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Tumor-infiltrating Foxp3$^+$ Regulatory T Cells Contribute to Partial EMT through the Snail$^+$ Tumor Cell Feedback Loop in Nasopharyngeal Carcinoma Patients

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ABSTRACT

Tumor-infiltrating FoxP3$^+$ Treg cells are crucial immune components associated with progressivity, metastasis, and prognosis in various malignancies, but the role in nasopharyngeal carcinoma (NPC) is not fully understood. Therefore, this study aimed to investigate the role of infiltrating FoxP3$^+$ Treg cells in epithelial-mesenchymal transition (EMT) in NPC patients. A total of 57 paraffin blocks from NPC patients were included in this study. The samples were then deparaffinized, and double immunohistochemical staining was performed to examine infiltrating Tregs that colocalize to express FoxP3$^+$ and TGF-β1. Single immunohistochemical staining was conducted to examine NPC tumor cells that express EMT markers Snail, E-cadherin, and vimentin. Chi-square and the Gamma correlation tests were used, with a *P*-value <0.05 considered statistically significant. The results showed that most NPC samples had low expression of Foxp3$^+$ Treg cells (59.6%), TGF-β1 (63.2%), E-cadherin (87.7%), and vimentin (75.4%), while Snail expression was high (66.7%). There was no relationship between the expression of Foxp3$^+$ Treg and pathologic variables except with Snail (P = 0.001; Gamma correlation test, r = 0.826, P < 0.001). TGF-β1 expression showed no association with Snail. Meanwhile, Snail was significantly associated with vimentin (P = 0.022; Gamma correlation test, r = 0.807, P = 0.003) but not with E-cadherin. Snail was also significantly associated with Foxp3$^+$ Treg expression (P = 0.003; Gamma correlation test, r = 0.826, P < 0.001). These results suggest that infiltrating Foxp3$^+$ Treg cells contribute to partial EMT in NPC with immunosuppressive function by forming a feedback loop with Snail$^+$ tumor cells.

Keywords: Nasopharyngeal carcinoma, tumor-infiltrating FoxP3$^+$ regulatory T cells, Transforming Growth Factor-β1, Snail, epithelial-mesenchymal transition

Introduction

Nasopharyngeal carcinoma (NPC), which arises from the nasopharyngeal epithelium, is the most prevalent head and neck malignancy.[1] According to 2020 global cancer statistics, over 75% of NPC cases occur in East and Southeast Asia, particularly in South China.[2] In Southeast Asia, NPC ranks as the 10th most common cancer overall, with an incidence in Indonesia of 10.71 per 100,000 in men and 3.03 per 100,000 in women.[3] NPC has a poor prognosis due to the high invasiveness and strong metastatic potential.[4] Due to the hidden anatomical location and nonspecific symptoms, most NPC patients are at an advanced stage during the initial diagnosis.[5] The administration of radiotherapy and chemotherapy based on tumor-node-metastasis (TNM) cancer staging system has recently significantly improved the prognosis of NPC patients. However, there is still a significant variation in the prognosis of patients receiving the same therapy at the same stage. Some continue to experience locoregional recurrence and distant metastasis. This suggests that the TNM system alone is insufficient to evaluate the overall status of NPC, guide treatment, and predict treatment response.[6-8] Tumor metastasis is a complex process in which epithelial-mesenchymal transition (EMT) plays a key regulatory role. During EMT, epithelial cells lose polarity and adhesion, acquiring mesenchymal-like traits that promote migration and invasion.[9] EMT is induced by factors such as hepatocyte growth factor (HGF), epidermal growth factor (EGF), and transforming growth factor-β (TGF-β), which activate transcription factors like Snail, Slug, and Twist. Snail and Slug repress E-cadherin and are related to metastasis, with Snail being a major EMT inducer.[10, 11]

Recent studies have emphasized that metastasis is not only driven by the intrinsic properties of tumor cells,[12] but also tumor microenvironment (TME), where immune cells play a major regulatory role.[7,13] Treg cells, an immunosuppressive CD4$^+$ T cell subset marked by Forkhead box Protein P3 (FoxP3),[14] are key components of tumor-infiltrating lymphocytes (TILs) in NPC.[13] Foxp3$^+$ Treg cells are associated with tumor progression and immune suppression, possibly through TGF-β1 secretion or direct contact inhibition. Previous studies have found that Treg cells are associated with metastasis and poor prognosis in non-small cell lung carcinoma (NSCLC),[15] as well as with poor clinical stage and lymph node metastasis in NPC.[16] Tregs also promote hepatocellular carcinoma invasion through TGF-β1-induced EMT.[13] In contrast, some studies have found that tumor-infiltrating Treg cells are associated with better outcomes or have no impact on prognosis in cancers, such as follicular lymphoma and squamous cell carcinoma.[17] However, the role of FoxP3$^+$ Treg cells in TME and the

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association with EMT in NPC remain understudied. This study explores the potential contribution to EMT and implications for NPC prognosis.

Materials and Methods

Samples

A total of 57 paraffin blocks from NPC patients diagnosed between 2018 and 2023 were included based on study criteria. Samples were obtained from the archives of the Anatomical Pathology Laboratory at Dr. M. Djamil Hospital, Padang, and the Anatomical Pathology Diagnostic Center, Faculty of Medicine, Universitas Andalas. Histopathological classification followed the World Health Organization (WHO) guidelines, including keratinizing squamous cell carcinoma (SCC), non-keratinizing SCC (differentiated and undifferentiated subtypes), and basaloid SCC type. This study received approval from the Research Ethics Commission of the Faculty of Medicine, Universitas Andalas (Certificate No. 51/UN.16.2/KEP-FK/2023).

Immunohistochemistry staining

Paraffin blocks were sectioned at 4 μm and mounted on poly-L-lysine-coated slides. Sections were deparaffinized in xylene and rehydrated in graded alcohol. Double immunohistochemical staining was performed using anti-TGF-β1 (TGF beta 1 Ab-AF1027-A Affinity Biotech, 1:200) and anti-FoxP3 (FOXP3 Ab-BF0630 Affinity Biotech, 1:100) antibodies. Antigen retrieval was performed via microwave heating in Tris-EDTA buffer (pH 9.0). Furthermore, endogenous peroxidase activity was blocked with BLOXALL solution, followed by non-specific protein blocking using 2,5% Normal Horse Serum. After applying primary antibodies, slides were washed with phosphate buffer and incubated with the secondary antibody ImmPRESS Duet reagent. DAB and ImmPACT Vector Red chromogen were then applied sequentially to visualize TGF-β1 (brown) and FoxP3 (red). Single immunohistochemical staining for Snail, E-cadherin, and vimentin was conducted using antibodies including anti-Snail (AF6032-A Affinity Biotech, 1:100), anti-E-cadherin (AF0131-A Affinity Biotech, 1:100), and anti-Vimentin V9 (347M-14 Cell Marque, 1:50). Heat epitope retrieval was performed by microwaving in citrate buffer (pH 6.0). Endogenous peroxidase was blocked with 3% H_20_2 and then 0.3% H_20_2 in PBS (pH 7.4). Non-specific proteins were blocked with 2% Normal Goat serum (NGS) in PBS (pH 7.4) at room temperature. Slides were incubated in a humid chamber overnight at 4°C with primary antibodies, followed by biotinylated Goat Anti-Rabbit IgG (BA-1000-1.5, 1:100), and Avidin-Biotin complex at room temperature. DAB was used as the chromogen, and slides were counterstained with hematoxylin. Microscopic evaluation was performed at 400x magnification using an Olympus CX 33 microscope, Sony Exmor CMOS Sensor Beta camera, Betaview Program, and ImageJ v1.49. FoxP3 and TGF-β1 expression was assessed by examining Treg cells in intratumoral and peritumoral areas that colocalize to express FoxP3$^+$ (red color in the nucleus) and TGF-β1 (brown color in the cytoplasm) using a semiquantitative score according to Kara et al., 2019 (<20% as low expression, >20% as high expression).[18] Snail expression was assessed in representative tumor areas with ≥ 400 cells, observed under 400x magnification. Positive staining appeared brown in the cytoplasm/and/or nucleus. The proportion and the intensity of stained tumor cells were determined according to Luo et al. 2012. The expression levels of Snail were assessed using the final immunoreactive score, which was calculated by multiplying the staining intensity scores and the proportion of positive tumor cells. On this basis, a score ≤4 was considered as patients with low expression and ≥6 as those with high expression.[19] E-cadherin and vimentin expression were similarly evaluated in ≥ 400 tumor cells, observed under 400x magnification. More specifically, E-cadherin staining appeared brown color on the membrane/and or cytoplasm, and vimentin in the cytoplasm/and or nucleus. The outcome measure was obtained by calculating the proportion of positive tumor cells as follows: 0 (no positive tumor cells), 1 (<10% positive tumor cells), 2 (10-50% positive tumor cells), and 3 (>50% positive tumor cells). Scoring criteria for staining intensity were graded as follows: 0 (no staining), 1 (light yellow staining/weak intensity), 2 (yellow staining/medium intensity), and 3 (brown staining/strong intensity). The coloration index was calculated by multiplying the proportion and intensity. E-cadherin and vimentin expression were assessed by determining the staining score (0, 1, 2, 3, 4, 6, or 9), with < 4 showing low expression and > 6 high.[20] Two pathologists independently assessed all samples.

Statistical analysis

Data were analyzed using SPSS version 25.0, with the Chi-square test assessing the associations between FoxP3$^+$ Treg expression and pathological variables in NPC. The Gamma correlation tests were used to evaluate the direction and strength of correlations between the variables.

Results and Discussion

Clinicopathological characteristics of NPC patients

In this study, NPC patient ages ranged from 10 to 71 years, with a median age of 46. The majority were male (33 cases, 57.9%). The most common histopathological subtype was non-keratinizing SCC undifferentiated (42 cases, 73.7%), with no basaloid SCC cases observed. Most samples showed low expression of Foxp3$^+$ Treg cells (34 cases, 59.6%) and TGF-β1 (36 cases, 63.2%). Snail expression was high in most cases (38 cases, 66.7%), while E-cadherin and vimentin expression were low in 50 cases (87.7%) and 43 cases (75.4%), respectively (Table 1). FoxP3$^+$ Treg cells and TGF-β1 expression in NPC were evaluated by double immunohistochemical staining, while Snail, E-cadherin, and vimentin were assessed by single staining. Co-expression of FoxP3$^+$ and TGF-β1 was observed in Treg cells (Figure 1). High Snail expression (Figure 2), low E-cadherin, and vimentin expression (Figure 3) were also observed in NPC tumor cells.

Expression of EMT markers and TGF-β1 in NPC tissue and its relationship with FoxP3$^+$ Treg expression

The relationship between FoxP3$^+$ Treg and TGF-β1 expression, as well as Snail, E-cadherin, and vimentin was assessed in NPC patients (Table 2). FoxP3$^+$ Treg expression was significantly associated with Snail (P = 0.003). Among cases with high Snail expression, 91.3% also showed high Foxp3$^+$ Treg, compared to 50.0% with low expression, indicating a significant difference (P = 0.003). There were no significant associations between Foxp3$^+$ Treg and TGF-β1 (P = 0.257), E-cadherin (P = 0.423), or vimentin (P = 0.074). Gamma correlation analysis further confirmed a strong positive correlation between FoxP3$^+$ Treg and Snail expression (r = 0.826, P < 0.001; Table 3).

TGF-β1 expression in NPC tissue and relationship with Snail expression

The relationship between TGF-β1 and Snail expression was analyzed in NPC (Table 4). The results indicated that there was no significant association, as shown by P = 0.771.

Snail expression in NPC tissue and the relationship with EMT markers

Snail expression showed a significant association with vimentin (P = 0.022). Among cases with high vimentin expression, 34.2% also showed high Snail, compared to only 5.3% with low expression. However, no significant association was observed between Snail and E-cadherin expression (P = 0.675) (Table 5). Gamma correlation analysis confirmed a strong positive correlation between Snail and vimentin expression (r = 0.807, P = 0.003; Table 6).

Snail expression in NPC tissue and its relationship with Foxp3$^+$ Treg expression

The relationship between Snail and Foxp3$^+$ Treg expression was examined in NPC (Table 7). Among cases with low FoxP3$^+$ Treg expression, 89.5% showed low Snail expression, while only 44.7% indicated high Snail. This difference was statistically significant (P < 0.05). Gamma correlation analysis confirmed a strong positive correlation between Snail and FoxP3$^+$ Treg expression (r = 0.826, P value < 0.001; Table 8).

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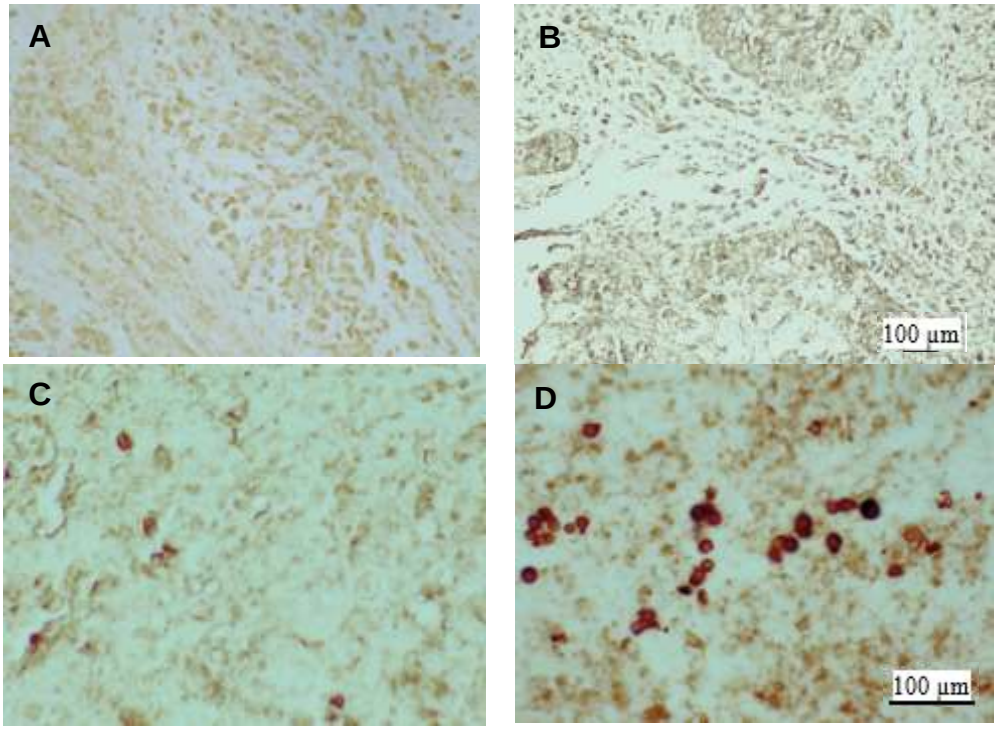

Figure 1: Double immunohistochemical staining of TGF-β1 and FoxP3 in NPC. TGF-β1 Immunoperoxidase (brown) and FoxP3 (FOXP3 alkaline phosphatase (red)). TGF-β1 appears to be expressed in some tumor cells and stromal cells. Treg lymphocyte cells ($FoxP3^+$) appear to express TGF-β1, with red and brown colocalization. Tumors with low (A, C) and high (B, D) FoxP3 (+)/TGF-β1 (+) densities. Double immunohistochemical staining, original magnification 100x (A, B) and 400x (C, D). Scale 100µm.

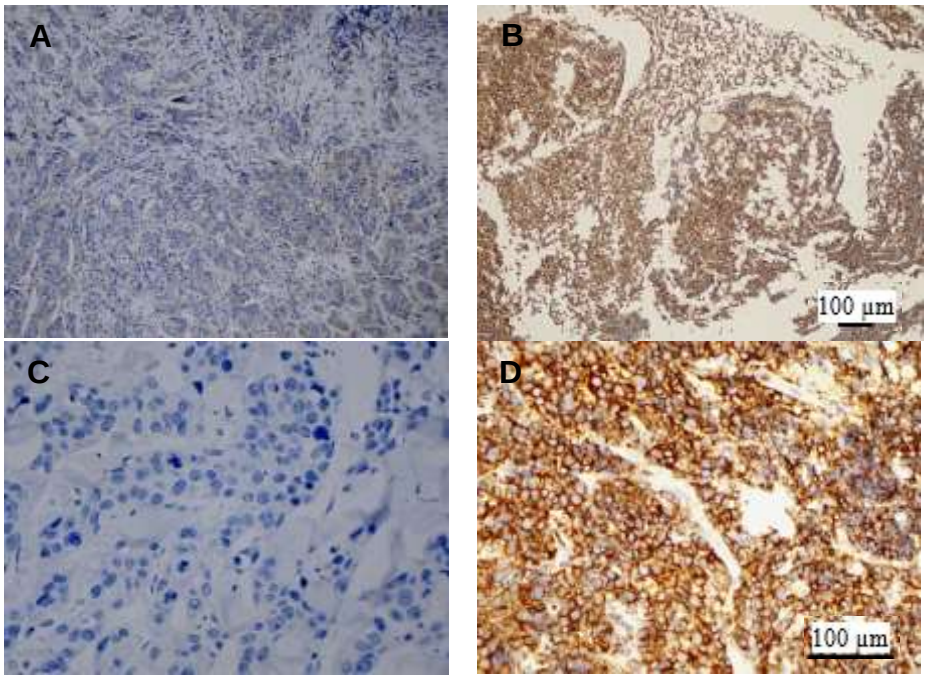

Figure 2: Snail immunohistochemistry in NPC. Snail expression was detected as a brown color in the cytoplasm. Representative samples with negative Snail expression on tumor cells (A, C) and samples with high Snail expression on tumor cells (B, D). Immunoperoxidase original magnification 100x (A, B), and 400x (C, D). Scale 100µm.

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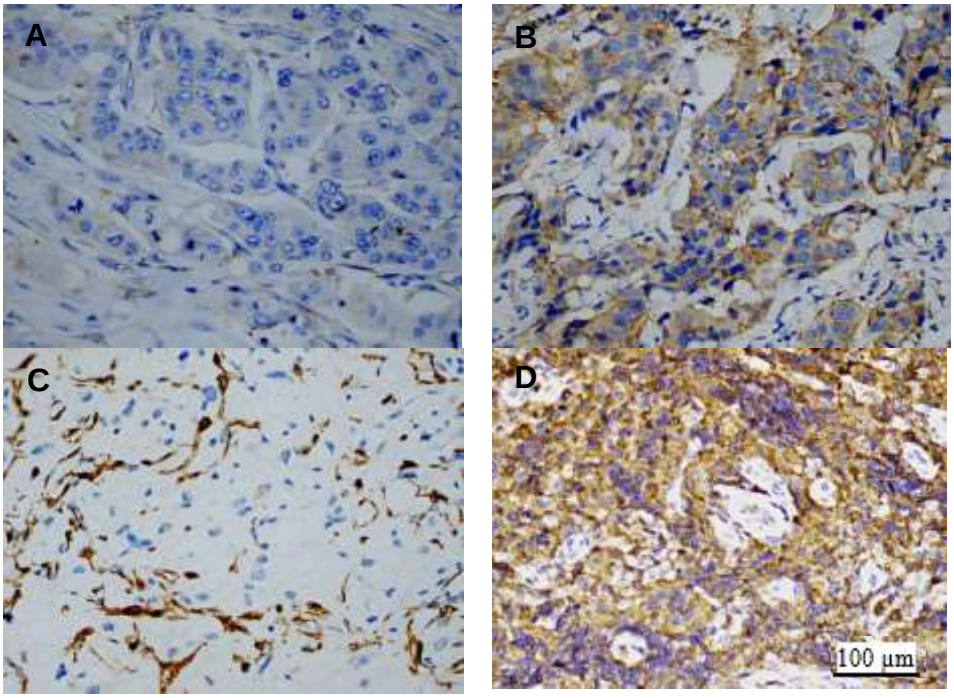

Figure 3: Immunohistochemistry of E-cadherin and vimentin in NPC. E-cadherin expression (A, B) was brown in the cell membrane and cytoplasm. Representative samples with negative E-cadherin expression in tumor cells (A) and positive in tumor cells (B). Vimentin expression (C, D) was detected as brown in the cytoplasm of the tumor and stromal cells. In representative samples with negative vimentin expression in tumor cells, vimentin was detected only in stromal cells (C) and was positive in tumor cells (D). Immunoperoxidase, original magnification 400x. Scale 100μm

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The critical role of the TME in tumorigenesis, EMT, invasion, and metastasis has been well established.[13] The TME consists of immune cells, endothelial cells, mesenchymal cells, inflammatory mediators, and extracellular matrix (ECM) molecules.[7] Regulatory T (Treg) cells, a key component of tumor-infiltrating lymphocytes (TILs), inhibit immune surveillance and suppress antitumor immune responses. FoxP3, the hallmark transcription factor of Tregs, is crucial for immunosuppressive function. Signals from TME, including TGF-*β*, can induce peripheral naïve T cells to become induced regulatory T cells (iTreg).[21] A better understanding of the mechanisms underlying Treg regulation in tumor initiation and progression is needed.

EMT was once viewed as a binary transition from epithelial to mesenchymal states, but is now understood to be a spectrum that includes a partial EMT phenotype.[22] Cells in this state show mixed epithelial and mesenchymal features, including reduced polarity, increased motility, and collective migration, thereby enhancing metastasis.[23] EMT also influences cell proliferation, apoptosis, budding, and immunosuppression, driven primarily by transcription factors, such as Snail, Slug, Twist1, Zeb1, and Zeb2, which are activated by signals, namely TGF-*β*, EGF, PDGF, VEGF, WNT, and Notch.[22] The TME contributes further to EMT through immunosuppressive elements like Tregs.[22]

The results showed that FoxP3$^+$ Treg cells contribute to partial EMT in NPC. Tumor cells showed both epithelial (E-cadherin) and mesenchymal (vimentin) markers, consistent with a partial EMT phenotype. These cells have enhanced tumor initiation potential, resistance to therapy, and survival advantages over fully epithelial or mesenchymal cells.[23] The phenotype also allows tumor cells to maintain adhesion while migrating collectively, facilitating intravasation and metastasis. The interaction between EMT and immune suppression forms a feedback loop that accelerates tumor progression.[23]

Although TGF-*β*1 is a known inducer of EMT and Snail activation in cancer,[24] it can be produced by tumor cells, stromal cells, and immune cells, including Treg cells.[13, 25, 26] A study by Shi et al.[13] showed that Treg promoted hepatocellular carcinoma invasion through TGF–*β*1–induced Snail activation. However, in this study, the lack of association between TGF-*β*1 and Snail expression suggests that TGF-*β*1 derived from FoxP3$^+$ Treg cells may not be the primary inducer. Snail expression may instead be influenced by TGF-*β*1 from tumor or stromal cells.

Snail has been shown to directly induce both EMT and Foxp3$^+$ Treg cells accumulation, contributing to immunosuppression and increased metastasis, as indicated in melanoma by Saito et al.[27] In line with previous results, Snail simultaneously promotes partial EMT and Treg cells expansion in NPC. Foxp3$^+$ Treg cells likely suppress CD4$^+$ and CD8$^+$ T lymphocyte responses, promoting tumor growth. Furthermore, tumor-derived TGF-*β*1 may upregulate Snail, completing a feedback loop that sustains both EMT and immune evasion. This loop reinforces the partial EMT phenotype, which plays a key role in tumor aggressiveness, resistance, and progression.[23]

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Table 1: Clinicopathological characteristics of NPC patients

Characteristics	n	%
Age (years)		
Median 46		
Minimum 10		
Maximum 71		
Gender		
Male	33	57.9
Female	24	42.1
Histopathology of NPC		
Keratinizing SCC type,	1	1.8
Non-keratinizing SCC type, differentiated subtype	14	24.6
Non-keratinizing SCC type, undifferentiated subtype	42	73.7
Basaloid SCC type	0	0.0
FoxP3$^+$ Treg expression		
Low	34	59.6
High	23	40.4
TGF-β1 expression		
Low	36	63.2
High	21	36.8
Snail expression		
Low	19	33.3
High	38	66.7
E-cadherin expression		
Low	50	87.7
High	7	12.3
Vimentin expression		
Low	43	75.4
High	14	24.6
Total	*57*	*100.0*

Table 2: Relationship of FoxP3$^+$ Treg expression with TGF-β1, Snail, E-cadherin, and Vimentin expression in NPC

	TGF-β1 expression				*P*-value	Snail expression				P-value	E-cadherin expression				*P*-value	Vimentin expression				*P*-value
	Low		High			Low		High			Low		High			Low		High		
	n	%	n	%		n	%	n	%		n	%	n	%		n	%	n	%	
FoxP3$^+$ Treg expression																				
Low	24	70.6	10	29.4	0.257ns	17	50.0	17	50.0	0.003*	31	91.2	3	8.8	0.423ns	29	85.3	5	14.7	0.074ns
High	12	52.2	11	47.8		2	8.7	21	91.3		19	82.6	4	17.4		14	60.9	9	39.1	
Total	36	63.2	21	36.8		19	33.3	38	66.7		50	87.7	7	12.3		43	75.4	14	24.6	

*: significant ($P < 0.05$); ns: non-significant ($P \geq 0.05$)

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Table 3: Gamma correlation analysis results between FoxP3$^+$ Treg and Snail expression in NPC

		Snail expression		Correlation	*P*-value
		Low	High	coefficient (*r*)	
FoxP3$^+$ Treg expression	Low	17 (50.0)	17 (50.0)	0.826	0.000*
	High	2 (8.7)	21 (91.3)		
	Total	19 (33.3)	38 (66.7)		

*: significant ($P < 0.05$); ns: non-significant ($P \geq 0.05$)

Table 4: Relationship between TGF-β1 and Snail expression in NPC

		Snail expression				
		Low		High		*P*-value
		n	%	n	%	
TGF-β1 expression	Low	13	36.1	23	63.9	0.771ns
	High	6	28.6	15	71.4	
	Total	19	33.3	38	66.7	

*: significant ($P < 0.05$); ns: non-significant ($P \geq 0.05$)

Table 5: Relationship between Snail expression and E-cadherin and Vimentin expression in NPC

	E-cadherin expression				*P*-value	Vimentin expression				*P*-value
	Low		High			Low		High		
	n	%	n	%		n	%	n	%	
Snail expression										
Low	16	84.2	3	15.8	0.675ns	18	94.7	1	5.3	0.022*
High	34	89.5	4	10.5		25	65.8	13	34.2	
Total	50	87.7	7	12.3		43	75.4	14	24.6	

*: significant ($P < 0.05$); ns: non-significant ($P \geq 0.05$)

Table 6: Gamma correlation analysis results between Snail and Vimentin expression in NPC

		Vimentin expression		Correlation	*P*-value
		Low	High	coefficient (*r*)	
Snail expression	Low	18 (94.7)	1 (5.3)	0.807	0.003*
	High	25 (65.8)	13 (34.2)		
	Total	43 (75.4)	14 (24.6)		

*: significant ($P < 0.05$); ns: non-significant ($P \geq 0.05$)

Table 7: Relationship between Snail expression and FoxP3$^+$ Treg expression in NPC

		FoxP3$^+$ Treg expression				
		Low		High		*P*-value
		n	%	n	%	
Snail expression	Low	17	89.5	2	10.5	0.003*
	High	17	44.7	21	55.3	
	Total	34	59.6	23	40.4	

*: significant ($P < 0.05$); ns: non-significant ($P \geq 0.05$)

Table 8: Gamma correlation analysis results between Snail and FoxP3$^+$ expression in NPC

		FoxP3$^+$ Treg expression		Correlation	*P*-value
		Low	High	coefficient (*r*)	
Snail expression	Low	17 (89.5)	2 (10.5)	0.826	0.000*
	High	17 (44.7)	21 (55.3)		
	Total	34 (59.6)	23 (40.4)		

*: significant ($P < 0.05$); ns: non-significant ($P \geq 0.05$)

Conclusion

In conclusion, infiltrating FoxP3$^+$ Treg cells contribute to partial EMT in NPC patients by forming a feedback loop with Snail$^+$ tumor cells. This effect appears to result from immunosuppressive function rather than TGF-β1 signaling. Based on the results, targeting the immunosuppressive activity of Foxp3$^+$ Treg cells may inhibit EMT, reduce therapy resistance, and improve prognosis in NPC patients.

Conflict of interest

The author`s 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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References

1. Guan S, Wei J, Huang L, Wu L. Chemotherapy and chemo-resistance in nasopharyngeal carcinoma. Eur J Med Chem. 2020;207:1-11.
2. Gong L, Kwong DLW, Dai W, Wu P, Wang Y, Lee AWM, Guan XY. The stromal and immune landscape of nasopharyngeal carcinoma and its implications for precision medicine targeting the tumor microenvironment. Front Oncol. 2021;11:1-15.
3. Su ZY, Siak PY, Leong CO, Cheah SC. Nasopharyngeal carcinoma and its microenvironment: past, current, and future perspectives. Front Oncol. 2022;12:1-20.
4. Berele BA, Cai Y, Yang G. Prognostic value of tumor infiltrating lymphocytes in nasopharyngeal carcinoma patients: Meta-Analysis. Technol Cancer Res Treat. 2021;20:1-13.
5. Yang L, Liu G, Li Y, Pan Y. The emergence of tumor-infiltrating lymphocytes in nasopharyngeal carcinoma: Predictive value and immunotherapy implications. Genes Dis. 2022;9:1208-1219.
6. Luo MS, Huang GJ, Liu BX. Immune infiltration in nasopharyngeal carcinoma based on gene expression. Medicine (Baltimore) 2019;98(39):1-7.
7. Zou Z, Ha Y, Liu S, Huang B. Identification of tumor-infiltrating immune cells and microenvironment-relevant genes in nasopharyngeal carcinoma based on gene expression profiling. Life Sci. 2020;263:1-12.
8. Liu S-X, Zhao G-X, Lin R-B, Zeng M-S, Zhong Q. Classifying the tumor microenvironment to stratify nasopharyngeal carcinoma patients. Annals of Nasopharynx Cancer. 2022;6(8):1-16.
9. Tang X, Sui X, Weng L, Liu Y. SNAIL1: Linking tumor metastasis to immune evasion. Front Immunol. 2021;12:1-11.
10. Jiang WG, Sanders AJ, Katoh M, Ungefroren H, Gieseler F, Prince M, Thompson SK, Zollo M, Spano D, Dhawan P, Sliva D, Subbarayan PR, Sarkar M, Honoki K, Fujii H, Georgakilas AG, Ameidei A, Niccolai E, Amin A, Ashraf SS, Ye L, Helferich WG, Yang X, Boosani CS, Guha G, Ciriolo MR, Aquilano K, Chen S, Azmi AS, Keith WN, Bilsland A, Bhakta D, Halicka D, Nowsheen S, Pantano F, Santini D. Tissue invasion and metastasis: Molecular, biological and clinical perspectives. Semin Cancer Biol. 2015;35:S224-S275.
11. Ribatti D, Tamma R, Annese T. Epithelial-mesenchymal transition in cancer: A Historical Overview. Transl Oncol. 2020;13:1-9.
12. Oh E, Hong J, Yun CO. Regulatory T cells induce metastasis by activating TGF-β and enhancing the epithelial–mesenchymal transition. Cells. 2019;8(11):1-15.
13. Shi C, Chen Y, Chen Y, Yang Y, Bing W, Qi J. CD4$^+$ CD25$^+$ regulatory T cells promote hepatocellular carcinoma invasion via TGF-β1-induced epithelial–mesenchymal transition. Onco Targets Ther. 2019;12:279-289.
14. Saleh R, Elkord E. FoxP3$^+$ T regulatory cells in cancer: Prognostic biomarkers and therapeutic targets. Cancer Lett. 2020;490:174-185.
15. Petersen RP, Campa MJ, Sperlazza J, Conlon D, Joshi MB, Harpole DH, Patz Jr EF. Tumor infiltrating FOXP3$^+$ regulatory T-cells are associated with recurrence in pathologic stage I NSCLC patients. Cancer. 2006;107:2866–2872.
16. Wang J, Luo Y, Bi P, Lu J, Wang F, Liu X, Zhang B, Li X. Mechanisms of Epstein-Barr virus nuclear antigen 1 favor Tregs accumulation in nasopharyngeal carcinoma. Cancer Med. 2020;9:5598-5608.
17. Zhang YL, Li J, Mo HY, Qiu F, Zheng LM, Qian CN, Zeng YX. Different subsets of tumor infiltrating lymphocytes correlate with NPC progression in different ways. Mol Cancer. 2010;9(4):1-11
18. Kara İ, Çağlı S, Vural A, Yüce İ, Gündoğ M, Deniz K, Kökoğlu K. The effect of FoxP3 on tumour stage, treatment response, recurrence and survivalability in nasopharynx cancer patients. Clinical Otolaryngology. 2019;44:349–355.
19. Luo WR, Li SY, Cai LM, Yao KT. High expression of nuclear Snail, but not cytoplasmic staining, predicts poor survival in nasopharyngeal carcinoma. Ann Surg Oncol. 2012;19:2971-2979.
20. Luo W, Fang W, Li S, Yao K. Aberrant expression of nuclear vimentin and related epithelial-mesenchymal transition markers in nasopharyngeal carcinoma. Int J Cancer. 2012;131:1863–1873.
21. Wang J, Gong R, Zhao C, Lei K, Sun X, Ren H. Human FOXP3 and tumour microenvironment. Immunology. 2023;168:248–255.
22. Taki M, Abiko K, Ukita M, Murakami R, Yamanoi K, Yamaguchi K, Hamanishi J, Baba T, Matsumura N, Mandai M. Tumor immune microenvironment during epithelial-mesenchymal transition. Clin Cancer Res. 2021;27:4669–4679.
23. Liao C, Wang Q, An J, Long Q, Wang H, Xiang M, Xiang M, Zhao Y, Liu Y, Liu J, Guan X. Partial EMT in squamous cell carcinoma: A snapshot. Int J Biol Sci. 2021;17:3036–3047.
24. Vincent T, Neve EPA, Johnson JR, Kukalev A, Rojo F, Albanell J, Pietras K, Virtanen I, Philipson L, Leopold PL, Crystal RG, Herreros AG, Moustakas A, Pettersson RF, Fuxe J. A SNAIL1-SMAD3/4 transcriptional repressor complex promotes TGF-β mediated epithelial-mesenchymal transition. Nat Cell Biol. 2009;11:943-950.
25. Wang Y, Liu T, Tang W, Deng B, Chen Y, Zhu J, Shen X. Hepatocellular carcinoma cells induce regulatory T cells and lead to poor prognosis via production of transforming growth factor-β1. Cell Physiol Biochem. 2016;38:306–318.
26. Fuxe J, Karlsson MCI. TGF-β-induced epithelial-mesenchymal transition: A link between cancer and inflammation. Semin Cancer Biol. 2012;22:455-461.
27. Kudo-Saito C, Shirako H, Takeuchi T, Kawakami Y. Cancer metastasis is accelerated through immunosuppression during Snail-induced EMT of cancer cells. Cancer Cell. 2009;15:195-206.