

Unlocking phenotypic plasticity

Phenotypic plasticity is undoubtedly a distinguishing feature that allows many distortion of differentiation of cell, including (i) transition from mature to primordial state (ii) precursor cell states to

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final differentiation (iii) There are three primary mechanisms of distorted differentiation that are critical to cancer pathogenesis: transdifferentiation into various cell lineages. [42] Cancer development and growth from cells of origin in such pathways are aided by altering the typical differentiation of precursor cells into adult cells in embryonic lineages in various ways. [1] Terminal differentiation is engaged in the formation, determination, and arrangement of cells into tissues so as to carry out homeostatic responsibilities during organ development, leading the expansion of progenitor cells to a halt. [43] As a result, the antiproliferative produced by cellular differentiation limits the continuous proliferation required for neoplasia. There is emerging proof that unlocking the generally limited capacity for phenotypic plasticity so as to prevent or escape terminal differentiation is an essential aspect of cancer formation. This plasticity can manifest itself in a variety of ways (Figure 8).[62] As a result, new tumor cells produced from a typical cell that has advanced down a pathway toward or reaching a completely differentiated state may return to progenitor-like cellular forms. Neoplastic cells originating from precursor cells that are supposed to follow a pathway that results in end-stage differentiation may refuse to participate in the process, allowing cancer cells to spread in a partly differentiated, progenitor-like state. Transdifferentiation, on the contrary , may take place when cells that were earlier dedicated to one differentiation route switch to a completely different developmental scheme, gaining characteristics that is tissue-specific that were not dictated by their typical cells-of-origin. [44]

Senescent cells

Cellular senescence is a nonreversible proliferative suppression that emerged as a defense strategy for tissue homeostasis sustainability, acting as an alternative to apoptosis. Senescence induces changes in structure, metabolism, and stimulation of a senescence-associated secretory phenotype (SASP), resulting in the secretion of proteins such as chemokines, cytokines, and proteases. Cell senscence is caused by nutrient deficiency, DNA damage, organelle and cell machinery damage, and signaling pathway dysregulation. Senescent cells aid in the genesis and growth of cancers in a variety of ways. SASP is the main process by which senescent cells enhance tumor phenotypes by paracrine expressing signaling molecules and proteases that stimulate or desequester them so as to transfer hallmark capacities to nearby viable cancer cells as well as other cells in the TME. Previous research has revealed that senescent cancer cells promotes proliferative signaling, resist cell death, induce vasculature, stimulate cancer spread, and decrease immunity of tumor. Furthermore, senescent cancer cells have an impact on cancer phenotypes, including transitory, reversible senescent cell states that allow senescent cancer cells to avoid expression of SASP, nonproliferative state, and therefore assume cell growth and exhibit full viable oncogenic cell abilities. [44] This sort of dormancy, which avoids targeted treatment of growing cancer cells, is most commonly observed in situations involving treatment resistance, but it can be more generally functional in other stages of tumor genesis, aggressive development, and migration. Notably, senescent cancer cells are not the only ones with the ability to propagate hallmarks. Cancer-associated fibroblasts (CAF) have been demonstrated shown to have senescence in malignancies, leading to senescent CAFs that are obviously tumor-promoting by imparting distinctive qualities to cancer cells in the TME.

Non-mutational epigenetic reprogramming

The enabling feature of genomic instability and alteration is a critical aspect of tumor creation and etiology. The term "non-mutational epigenetic reprogramming" refers to an autonomous genome-reprogramming approach involving completely epigenetically mediated alterations in the expression of genes. The basic process controlling formation of an embryo, differentiation, and organ development is, of course, non-mutational epigenetic modulation of expression of genes. Adult memory retention, for example, involves alterations in gene and histone modification, chromatin organization, and transcription switch stimulation, all of which have been reliably sustained continuously by both positive and negative feedback mechanisms. Growing data suggests that comparable epigenetic changes enable the acquisition of hallmark capacities throughout cancer formation and growth. A growing body of evidence suggests that, aside from oncogenic mutations, cancer cell genomes can still be reprogrammed by indicating that the abnormal physical properties of the TME can cause wide variation in the epigenome, from which modifications that is useful to the phenotypic selection of hallmark abilities may lead to clonal outgrowth of cancer cells with enhanced fitness for proliferative expansion. Hypoxia, caused by inadequate vascularization, is a typical feature of malignancies. Hypoxia lowers the activity of TET demethylases, resulting in significant methylome alterations, particularly hypermethylation. Inadequate vascularization most likely restricts the bioavailability of key blood-borne nutrients and nutrient deficiency has been demonstrated to disrupt translational control and, as a result, improve the malignant phenotype of breast cancer cells. Furthermore, it is becoming clear that non-mutationally based epigenetic heterogeneity exists. The linker histone H1.0, which is dynamically expressed and repressed in subpopulations of cancer cells across a variety of tumor types, resulting in sequestration or accessibility is a good example. Also, cancer cells with repressed H1.0 were found to have stemlike features, increased tumor-initiating ability, and a poor prognosis in patients.

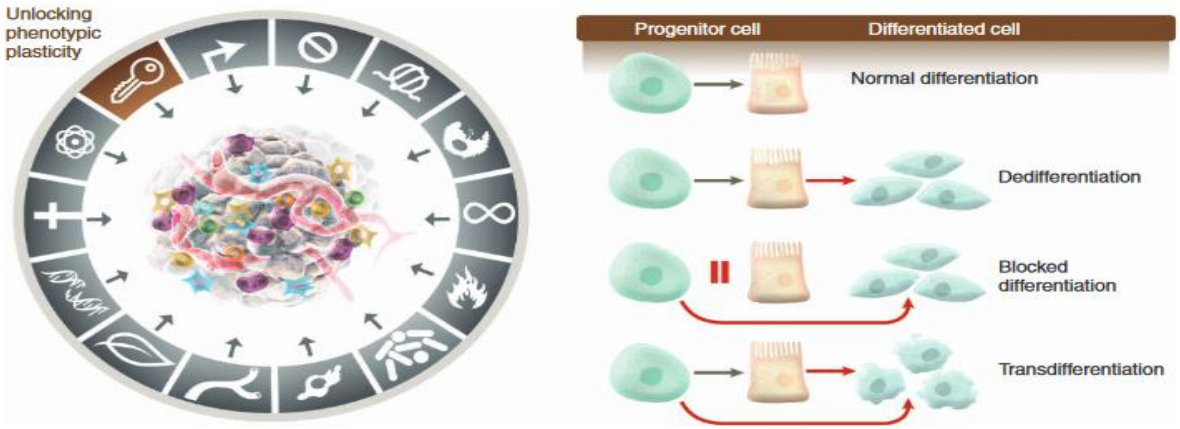

Figure 8: From progenitor cells to adult cells, a graphic summary of unlocking phenotypic flexibility. [62]

Another example of epigenetically regulated plasticity has been described in human oral squamous cell carcinomas (SCC), where cancer cells at the invasive margins adopt a partial EMT (p-EMT) state that lacks mesenchymal TFs but expresses other EMT-defining genes not present in the center of the cancer. The extracellular cells in the TME which lead to the accumulation of hallmark capacities are not prone to mutations and do not undergo mutational rewiring to improve their function, in promoting tumor formation. Cancer-related fibroblasts, innate immune cells, endothelial cells, and tumor vasculature pericytes, on the other hand, are epigenetically rewired

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following recruitment by polar analogues. [1] A recent study found that such rewiring can involve epigenetic alterations as well as the inductive interplay of cytokines, chemokines, and growth factors, all of which alter intracellular signaling pathways across all of these cell types.

Polymorphic microbiomes

Polymorphic microbiomes relate to mutation and gene instability, as well as tumor-promoting inflammation. They can be present in the colon, mucosa, and associated organs, as well as malignancies. Many of the hallmark capabilities are influenced by polymorphic microbiomes by promoting or suppressing them. Polymorphic microbiomes are thus a possible tool and quasi-independent factor in the riddle of how malignancies grow, advance, and respond to treatment. Multiple tissue microbiomes have been linked to tumor phenotype modulation. In several tumor forms, tissue, gut, and tumor microbiomes are important in regulating the acquiring of either negative or positive hallmark characteristics. The gut microbiome is critical for the proper functioning of the colon in digestion and nutrient entry into the body as part of the metabolic equilibrium. According to research, dysbiosis in the colon's population of microbes can induce a range of physiologic problems. [45] There is a notion that microbiota influences the susceptibility, development, and pathophysiology of colon cancer. Bacterial toxins and other chemicals produced by microbiomes either directly damage DNA or disturb the systems that preserve genomic integrity, or stress cells in other ways that decrease the fidelity of DNA replication and repair. Furthermore, bacteria have been shown to bind to the surface of colonic epithelial cells and produce ligand mimics that stimulate epithelial proliferation, contributing to the hallmark capability for proliferative signaling in neoplastic cells. [46] Because of their increased population, certain bacterial species that produce butyrate induce carcinogenesis in colon cancer patients. Butyrate synthesis has diverse physiologic implications, including the generation of senescent epithelial and fibroblastic cells. [44]

Tumor microenvironment and its role in cancer progression

Tumor cells cause considerable molecular, cellular, and physical alterations in the surrounding tissues, leading to the formation of a complex and dynamic tumor microenvironment (TME). The TME is a dynamic and complex network of cells and extracellular matrix (ECM) that surrounds and interacts with cancer cells. [47] Though the component of the TME differs among tumor types, hallmark composition include a variety of immune cells, blood vessels, stromal cells, extracellular matrix proteins, and signaling molecules that can either promote or inhibit tumor growth and progression (Figure 9). [48] Current pool of evidence shows that both innate immune cells (such as macrophages, dendritic cells, neutrophils, innate lymphoid cells, myeloid-derived suppressor cells, and NK cells) and adaptive immune cells (T cells and B cells) present in the TME, play essential roles in tumor progression when present, and it has become a focus of intense study in recent years. [49] The tumor microenvironment (TME) is a made up of a mixture of cellular and non-cellular components that provide a self-sustaining environment for the development and progression of cancer cells.[50] Also, the TME also attracts and maintains various stromal and immune cells to support the tumor's growth and progression. [51] Regulation of the immune response to cancer cells is one of the essential functions of the TME. The immune system has evolved to identify cancer cells and eliminate them as abnormal or foreign bodies. However, cancer cells has also been able to evade the immune system by creating an immunosuppressive microenvironment or expressing molecules that suppress the immune response. [52]

Another critical component of the TME is the extracellular matrix (ECM), which serve as a biochemical and structural support to surrounding cells, including cancer cells. The ECM can affect various aspects of cancer cell behavior, such as proliferation, migration, invasion, and metastasis. [53] In many cancers, the ECM becomes dysregulated, leading to the formation of an abnormal matrix that promotes tumor growth and invasion. For example, the deposition of hyaluronan, a glycosaminoglycan, in the ECM can create a highly viscous and dense matrix that limits drug penetration and immune cell infiltration.

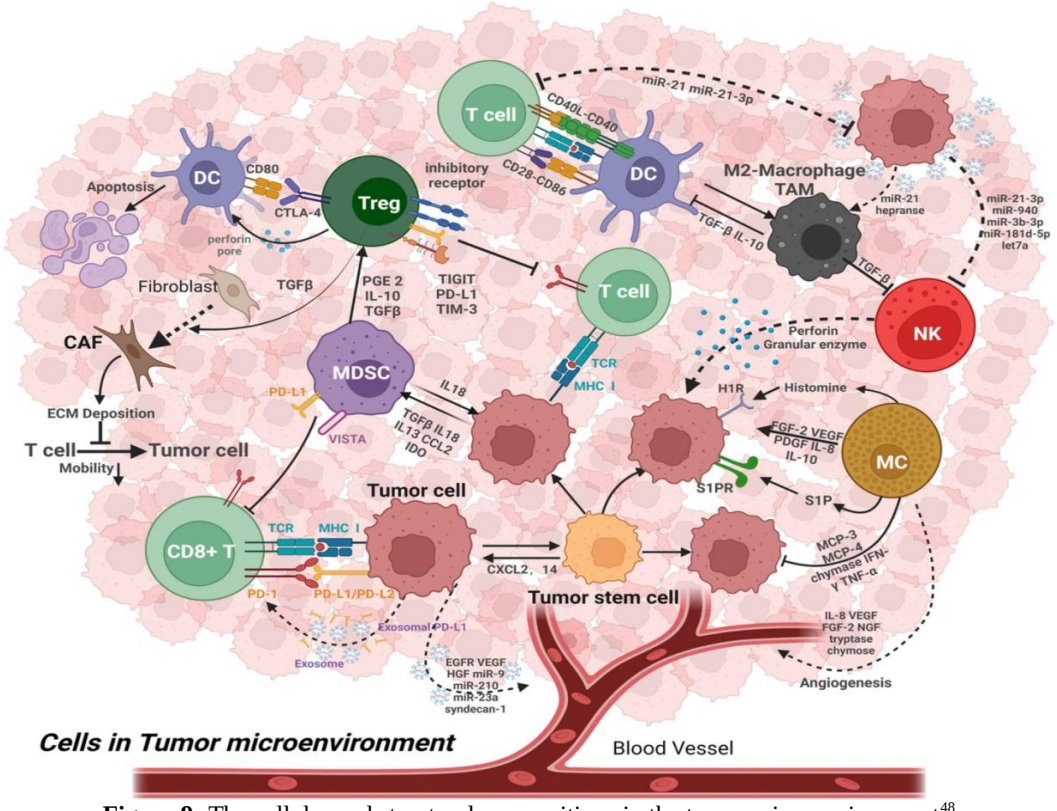

Figure 9: The cellular and structural compositions in the tumor microenvironment[48]

The remodeling of the ECM in the TME can also contribute to the formation of a desmoplastic reaction, which is a dense fibrotic reaction that can limit drug penetration and immune cell infiltration.

Cells and components of the TME involved in cancer progression
Cells of Tumor Microenvironment
Stromal Cells: The stromal cells in the TME, including fibroblasts, endothelial cells, and pericytes, can also influence cancer progression. Stromal cells can secrete growth factors, cytokines, and extracellular matrix proteins that promote cancer cell survival, proliferation, and angiogenesis. Cancer-associated fibroblasts (CAFs); an example of stromal cells which are present in higher amounts in the TME of primary Prostate cancer compared to the normal prostate stroma where the smooth muscle cells are abundant, have been found from the report of several studies to have tumor-promoting properties. [54] Multiple studies have demonstrated that during the tumorigenesis of prostate, there is a phenotypic and molecular transformation of CAFs which lead to a transition from fibroblast to myofibroblast (MFBs). These "MFB-like" CAFs cause remodeling of the ECM, which encourages the invasiveness of Prostate cancer cells and triggers the liberation of growth factors that are bound to the ECM, such as TGF-β, FGFs, and HGF, thereby sustaining the proliferation of tumor cells. [55] For example, cancer-associated fibroblasts (CAFs) can produce transforming growth factor-beta (TGF-β) and matrix metalloproteinases (MMPs), which can promote tumor growth and invasion. [56] Tumor cells require the support of stromal cells to sustain progressive growth and propagation at metastatic sites. Cancer-associated fibroblasts (CAFs) secrete growth factors and cytokines, such as TGF-beta, HGF, FSP1, and SDF-1, which promote cancer cell growth and angiogenesis. [57]
CAFs can also act as mutagens, generating reactive oxygen species under low pH and hypoxia environments that directly act as mutagens on surrounding cells. TGF-beta is a potent chemoattractant for fibroblasts and is the growth factor that is known to transdifferentiate fibroblasts into CAFs. [58] Being a prevalent cell type in the TME, CAFs can also influence the growth of cancer cells by regulating their metabolic pathways. This involves complementary metabolic pathways to maintain anaerobic glycolysis. [58,59]
Immune cells: The Tumours micro environment is complex and dynamic and support the development of tumour cells by influencing their growth, invasion, and metastasis. [60] The interaction between the immune system and cancer is a complex and multifaceted process. [61] Immune cells can have either a suppressive or a promoting effect on tumor growth, depending on various factors such as the type of immune cell, the stage of cancer progression, and the tumor microenvironment. [67,80] Cytotoxic T-cells, also known as CD8+ T-cells, play a crucial role in detecting and eliminating cancer cells through cell-mediated cytotoxicity. However, cancer cells can evade detection and destruction by the immune system through downregulation or modification of tumor antigens and the release of molecules that inhibit cytotoxic T-cell activity. [62] Regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSCs) are immune cells that have been shown to suppress immune activity and promote tumor growth. [63] The mechanisms by which Tregs and MDSCs promote tumor growth involve the suppression of T-cell activation, the inhibition of antigen presentation, and the secretion of immunosuppressive factors. [64]
Tregs are a particular subtype of T-cells that have an essential role in suppressing immune homeostasis by inhibiting the activation of effector T-cells. Tregs express the transcription factor FoxP3 and are identified by the presence of surface markers CD4, CD25, and CTLA-4. In the tumor microenvironment, Tregs have been shown to suppress the immune response against cancer cells by inhibiting the activation of effector T-cells. Tregs can do this by secreting immunosuppressive cytokines like interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which can suppress the activation of effector T-cells. [65,66] MDSCs are a heterogeneous population of immature myeloid cells that can suppress immune activity in various ways. MDSCs can suppress immune activity by inhibiting antigen presentation, which is a crucial step in the activation of T-cells. [65,67] MDSCs can do this by expressing low levels of major histocompatibility complex (MHC) class II molecules, which are required for antigen presentation. [68] In addition, MDSCs can secrete immunosuppressive factors such as IL-10 and TGF-β, which can further suppress immune activity. [69]
The regulatory T cells (Tregs) on the other hand, can suppress immune responses and promote tumor development by several mechanisms; including the suppression of the function of antigen presenting cell (APC) through CTLA-4, utilizing IL-2, generating immunosuppressive cytokines, and producing metabolites that suppress the immune system. [70] One such mechanism is the modulation of natural killer (NK) cell homeostasis, which can impair the immune system's ability to recognize and eliminate cancer cells. Tregs can also support the survival of cancer cells through the secretion of growth factors. Understanding the complex interplay between immune cells and cancer is crucial for the development of effective cancer therapies. In contrast, increased levels of Th1 cells within the tumor microenvironment have been linked to a favorable prognosis across various tumor types. [71] Th1 cells secrete interleukin-2 (IL-2) and interferon gamma (IFN-γ), which can support the activity of cytotoxic T-cells and suppress tumor growth. [72] In addition, IFN-γ secreted by Th1 cells can also suppress angiogenesis, the process by which new blood vessels form to supply nutrients to tumors. Several studies have investigated the roles of Tregs and Th1 cells in cancer, including their effects on tumor growth, immune responses, and patient outcomes. A study by Zhang et al. (2020) found that high levels of Tregs and low levels of Th1 cells were associated with poor prognosis in patients with non-small cell lung cancer. Understanding the roles of Tregs and Th1 cells in cancer can inform the development of novel immunotherapeutic strategies to improve patient outcomes.
Epithelial Cell: Epithelial cells can form new blood vessels that supply oxygen and nutrients to cancer cells, and pericytes can regulate blood vessel stabilization and permeability. The progression of cancer is as a result of continuous growth and alteration in the genetic material as supported by the environment. Due to the increased requirement of nutrients, oxygen, and the ability to metastasize, tumor cells surround itself with various factors and blood vessels. These factors help initiate an angiogenic switch through the activation of HIF-1 and -2, leading to the creation of pro-angiogenic growth factors like Vascular Endothelial Growth Factor (VEGF). [73] VEGF promotes the survival, migration, and invasion of endothelial cells, leading to the formation of a disorganized and highly permeable tumor vascular network. This allows for increased transportation of oxygen and nutrients to the tumor site. [74]

Extracellular Matrix (ECM)
The extracellular matrix (ECM) produces structures such as sheet-like networks that form the basis of tissues and organs and fibrilsThe ECM is a complex network consisting of glycoproteins (including tenascin C, laminins, and fibronectin 1), fibrous proteins (such as collagen and elastin), and glycosaminoglycans (e.g., hyaluronic acid), proteoglycans (such as heparan sulfate and chondroitin sulfate). [75] While many types of cells can produce ECM proteins, cancer-associated fibroblasts (CAFs) are the primary source for synthesizing, secreting, assembling, and modifying the ECM. [60] The biophysical properties of the extracellular matrix (ECM) include not only its biochemical composition but also its topography, stiffness, molecular density, and tension. [60] Therefore, the ECM is highly adaptable and can be modified by both tumor stroma and cancer cells. This process involves communication that is mediated by various factors, such as growth factors, chemokines, and circulating tumor cells, which interact with the ECM. Additionally, changes in metabolism within the tumor bulk also play a role. [76]
The ECM can either hinder drug delivery by increasing tissue stiffness and desmoplasia, or facilitate metastasis by penetrating the basement membrane. [60] Furthermore, soluble factors and circulating tumor cells/exosomes from primary tumors can manipulate the ECM of distant organs to create an environment that either promotes or inhibits the growth and spread of metastatic cancer cells. The TME is a heterogeneous and dynamic environment that can vary between different cancer types, stages, and locations within the same tumor. Understanding the complex interactions that occur within the TME is critical for the development of novel therapeutic strategies for cancer

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treatment. [77] Several therapeutic approaches that target the TME are under investigation, including immunotherapy, targeted therapy, and stromal cell targeting. For example, immune checkpoint inhibitors, such as anti-PD-1 or anti-PD-L 1, are under investigation as potential cancer treatments. These drugs block the interaction between immune checkpoint molecules and their ligands, which can release the brakes on the immune system and enable it to attack cancer cells. [60]

Role of genetic and epigenetic alterations in cancer development

The development of human cancers is attributed to the build-up of genetic and epigenetic changes; Figure 10. [97] Recent research has revealed that these alterations are not only found in cancerous cells but also in healthy cells well before cancer onset. The gradual accumulation of these changes is linked to the risk of developing cancer, and can be used to diagnose cancer risk. [78]

Genetic Alterations and cancer development

Alterations in the DNA sequence that makes up a gene are triggered by a variety of factors such as aging, mutagenic chemicals, radiation, ultraviolet light (UV), and oxygen radicals. Aging is recognized as the primary risk factor for cancer, and the overall number of stem cell divisions, which varies depending on the type of tissue, is strongly associated with the likelihood of developing cancer. [78] Somatic mutations, single nucleotide polymorphisms (SNPs), and copy number variation (CNV) are the three primary ways that genetic alterations occur (Figure 11). [100] Somatic mutations refer to genetic changes that take place in any non-reproductive cells within an individual's body. SNPs, on the other hand, are alterations that involve the change of a single nucleotide in specific individuals within a given population. CNV, meanwhile, involves changes in the number of copies of specific regions of the genome by more than 1,000 nucleotides, such as the loss or deletion of one or both copies, as well as a gain in copy number. It should be noted that unlike epigenetic alterations, genetic alterations are often challenging to reverse. [78] A significant number of somatic mutations tend to amass during the initial stages of an individual's lifespan when stem cells are highly active in dividing. Apart from the natural process of aging, the occurrence of somatic mutations in human tissues that can lead to cancer is also caused by exposure to mutagenic elements. [79] When an individual is exposed to a particular substance, it can trigger a distinct set of mutations known as a "mutation signature." These signatures are typically found in cancerous tissues where both critical and noncritical mutations can be easily identified due to the clonal expansion of cancer cells. In a recent study, over 23,829 cases of cancer were analysed, comprising approximately 85,000,000 mutations categorized into single base substitutions (SBS) across 96 trinucleotide contexts, doublet base substitutions (DBS), and small insertions and deletions. [80,81]

Epigenetic mechanisms and cancer development

Epigenetics is the study of changes in gene expression that occur without changes in the underlying DNA sequence. [82,84] Epigenetics mechanisms include DNA methylation, histone modifications, non-coding RNA expression (Figure 12). Alterations or inadequacy in these mechanisms may lead to inappropriate initiation or inhibition of gene expressions and subsequently lead to pathological changes, particularly cancer. [83,84] These alterations are reversible and are often caused by environmental exposures, lifestyles, and aging. Accumulation of genetic and epigenetic alterations often results into cancer development. Owing to the significance of epigenetics alteration in cancer development, epigenetic-targeted treatment (which may be a monotherapy or in combination with other therapy) is an emerging approach in cancer therapy.

In deciphering how cancer progress, the cancer stem cell and clonal evolution models have been suggested, and epigenetic alterations play a critical role in them, due to their ability to regulate genetic deregulation and some specific mutations. [83] Epigenetic alterations are always consistent with the processes that involves activation of oncogenes and/or suppression of tumor suppressor genes which are significant factors contributing to cancer development. [83,84] Epigenetic alterations such as anomalous DNA methylation, disrupted form of post-translational modifications and histone modifications are largely due to disordered epigenetics mechanism (Figure 13). [84]

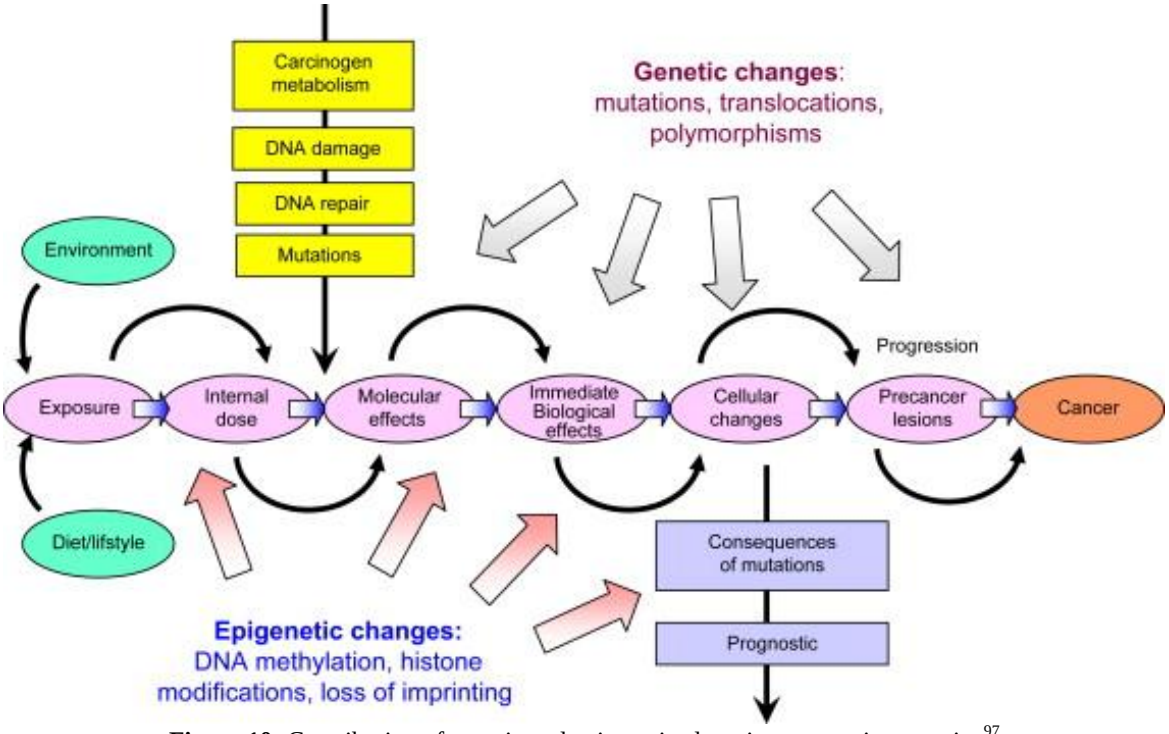

Figure 10: Contribution of genetic and epigenetic alterations to carcinogenesis. [97]

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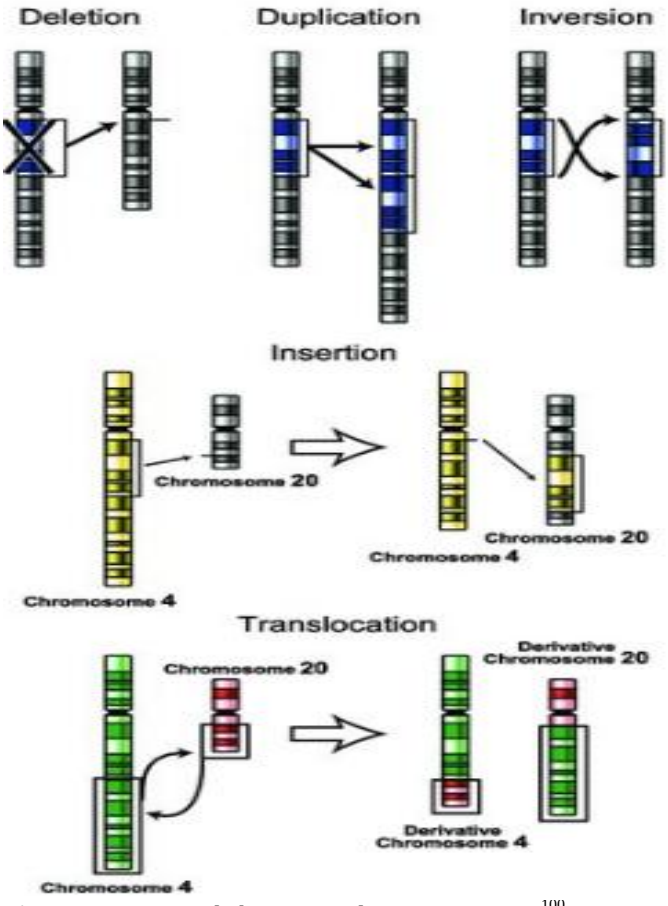

Figure 11: Structural chromosomal rearrangements. [100]

In normal cells, epigenetic mechanisms are important for the development and conservation of tissue-specific gene expression patterns in mammals. The structure of a repeating unit of nucleosomes called chromatin is modified by epigenetic mechanisms such as DNA methylation, covalent histone modifications, histone variants incorporation and nucleosome remodeling, and non-coding RNAs. The normal operation of the genome is regulated by the collaborative effects of these modifications which leads to an alteration in the chromatin structural dynamics. The interconnection between these alterations results in an "epigenetic terrain" which controls how the mammalian genetic material is expressed in diverse cellular types, stages of development, and health conditions, including cancer. [82,84] Epigenome, which is a combination of these modifications, play a crucial role in determining cell destiny and gene expression levels. [86]

In cancer cells, the well-balanced and precise epigenomic terrain are extensively distorted. The development of malignant cancer from healthy cells is a complex process that involves genetic and epigenetic abnormalities. Epigenetic changes during human carcinogenesis are driven by both genetic and environmental factors. The transformation of normal cells into cancer cells occurs through a series of genetic and epigenetic alterations. Like genetic mutations, epigenetic modifications can vary and affect the structure and function of the genome, leading to uncontrolled growth and the characteristic features of cancer cells. [84] The epigenome of cancer is distinguished by broad modifications in DNA methylation, histone adjustments, and the regulation of gene expression by non-coding RNA (Figure 14) (ncRNA). These alterations give tumour cells a growth advantage, thereby fostering the development of cancer. [82]

Nucleosomes are formed by DNA wrapped around a histone octamer that allows DNA to be condensed into chromatin and finally chromosomes. The regulation of chromatin structure occurs through various post translational histone modifications such as, acetylation, phosphorylation, ubiquitylation, methylation. All these histone modification results in weakening of histone interaction with DNA to increase chromatin accessibility. DNA methyltransferases (DNMT) methylate CpG islands near transcription start (promoter) sites inhibiting gene expression by impeding transcription factor binding to DNA. The regulation of transcription also occurs via non-coding RNA.[82]

DNA methylation

DNA methylation is the most studied and well recognized epigenetic mechanism. It is catalyzed by DNA methyltransferases (DNMTs) and involves the addition of methyl group to the carbon 5 position of cytosine rings of CpG island resulting in the production of C5-methyl-cytosine. [82,84] The presence of an extra methyl group has a direct impact on gene expression, as it attracts proteins that play a role in regulating the expression of a specific gene. Additionally, it hinders the ability of transcription factors to bind to DNA binding sites. [82] A significant factor in the onset of various cancers is the excessive methylation (hypermethylation) of CpG islands in the promoter regions of tumor suppressor genes. This can alter genes that play a role in controlling the cell cycle, DNA repair, cell communication, programmed cell death, and the formation of new blood vessels, all of which are crucial pathways associated with the development of cancer. [82] Adult cells usually methylate CpG sites to preserve chromosomal stability, but there are specific regions in DNA, called CpG islands, which have a higher concentration of CpG sites and are generally not methylated in normal cells. These regions, located in the promoter region of DNA, contain regulatory elements that manage gene transcription. However, in cancer cells, the balance between methylation and demethylation is disrupted, causing hypermethylation of CpG islands in the promoter region and deactivating Tumor Suppressor Genes (TSGs). [82]

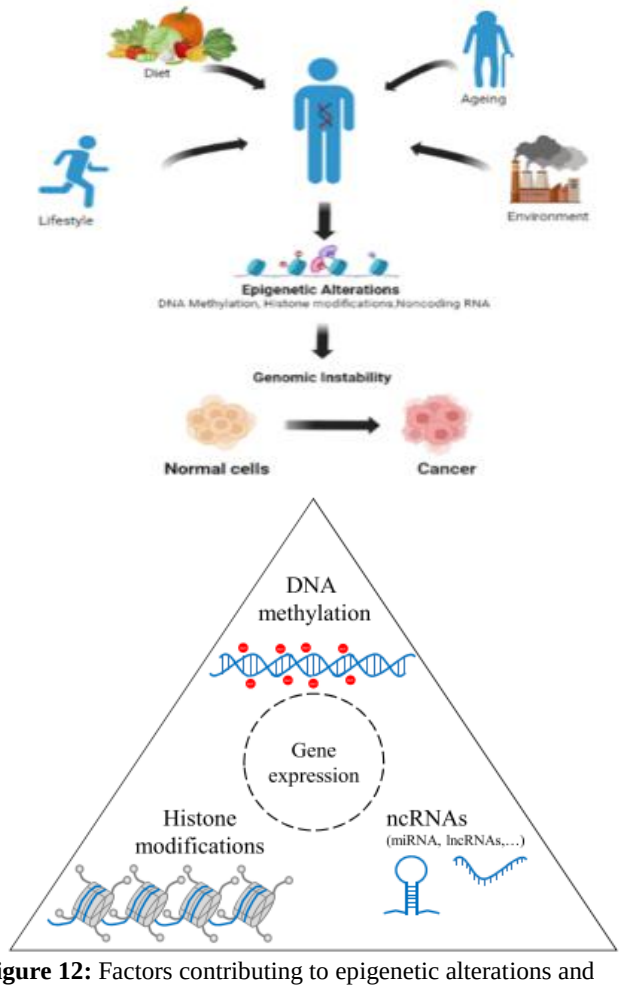

Figure 12: Factors contributing to epigenetic alterations and epigenetic mechanisms

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Mutations in or silencing of alleles of tumor suppressor genes has also been linked to cancer development where silencing of either one or two of the alleles by DNA methylation can result to carcinogenesis.[87] In addition, DNA methylation can lead to the Warburg Effect, a characteristic of cancer where cells exhibit increased consumption of glucose, higher rates of glycolysis, and preferential lactate production, even when enough oxygen is available. [88] Three significant pathways have been recognized through which CpG methylation can contribute to the oncogenic phenotype. The first is through the general hypomethylation of the cancer genome. The second is through the occurrence of focal hypermethylation at Tumour Suppressor Gene (TSG) promoters. The third is through the direct mutagenesis of sequences containing 5mC caused by exposure to UV radiation, deamination, or other carcinogens. [84]

Histone modifications

Histone modifications are another essential epigenetic mechanism in gene expression. Histones are protein octamers that provide structural support to DNA by giving it a compact shape, allowing it to fit inside cell nuclei. This compact shape makes the DNA strands tightly coiled around the histones, inhibiting gene transcription. This coiling occurs because the DNA is negatively charged, while histones are positively charged. To enable gene expression, the DNA needs to unwind, which only happens when histones undergo modification, such as acetylation or methylation. These modifications target the lysine residues of the N-Terminal region of the histone, which protrudes from the histone core, and regulate access to DNA for transcription. The enzyme acetyltransferases catalyze acetylation reaction. During this reaction, the acetyltransferase enzyme transfers an acetyl group from acetyl-COA to the lysine amino acid, converting it into ε-N-acetyl lysine. Epigenetic histone modifications that deviate from the normal pattern have been linked to the development of cancer and can affect clinical outcomes. [89] Histone acetylation and deacetylation imbalance have been associated with tumor development and progression. Histones undergo several modifications including phosphorylation, methylation, acetylation, and ubiquitination. Mistakes in these post-transcriptional modifications can cause alterations in gene expression that may contribute to cancer formation. [82,84,90]

Non-coding RNA modifications

Non-coding RNAs are a group of RNAs that don't have the ability to produce functional proteins, yet they have a crucial role in the regulation of gene expression through epigenetic mechanisms. Recently, non-coding RNAs (ncRNAs) have gained a lot of attention due to their involvement in various epigenetic mechanisms that control gene expression. These mechanisms include the modulation of chromatin structure, transcriptional regulation, and posttranscriptional modification (82)]. Around 70% of the human genome is composed of non-coding RNAs, which can be categorized by size into two groups: micro RNAs (miRNAs) with approximately 20 nucleotides, and long non-coding RNAs (lncRNAs) with over 200 nucleotides. [82,91] Earlier studies have proposed that miRNAs are subject to epigenetic regulation and their deregulation has been extensively examined in cancer. In cells, miRNAs participate in the regulation of essential processes such as cell cycle progression, apoptosis, and differentiation. Dysregulation of miRNAs through epigenetic mechanisms is associated with various types of cancers. [84] Playing a role in the hallmarks of cancer, miRNAs, such as miR-15 and miR-16 located on chromosome 13q14.3, are often deleted in chronic lymphocytic leukemia, leading to abnormal expression of anti-apoptotic genes. Additionally, while miR-9 is often overexpressed in brain cancer, hypermethylation of miR-9 loci has been observed in various tissues, including colon, neck, and lung carcinoma. [84] Aberrant expression of lncRNAs has been observed in several types of cancers, and they can act as oncogenic or tumor suppressor factors, making them a promising target for both diagnosis and therapy. [82]

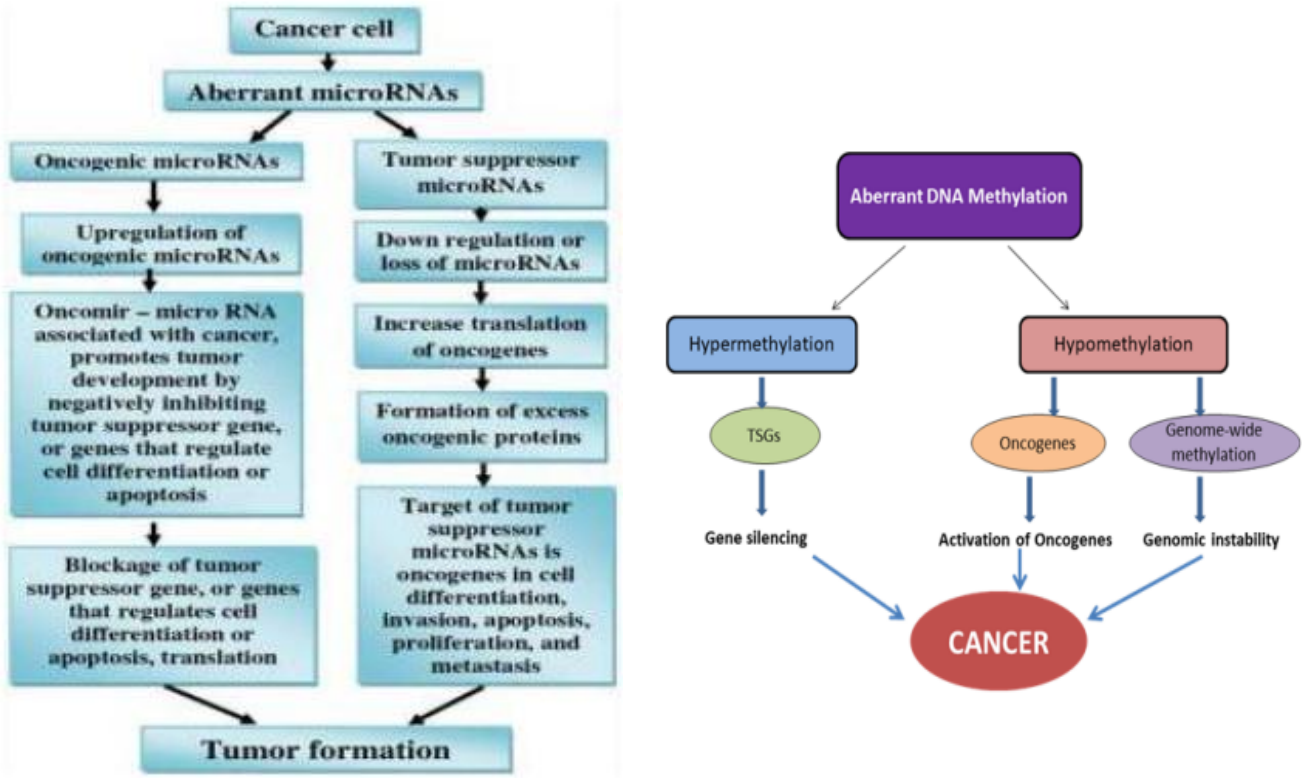

Figure 13: Contribution of aberrant DNA methylation and microRNAs to cancer development. [84]

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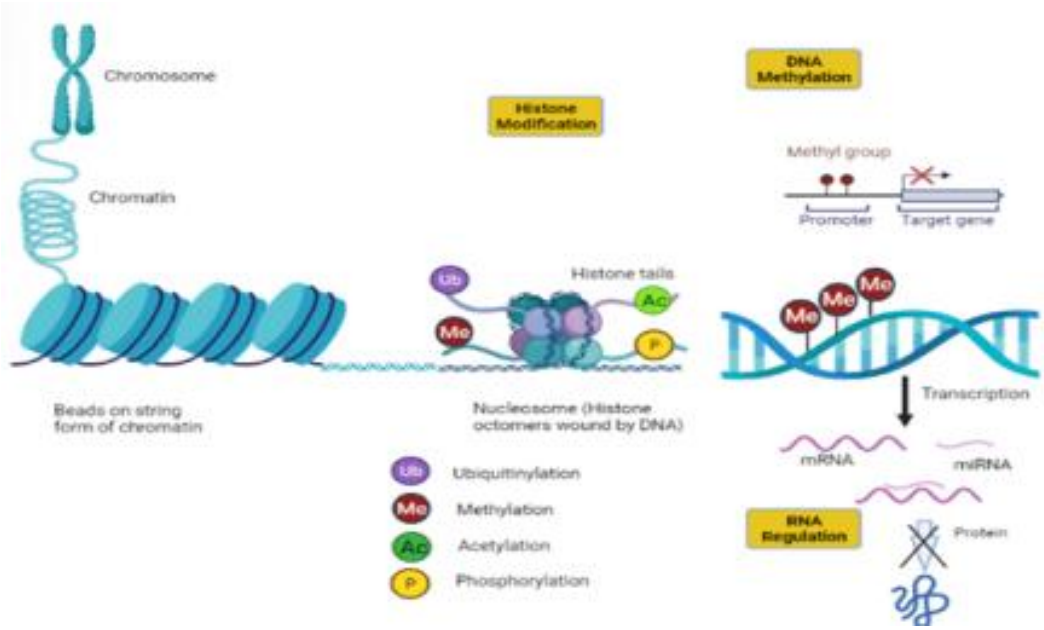

Figure 14: Overview of epigenetic mechanisms of gene expression. [82]

Cancer Therapy

Cancer therapies are treatments used to destroy or control cancer cells in the body. There are several types of cancer therapies, including surgery, chemotherapy, radiation therapy, targeted therapy, immunotherapy, and hormone therapy. Surgery involves removing cancerous tumors or tissues from the body. Chemotherapy involves using drugs to kill cancer cells throughout the body. Radiation therapy uses high-energy radiation to kill cancer cells. Targeted therapy targets specific molecules involved in cancer growth. Immunotherapy uses the body's own immune system to attack cancer cells. Hormone therapy targets hormones that may be fueling certain types of cancer. Often, a combination of these therapies is used to treat cancer, depending on the type and stage of the cancer. A lot of attention have been given to plant materials as source of bioactive compounds to help combat cancer. [208,209]

Current standard treatments

The main objective of cancer treatment is to cure the disease and allow patients to live healthy and normal life. However, in some cases, the goal of treatment may be to control cancer, relieve symptoms, and improve the patient's quality of life. [112] There are several types of cancer treatments available, including surgery, radiation therapy, chemotherapy, immunotherapy, targeted therapy, and hormone therapy. [113] The choice of treatment depends on various factors, such as how chemotherapy drugs work by targeting cells in different phases of the cell cycle, the type and stage of cancer, the patient's overall health, and personal preferences. It is important to discuss all available treatment options with a healthcare provider to make an informed decision. [114] It is also essential to follow the treatment plan and attend all appointments to ensure the best possible outcome. In addition, cancer patients may benefit from complementary therapies, such as meditation, acupuncture, and massage therapy, to manage side effects and improve their well-being. [115]

The four categories of cancer treatment are primary treatment, adjuvant treatment, neoadjuvant therapy, and palliative treatment. [116] Primary treatment seeks to eradicate cancer cells entirely or eliminate cancer from the body. Surgery is the most common type of primary treatment. Adjuvant treatment, on the other hand, is administered after primary treatment to eliminate any residual cancer cells that may cause cancer recurrence. Neoadjuvant therapy is like adjuvant therapy but is given before the primary treatment to improve its effectiveness. [117] Palliative treatment is used to alleviate the symptoms of cancer or side effects of treatment and can be administered concurrently with other curative treatments. [118] Surgery is the most common treatment for localized cancer and involves the removal of the tumor and surrounding tissues. [119] Chemotherapy, which uses drugs to kill cancer cells, is administered systemically and can be used alone or in combination with surgery or radiation therapy. [120] Radiation therapy uses high-energy X-rays to kill cancer cells and is often used in combination with surgery and chemotherapy. [121] Targeted therapy involves targeting specific proteins or genes that are involved in the growth and spread of cancer cells and can be used alone or in combination with other therapies. Immunotherapy, which stimulates the body's immune system to attack cancer cells, has emerged as a promising new treatment modality and is often used in combination with other therapies. [122]

Chemotherapy drugs are used to treat cancer, and they can be administered alone or in combination with other treatments. These drugs vary in their chemical composition, how they are given, and their effectiveness in treating different types of cancer. Chemotherapy drugs work by targeting cells in different phases of the cell cycle. [123] Since cancer cells divide more quickly than normal cells, chemotherapy drugs are more effective at targeting them. However, these drugs can also harm normal cells, which can result in side effects. The types of chemotherapy drugs include alkylating agents, nitrosoureas, antimetabolites, and anti-tumor antibiotics. [124] Each of these types of drugs works differently, and they have different side effects. Knowing how each drug works is important for predicting side effects and planning treatment. [125] The use of ionizing radiation to treat cancer started soon after the discovery of radium by M.S. Curie and P. Curie in 1898. [126] The first histologically documented cancer cures using radiation were performed in St. Petersburg in 1903 by S.W. Goldberg and Efim Semenovich London. Radiotherapy is currently an essential component in the management of cancer patients, either alone or in combination with surgery or chemotherapy, both for cure and for palliation. Of those cancer patients who are cured, it is estimated that 49% are cured by surgery, about 40% by radiotherapy alone or combined with other modalities, and 11% by chemotherapy alone or combined. [127] Despite the significant progress made in the development of new treatments, cancer therapies' efficacy still varies among different cancer types and stages. This is why combination therapy, where two or more treatment modalities are used, is often employed to increase treatment efficacy. [128] Advances in cancer therapy have led to the development of targeted immunotherapies, which have shown promising results in clinical trials. [129] However, challenges such as resistance to therapy, side effects, and access to care persist.

Targeted therapies and Immunotherapy

For several decades, the options available for cancer treatment have been limited to surgery, radiation therapy, and chemotherapy, either used individually or in combination. [92] Although these conventional methods have demonstrated some effectiveness, a major obstacle lies in their lack of specificity for cancer cells. Most drugs used in these treatments affect both healthy and diseased tissues, leading to severe side effects, however, extensive research is currently underway in the field of oncology to discover new and efficient therapies that can minimize the side effects associated with traditional treatments and selectively target cancer cells. [93]While cancer chemotherapy utilizes drugs to selectively kill cancer cells that are more prone to death than non-malignant host cells, recent drug development efforts have shifted toward identifying and targeting specific molecular drivers of cancer. [94] Currently, various technologies are being evaluated in clinical trials or have already been introduced into clinical practice. The most frequently explored areas in cancer therapy trials listed in the clinical trials database (www.clinicalTrials.gov) include stem cell research, targeted therapy, immunotherapy, and gene therapy, as they hold great promise and effectiveness. [92]

Targeted Therapies

Targeted therapy refers to the development of treatments designed to specifically affect certain targets, such as enzymes or receptors, these therapies can either block or enhance the function of their designated targets to treat specific diseases, including cancer. [95] In cancer therapeutics, targeted therapies aim to inhibit specific molecular targets responsible for promoting tumor growth. [96] By leveraging the unique characteristics of cancer cells, targeted therapies achieve their anticancer effects while minimizing harm to normal cells. [97] As a result, the identification of molecular targets has become a driving force behind the development of targeted cancer therapies using novel technologies and approaches. [98] Compared to traditional chemotherapy drugs, targeted drugs exhibit high potency and low toxicity due to their ability to specifically target cancer cells while sparing normal cells. [99] Molecular targeted therapy is gaining significant attention for its potential to selectively eradicate cancer cells while minimizing harm to healthy tissues. [98]

Types of Targeted Therapies

Two major types of targeted therapy are monoclonal antibodies and small-molecule inhibitors.

*Monoclonal Antibodies***:** Monoclonal antibodies (mAbs) are generated from clones of a unique B cell that binds to specific portions of an antigen (epitope). They are primarily designed to target sites located outside cells, as they are relatively large to penetrate cell membranes. [100] These antibodies possess the remarkable ability to directly kill tumor cells while engaging the host immune system to develop lasting responses against the tumor. Targeted mAbs directed against antigens unique to or overexpressed by tumor cells can induce tumor cell death through various mechanisms, with the blockade of growth factor receptor signaling being a prominent mechanism. [101] Examples of monoclonal antibodies used in cancer treatment include trastuzumab (Herceptin) for HER2-positive breast cancer and rituximab (Rituxan) for specific types of lymphoma. [102]

*Small-Molecule Inhibitors***:** Small-molecule inhibitors function by binding to specific target proteins and inhibiting their function. Unlike antibodies, small-molecule inhibitors can target a wider range of extracellular and intracellular molecules due to their smaller size. [98] These inhibitors primarily regulate the activity of protein targets involved in tumorigenesis, such as enzymes and receptors. Protein kinase inhibitors represent the largest category of small-molecule inhibitors, while other types include receptor agonists and antagonists. [103] One significant advantage of small-molecule inhibitors is their oral administration route, in contrast to subcutaneous or intravenous administration required for antibodies. Moreover, some small-molecule inhibitors have the ability to penetrate the blood-brain barrier, allowing for the treatment of intracranial lesions. [104] The application of small-molecule inhibitors in cancer encompasses targeting DNA damage/repair pathways, endocrinology and hormone pathways, metabolism pathways, angiogenesis pathways, and immune checkpoint blockers. [103] The use of targeted therapy has substantially improved survival rates for certain diseases. For instance, the addition of erlotinib to standard chemotherapy has increased the survival rate from 17% to 24% in patients with advanced pancreatic cancer. Similarly, imatinib has shown remarkable effectiveness in chronic myeloid leukemia, while rituximab, sunitinib, and trastuzumab have revolutionized the treatment of renal cell carcinoma and breast cancer, respectively. [92]

Immunotherapy and its various approaches

The immune system is used in immunotherapy to combat cancer. It functions by assisting the immune system in identifying and eliminating cancer cells. Immunotherapy can be used alone or in conjunction with other cancer treatments. Some cancers are commonly treated with immunotherapy. [144] Immune surveillance is the process by which the immune system's sophisticated monitoring capabilities identify cells in the body that have undergone a neoplastic change and trigger an adequate immune system reaction. However, through a variety of changing molecular processes, developing cancers use many strategies to resist immune-mediated clearance. The immune response of the body assists in the fight against illnesses and diseases. Its constituents include organs, lymphatic system parts, and white blood cells. Immunotherapy is one type of biological therapy. The body's immune system recognizes abnormal cells, destroys them, and likely inhibits or delays the growth of many cancers as part of routine function. [145] These lymphocytes, also referred to as tumor-infiltrating lymphoid cells or TILs, are proof that the immune system has detected the tumor. Different cells fight various forms of cancer. For instance, the immune system's response fights cancer by releasing a particular type of white blood cell known as T-cells: Cancer cells are viewed by the T-cells as "foreign" cells that are not permitted in the body. Attacking and attempting to kill malignant cells are the T-cells. T-cells are the key participants in the body's immune system's fight against cancer because they are the immune cells that recognize particular antigens during antigen presentation. [146]

Extrinsic and intrinsic mechanisms can both contribute to tumor immune escape. Intrinsic mechanisms include alterations in the tumors themselves, weak antigen expression during the early stages of tumor growth, the absence of epitopes, physical obstacles avoiding effector lymphocytes from entering solid tumors, the loss of the presentation of antigens, and the production of resistant inhibitory signals like immune checkpoints. [147] While the host immune system confers tumor extrinsic mechanisms, such as tolerance to the immune system, fatigue of tumor-specific T cells, synthesis of soluble ligands that restrict lymphocyte activation, and deficiencies in expert APC antibody presentation and maturation.

Monoclonal antibodies (MABS): Antibodies found in our blood naturally aid in and combat infection. The MAB therapies are produced in a laboratory and imitate natural antibodies as a tool. A monoclonal antibody is an antibodies manufactured inside a cells, it operates via recognizing and targeting specific protein on cells. Others concentrate on cancerous cells, whereas some target immunity system cells' proteins. A different protein is recognized by each MAB. They behave differently depending on the protein they are concentrating on. MABs function as immunotherapy in several ways. Rituximab/Mabthera (used to treat chronic lymphocytic leukemia and some forms of Cetuximab/Erbitux (used to treat advanced bowel cancer, head and neck cancer),non-Hodgkin lymphoma, and Trastuzumab/Herceptin (which are utilized to treat breasts and gastrointestinal cancer) are a few examples of monoclonal antibodies. Certain MABs connect to cancer cells, which facilitates the immune system's cells' ability to identify those cells. This process is known as antibody-dependent cell-mediated cytotoxicity (ADCC). [148]

Immune checkpoints inhibitors: A common part of the immune system's functioning as immunological checkpoints. They are there to prevent healthy cells in the body from being harmed by an immune response that is too strong. When connected protein on other cells, such as specific tumor cells, are detected and linked to protein on the outside of immunological cells known as T cells, immunological checkpoints are triggered. Immunological proteins that regulate checkpoints are the name given to these proteins. [105] The T

lymphocytes obtain a "off" sign once protein checkpoints and associated protein link properly. It could restrict the immunity the system's capacity to eradicate the malignancy. Immune checkpoints inhibitors are drugs used in immunotherapy to stop the interaction between companion proteins of checkpoint proteins and other proteins. Since the "off" signal is not transmitted, T lymphocytes are able to eliminate cancer cells as a result. [106]

Checkpoint protein on tumor cells, such as PD-L1, and on T cells, such as PD-1, control immune system reactions. The interaction of PD-L1 with PD-1 blocks the destruction of cancerous cells by the body's own T lymphocytes (left panel). T cells can kill tumor cells by preventing PD-L1 from adhering to PD-1 when using inhibitors of immune checkpoints (anti-PD-L1 or anti-PD-1) (also known as the panel). [107] Examples of immune checkpoints are; Pembrolizumab (Keytruda): in cancer immunotherapy, transformed antibodies are used to treat some types of breast cancer, Hodgkin lymphoma, cancer of the stomach, lung cancer, carcinoma of the head and neck, and melanoma. Keytruda is the trade name for the medication pembrolizumab. When delivered, pembrolizumab interacts to PD-1, an inhibitory signals receptors that appears on the top layer of activated T cells, and blocks its ligands from activating PD-1, which would otherwise stimulate T-cell-mediated immune responses against tumor cells. [108]

Anti-CTLA-4 inhibitor, known ipilimumab, is a type of immunotherapy that supports the immune system of the body in eliminating cancer cells. Ipilimumab is used alone to treat melanoma patients after surgery to remove the disease's cutaneous and lymph node sources. Ipilimumab is a medication.Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is a protein that binds to the human monoclonal antibody ipilimumab, preventing it from interacting with CD80 and CD86, which are two of its ligands. An "immune checkpoint" that blocks T-cell activation pathways and reduces autoimmunity is known as immunoglobulin G1 (IgG1)-kappa immunoglobulin, which is produced in mammal (Chinese hamster ovary) cell culture. It is available as a sterile, preservative-free intravenous (IV) infusion solution in disposable vials of 50 mg/10 mL and 200 mg/40 mL. By obstructing this function, which results in unregulated T-cell proliferation, ipilimumab increases the malignant T-cell response. [31,34] Therefore, ipilimumab's impact on melanoma patients is indirect and most likely brought on by T-cell-mediated antitumor immune responses. [109]

Adoptive cell therapy (act): T cells, an immune system cell, are given to a patient as a form of immunotherapy to help the body's defenses battle diseases like cancer. During cancer treatment, T cells are often removed out of the individual's own platelet or tumor tissue, amplified in number in the laboratory, and then administered back to the individual's body to support the body's fight against the illness. [110] The T cells are periodically altered in the lab to enhance their capacity to recognize and eliminate the patient's cancer cells. Examples of adoptive cell treatment include tumor-infiltrating lymphocytes (TIL) therapy and chimeric antigens receptors T-cell (CAR T-cell) therapy. Adoptive treatment with cells, which uses T lymphocytes from a donor, is used to treat a few types with cancer as well as a few infections. Sometimes referred to as cellular adoptive immunotherapy, adoptive cell transfer, and T-cell transfer therapy. [111]

Oncolytic virus: Oncolytic viruses are particles that enter our bodies and replicate by using the genetic programming of the cell in order to spread to nearby healthy cells. The viral infection known as human papilloma virus (HPV), which causes cancer of the cervical cavity and cancer of the head and neck, and the virus that transmits hepatitis B (HBV), which causes liver cancer, have been shown to contribute to the development of certain cancers. The ability of cancer vaccines to both prevent infection and offer protection against the emergence of both hepatitis and HPV-related cancers has been established. Viruses have targeted and attacked cancers that have already formed. For a number of reasons, these viruses, also known as oncolytic viruses, offer a promising strategy for treating cancer. Many of these have been genetically modified, but not all of them. Because they usually have poor antiviral defenses, cancerous cells are vulnerable to infection. [112] These naturally occurring viruses can be altered to have advantageous properties, such as a diminished capability to infect healthy cells, the ability to distribute therapeutic payloads specifically to tumors, and the ability to release immune-stimulating compounds after infecting tumor cells. After infection, these viruses are oncolytic and have the capacity to "burst" cancer cells, eradicating them and exposing cancer antigens. Any remaining tumor cells in the location, as well as possibly elsewhere in the body, can be found and removed after these antigens have stimulated immune responses. [113]

Cancer vaccines: Many varieties of Vaccines are medications that help the immune system of the body. They can instruct the body's immune system to recognize and get rid of potentially harmful cells and bacteria. Throughout your life, you will receive a number of immunizations to guard against common diseases. Additionally, cancer immunizations are readily available. There are vaccines available for both cancer treatment and cancer prevention. Types of cytokines called interleukins and interferons are used to treat cancer. [106] There are several vaccines that can protect healthy people from developing certain virus-related cancers. Similar to immunizations against the common cold or chicken pox, these vaccines provide the body with protection against certain viruses. The only people who will benefit from this type of immunization are those who get it before getting the virus vaccine against HPV. The human papillomavirus vaccine provides protection from it. If this virus lingers in the body for a long time, it may contribute to some malignancies. The FDA has approved HPV vaccinations to prevent sex-related warts, throat cancer, and cervix, vaginal, and vulvar cancer. Furthermore, HPV can cause conditions like mouth cancer which is why the FDA is yet to approve the vaccination. Obtaining a hepatitis B vaccine offers protection against the Hepatitis B virus (HBV). The virus that causes liver cancer. [106]

Antigens are substances found on the outermost layer of cells that the body interprets as dangerous. The immune system attacks antigens and usually destroys them. These antigens are now part of the immune system's "memory" to help develop additional defense against them. The ability of the immune system to detect and destroy antigens is enhanced by cancer vaccines. Cancer cells usually have chemicals on their surface called cancer-specific antigens, but healthy cells do not. When given to a person by a vaccine, these molecules serve as antigens. These substances direct the body's immune system to look for and destroy cancer cells that contain these substances. A few specific cancer vaccines exist. This implies that they are distinct objects. Utilizing patient cancer specimens that were surgically removed, this type of vaccination is made. Most cancer vaccinations do not specifically target personalized antigens for cancer that are particular to an individual. Doctors give these vaccines to individuals with malignancies that have antigens like these on the outermost layer of the tumor cells. [114]

Resistance to therapy and strategies to overcome it

Resistance may form when cancer cells within a tumor have molecular changes that make them resistant to a particular drug even before therapy begins. Since cancerous cells inside the same tumor usually display a variety of genetic changes, the inherent resistance is common. If the therapeutic targets are altered, a complicated process known as anticancer drug resistance results. [115] Drug resistance can be fought in novel ways thanks to the creation of customized medications, breakthroughs in proteomics research, and DNA microarray technology. Despite the rapid advancement in the invention of new chemotherapeutic drugs, none of them are yet efficient against cancer in its later phases (which includes invasion and metastasis). The genetic differences of the person, especially among tumoral somatic cells, may contribute to the cancerous cells' resistance to anticancer medications. Drug resistance can be fought in novel ways thanks to the creation of customized medications, breakthroughs in proteomics research, and DNA microarray technology. Despite the rapid advancement in the invention of new chemotherapeutic drugs, none of them are yet efficient against cancer in its later phases (see Figure 16). The genetic differences of the person, especially among tumoral somatic cells, may contribute to the cancerous cells' resistance to anticancer medications. [116]

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Tumor heterogeneity

It explains the naturally occurring development of variations that are regarded as to have various genetic, proteomic, transcriptomic, and epigenetic features and includes genetic changes, gene amplifications, eliminations chromosome rearrangements, transpositions of the genetic components, translocations, and alterations to microRNAs. Genomic instability contributes to the substantial intercellular genetic heterogeneity found in cancer. Due to the cancer stem cell concept, basic genotypic differences may result in an increase in epigenetic variables including miRNA, transcriptome, and proteome heterogeneity, but they can also represent a cell's developmental stage, stochastic variations among cells, or cell hierarchy. These alterations, which are sometimes referred to as intrinsic factors, contribute to tumor heterogeneity. Examples of extrinsic impacts include a lack of oxygen pH, and connections to stroma and additional cancer cells via paracrine signaling. These factors change, improve, or weaken genes in ways that directly result in the emergence of therapeutic resistance and unfavorable prognosis. [115]

Tumor microenvironment

In the discussion of treatment resistance as the main factor for cancer recurrence and incurability, mounting data supports the fundamental significance of the tumor microenvironment. The tumor microenvironment contains a layer of extracellular matrix (ECM), healthy stromal cells (SC), and a multitude of soluble compounds, such as cytokine and growth factors. Tumor-stromal cell interaction, tumor-cell interaction, and tumor-ECM interface all have an impact on the direct cell connection caused by treatment resistance. In addition, the tumor microenvironment's 15 proliferative factor (GF) cytokines signal the growth and persistence of tumor cells SDF-1 (stromal cell-derived factor-1), M-CSF (macrophage colony stimulating factor), "Environment-mediated drug resistance" (EM-DR) is essentially the same as "cell adhesion-mediated drug resistance" (CAM-DR) and "relatively readily soluble factor-mediated drug resistance" (SM-DR) products like VEGF (vascular endothelial growth factor), bFGF (basic fibroblast growth factor).

Cancer stem cells

It has been discovered that groups of cancer stem cells are present in many hematological and solid tumors. These populations could be at the origin of hematopoietic and substantial tumors. Notwithstanding the reality that chemotherapy kills many cancerous cells, it has been identified that cancer stem cells have their own systems for drug removal, which may contribute to treatment resistance. For instance, it has recently been shown the ATP-binding cassettes (ABC) over-expression, the P-glycoprotein-encoding ABCB1 drug transporter, and the ABCG2 drug transporter, which was first identified in mitoxantrone resistance cells, all protect tumor stem cell lines from being subjected to chemotherapeutic treatments. A vasculature sector, inactivity, hypoxic stability, and enhanced activity for repair enzymes are among the traits shared by cancer stem cells and normal stem cells that enable them to live a long time. Additionally, they can actively repair DNA, are relatively quiet because of the replication of medication efflux transporters, and are resistant to toxins and drugs. According to the features of cancer cells discussed previously, these tumor-causing cells can either stay constant among individuals who seem to be recovering or migrate to other parts of the body and lead to a cancer recurrence. Finding and eliminating these little collections of cancer cells will therefore greatly aid in eliminating treatment resistance.

Inactivation of the anticancer drugs

Anticancer drugs' efficacy and effectiveness are based on complex mechanisms. Interactions with specific proteins can cause changes in the molecular characteristics of drugs that can eventually cause them to become activated (in vivo). By reducing the activity of drugs, cancer cells gain resistance. Acute myeloid leukemia (AML) treatment with cytarabine (AraC), an anti-cancer drug nucleotide that can be converted to cytarabine triphosphate (AraC-triphosphate) following multiple phosphorylations, is a case in point. AraC initially has no effect on cancerous cells, but its phosphorylation version causes cell death and destruction. AraC expression is increased in drug-resistant cancer cells as a result of down-regulation of or mutation in the enzymes and proteins linked in this route (phosphorylation processes).

Multi-drug resistance (MDR)

Multi-drug resistance (MDR) is the term used in cancer treatment to describe the ability of malignant cells to develop a resistance to a variety of anti-cancer treatments. MDR pathways may emerge as a result of greater release of drugs outside of the cells. As a result, these cells only absorb a small amount of medication.

Increasing the release of drugs outside the cell

Molecules like nutrients are moved across the membrane via an assortment of ATP-dependent transporters. The ABC transporters are made up of a pair of transmembrane domains (TMDs) and two cytoplasm ATP-binding cassette (ABC) domains. The three ABC family members are P-glycoprotein (PGP), multidrug resistant-associated protein 1 (MRP1), and cancer chemotherapy resistance protein (BCRP/ABCG2), P-Glycoprotein (P-gp), the membrane transporter for a number of medications, is frequently known as a pump that removes chloride from cells and has the ability to bind to a number of chemotherapy treatments, including Doxorubicin, Vinblastine, and Taxol. Following binding, ATP undergoes hydrolysis, altering the molecular makeup of P-gp. As a result, the medication spreads across the extracellular environment. Following the second phase of ATP hydrolysis, the transporter reverts to its fundamental configuration, enabling it to transport the drug outside the cell.

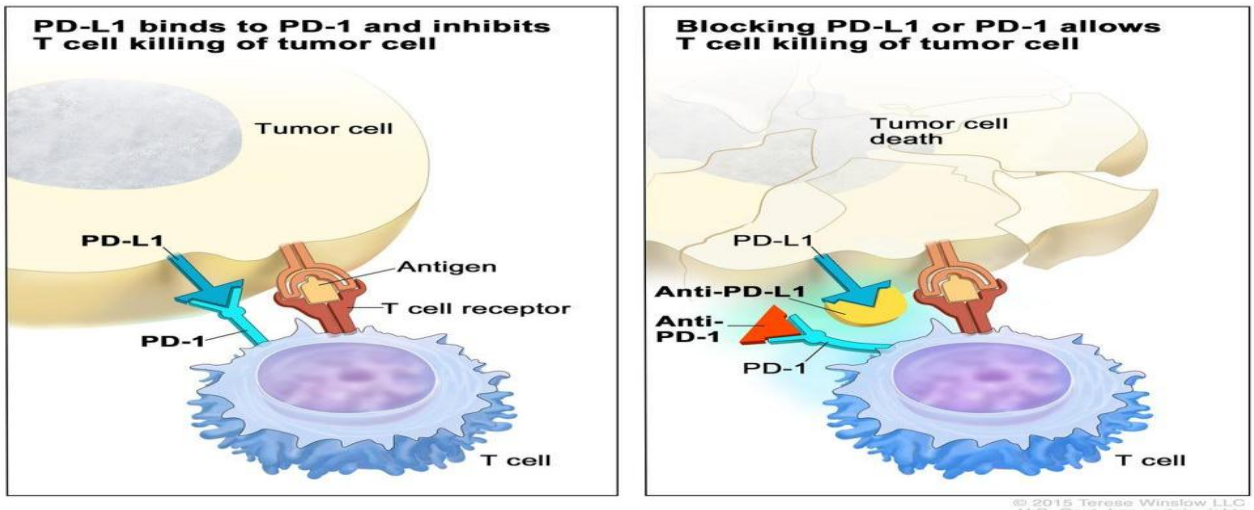

Figure 15: General mechanism of action of checkpoint inhibitors. [211]

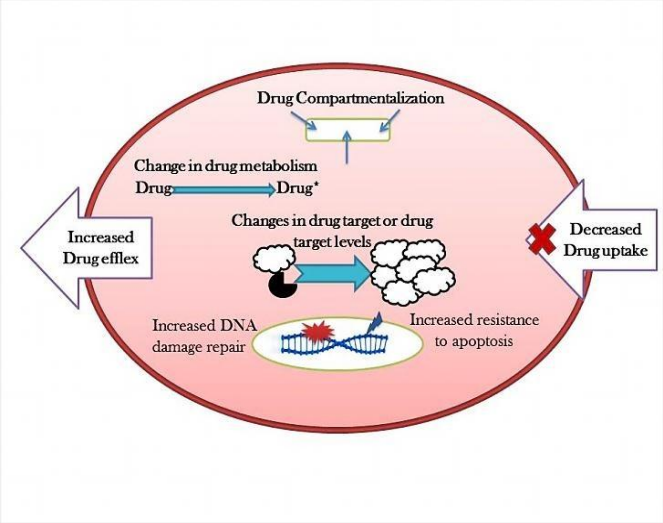

Figure 16: Mechanism of drug resistance. [198]

Emerging technologies and their potential impact on cancer care and management

Emerging technologies refer to the latest innovations and advancements that have the potential to revolutionize various industries. These technologies are typically in the early stages of development and have not yet been widely adopted. However, they have the potential to transform the way we live and work in the future. Examples of emerging technologies include artificial intelligence (AI), nanotechnology, personalized cancer vaccines, molecular profiling, and gene therapy or CRISPR/Cas9. AI involves the development of computer systems that can perform tasks that typically require human intelligence, such as speech recognition and decision-making. Emerging technologies hold great promise for improving cancer care and management by providing new tools and strategies for understanding the biology of cancer and developing more personalized and effective treatments. Here are a few examples of emerging technologies and their potential impact:

Nanoparticles: They are a promising new approach to treating cancer. Recent research has shown that nanoparticles could be a promising alternative for cancer treatment. Nanoparticles are tiny particles that are smaller than a cell and can be engineered to deliver drugs directly to cancer cells. [161] One of the advantages of using nanoparticles is that they can target cancer cells specifically and destroy them, leaving healthy cells unharmed. This targeted approach reduces the risk of side effects and increases the effectiveness of the treatment. For example, encapsulating a single nanoparticle (NP) with several active pharmaceutical ingredients (API) has the potential to produce synergistic effects to enhance the efficacy of treatments. Another advantage of nanoparticles is their ability to carry multiple drugs at once. This means that different drugs can be combined into a single nanoparticle, allowing for a more comprehensive treatment. [162] Nanoparticles can also be designed to release drugs slowly over time, ensuring a sustained effect that can last for days or even weeks. Despite the potential benefits of nanoparticles, there are still some challenges that need to be addressed. One of the main challenges is ensuring that the nanoparticles are biocompatible and do not cause any harm to the patient. [163] Another challenge is ensuring that the nanoparticles reach the cancer cells effectively. This requires careful engineering of the nanoparticles to ensure that they can penetrate the tumor and deliver the drugs directly to the cancer cells. [164] Despite these challenges, the use of nanoparticles for cancer treatment is a rapidly growing field, with many promising results in preclinical studies. With further research and development, nanoparticles could become a valuable tool for fighting cancer and improving patient outcomes. Nanoparticles are an emerging treatment for cancer that shows great promise. Their ability to target cancer cells specifically, carry multiple drugs at once, and release drugs slowly over time makes them a promising alternative to traditional cancer therapies. While there are still some challenges that need to be addressed, the future of nanoparticle-based cancer treatment looks bright.

CRISPR-Cas9: The Nobel Prize in chemistry for CRISPR-Cas9 was awarded to two women, Emmanuelle Charpentier and Jennifer Doudna in the year 2020, for their discoveries in the field of DNA manipulation with the CRISPR–Cas9 system called "genetic scissors". [165] CRISPR-Cas is a gene editing tool that allows researchers to modify the DNA of cells, including cancer cells. This technology has the potential to develop more targeted and effective cancer therapies by selectively targeting cancer cells while leaving healthy cells intact. CRISPR-Cas9 is a powerful tool for editing genomes and modifying the genetic sequence of cells and organisms. It has the potential to revolutionize cancer treatments by introducing epigenetic and transcriptional modifications. It works by cutting out and replacing specific genes in a person's DNA, which could help to remove cancerous cells from the body by involving several bioinformatics and experimental steps to screen target sites in cancer genes. [166]

Artificial Intelligence and Machine Language: Artificial intelligence and machine learning techniques have the potential to advance cancer research and help scientists make useful decisions based on big data and medical imaging. Artificial intelligence and machine learning techniques are expanding into biomedical research and health care, including cancer research (oncology), radiology, and pathology, where their applications are vast. These encompass identifying and diagnosing cancer, categorizing subtypes, improving cancer therapy, and discovering potential targets for drug development. [167] In vitro, cultures have been made using 3D cell cultures, tissue engineering, and microfluidics on a cancer chip to model the tumor microenvironment toward understanding drug implications and improving predictive drug screening models, which allows for high throughput analysis. [168] AI has been utilized to identify malignancy, predict the probability of tumor response to treatments, provide prognosis on patients' risk of cancer-related mortality, identify biomarkers from digital imaging, and create dependable predictive models for personalized cancer treatments. [169]

Molecular Profiling: Molecular profiling has emerged as a powerful tool in the fight against cancer. Analyzing the genetic and molecular makeup of a patient's tumor beyond genomics, such as transcriptomics, epigenetics, and immunophenotyping, and the evaluation of drug combinations beyond monotherapy approaches will hopefully increase the clinical utility and scope of precision medicine and help doctors develop personalized treatment plans that are tailored to the unique characteristics of each individual case. [170] Traditionally, cancer treatment has been based on the location and stage of the tumor. However, this approach has limitations, as tumors can vary greatly even within the same type of cancer. Molecular profiling allows doctors to better understand the underlying biology of a tumor, and to identify specific mutations or other molecular abnormalities that may be driving its growth. [166] Several different methods of molecular profiling are currently available, including immunohistochemistry or IHC, Fluorescence in situ hybridization, commonly called FISH DNA sequencing, RNA sequencing, and protein analysis. These techniques allow doctors to identify a wide range of molecular abnormalities, including mutations, gene fusions, and changes in gene expression by examining patient's biomarkers and their genetic makeup, also to regulate the activity of certain molecular targets in cell signaling, proliferation, metabolism, and death.

Liquid biopsy: Liquid biopsy involves analyzing a patient's blood for circulating tumor cells or fragments of tumor DNA, which can provide information about the genetic makeup of a tumor without the need for a tissue biopsy. This technology has the potential to improve early cancer detection, monitor treatment response, and detect cancer recurrence.

3D printing: 3D printing has the potential to revolutionize cancer treatment by allowing clinicians to create personalized implants and prosthetics for cancer patients. For example, 3D printing can be used to create patient-specific surgical guides that help surgeons precisely remove cancerous tissues. These emerging technologies are just a few examples of the potential impact they can have on cancer care and management. As researchers continue to develop and refine these

technologies, we can hope to see even more improvements in cancer diagnosis, treatment, and management, leading to better patient outcomes and quality of life.

Future directions in cancer research and therapeutics

Cancer remains the leading cause of death after cardiovascular disease with about 10 million deaths in 2020, with various advances made in the understanding of tumor biology and therapeutics, there is a need to focus on improving cancer detection, targeting resistance mechanisms, which may involve finding new drug target, combination therapies, predictive biomarkers for resistance. [117] A tyrannical challenge with cancer is often late diagnosis of cancer, hence patients miss the therapeutic window before discovery. [118] There is therefore a need to major on highly specific, cost effective, early cancer detection tools rather than a symptom presenting type of cancer diagnosis. [119,120] Blood based liquid biopsies which are less invasive are currently been harnessed in several types of cancer, especially prostate cancer. [121] It is established as a valuable resource in prostate cancer for identifying predictive, and response biomarkers. Blood samples can yield traces of tumors because cancer shed intact tumor cells into the bloodstream referred to as circulating tumor cells in the blood, which can reveal crucial information about tumor characteristics. [122] By leveraging these less invasive biopsy, clinicians can obtain valuable guidance for making diagnoses and selecting appropriate treatments. It has however been identified that patients with metastatic cancer have extremely low abundance of circulatory tumor cells in the blood stream, which is typically less than 10cells/ml. [122] A major challenge and a future direction in the use of liquid biopsy is the need for advancing detection and isolation methods for circulatory tumor cells in metastatic cancers.

The growth of nanotechnology is not only limited to its therapeutic capacity but also highly effective as a diagnostic tool which expresses high specificity for tumor site. [123] The advantage of this approach lies in the higher concentration of nanostructures at the exact location of the tumor, resulting in an improved signal-to-noise ratio and greater accuracy in illuminating cancerous tissues while minimizing the impact on healthy tissues nearby. [124] In addition, imaging agents which are nano-sized typically have a size greater than 10 nm, preventing their removal from the circulatory system by the kidneys and leading to extended circulation periods in comparison to smaller particles. [125]

A better understanding of tumor biology has led to the development of targeted therapy such as immunotherapy. Immunotherapy seems to be the future of cancer treatment by improving overall survival rate of cancer patients however it has been met by an idiosyncratic response such as resistance, immune related toxicities. [126] This has led to the need for exploiting predictive biomarkers for immunotherapy treatment to identify patient who would better benefit from immunotherapy (127)]. PD-L1 is presently being exploited has a predictive biomarker, however, there is a need to target more sophisticated and reliable biomarkers. [127] Current researches focus on Neoantigens which is a product of tumor mutational burden and has been correlated with improved responses to checkpoint inhibitors. [128]

A future initiative should involve identification of novel immune checkpoint target, or novel combination of immunotherapy drugs and by extension, combination of immunotherapy drugs with other traditional drugs while finding a way to standardize immunotherapy to reduce toxicity.

Similarly major focus should be channeled towards the development of predictive biomarkers for all cancer treatment options. All cancer patients will not respond to chemotherapy neither immunotherapy, however, there is need to understand what predisposes a patient to respond to a certain form of treatment which is not efficacious in another. [129] Gong and colleagues correlated higher neoantigen load with a better disease free survival in squamous cell type of lung carcinoma which is absent in lung adenocarcinoma. They also correlated a better response to adjuvant chemotherapy with low neoantigen load hence carrying out this kind of study on a larger cohort, different ethnic populations, and different types of cancer may be the way out in beating idiosyncratic response to cancer. Secondly, an in-depth focus should be placed on cancer stem cell biology. The knowledge of cancer stem cells in recent times has led to the several poking studies and has been attached to resistant to treatment, relapse and metastasis. [130] Cancer stem cells have been posited to have over expression of drug transporters which allows the efflux of cancer drugs hence leading to resistance. [131] Stem cells are characterized with the innate ability to evade apoptosis, active DNA repair mechanisms, drug efflux pumps, and even dormancy. [132] A focus on the eradication of cancer stem cells can be viewed as an effective approach to comprehending the underlying mechanisms of tumor formation and developing anti-cancer treatments, which may lead to improved outcomes for cancer patients. [133] There is a possibility for the role of AI in determining the stemness of cancer cells which can then be targeted for treatment. Focusing our attention on writing algorithms which can accurately determine the cancer stem cells will be a long stride in eradicating the burden of cancer. Scientists utilized a risk score model and nomogram based on stemness subtypes to develop ETV2 as a diagnostic and prognostic tool. [134] Research has shown that ETV2 is implicated in the process of glioma invasion, migration, and epithelial to mesenchymal transition. [134]

Conventional drug molecules cannot be looked away from hence the need for certain modifications in preempting challenges associated to them which include, difficulty in delivery to target site, reduced bioavailability, lack of specificity in the target of cancer cells. [135] This make it necessary to focus on developing more efficient and time-saving treatments that incorporate nanostructures. Nanostructures can therefore act as carriers to drug molecules. [136] For effective use of nanostructures for cancer treatment, the substance of target may be a receptor or an antigen that is exclusively expressed on malignant cells and is almost absent or present at very low levels on healthy cells. . Nanomaterials can assist in the direct targeting of tumor cells, leading to improved drug delivery while minimizing the harmful effects of the medication on non-target tissues. Consequently, the quality of cancer therapy is enhanced. The possibility of nanostructures defining cancer therapeutics requires finding novel materials that will release drugs at cancer target sites, they must be degradable after their activity or harmless if not degradable. [124] Novel nanoparticles with favourable delivery option should be looked into with focus on reducing toxicity from drugs, carrier of the drugs, that is, the nanoparticle itself, and should be harnessed for combinatorial delivery of drugs. The particularly small size of nanoparticle may allow its entry into the nucleus, it may therefore be effective in the modulation of the nuclear transcription factors which is an important tool for cancer cells uncontrolled proliferation. [137] There should be a further look into the drug been formulated at a nanoscale itself and how it can be made to function as nanoparticle in other to evade safety complication of synthetic nanoparticle constituents. The efficacy of nanostructures for cancer treatment invariably depends on the durability of nanomaterial-drug complex durability, tumor delivery of nanomaterial-drug matrix, release of drug from nanomaterial medicine framework, and elimination of nanomaterial after drug release. [124] Future research should also harness the multivalent potential of nanoparticles to allow a multiple target of tumor cells which increases sensitivity and reduces toxicity to normal cells. To facilitate the uptake of nanomaterials into cells, peptides can be attached to the surface of the nanomaterials to enhance their intracellular absorption. [138] Current and future researches should therefore pay attention to the multifunctional potential of nanostructures as a form of targeted therapy and also an effective diagnostic while paying attention to the pitfalls to modulate them. [139]

Conclusion

Recent advances in cancer biology have improved our understanding of the genetic and molecular mechanisms underlying cancer, leading to the development of new therapeutic approaches such as targeted therapies and immunotherapies. While these treatments have shown promising results in clinical trials, there are still challenges in developing effective and personalized cancer therapies. As discussed in this review article, emerging technologies and areas of investigation hold promise for improving cancer treatment outcomes, but continued research is needed to fully realize their potential. We therefore thoroughly present latest cancer research advances, placing emphasis on novel therapeutics which researchers are exploring to improve

cancer prevention, diagnosis, and treatment. We also took a look at the future directions in cancer research and its therapeutics. By working to better understand the complex biology of cancer and developing personalized treatment strategies, we can improve the survival rate of cancer patients and bring closer, a future where cancer is no longer a devastating, life-threatening disease.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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