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Research Progress on TGF-β/SMAD3/PAI-1 Pathway in Thyroid Fibrosis and Tumorigenesis

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Abstract: ***The TGF-β/SMAD3/PAI-1 signaling pathway plays a crucial regulatory role in thyroid fibrosis and tumorigenesis, becoming a hot topic in both basic and clinical research in recent years. This pathway participates in the pathological remodeling of thyroid tissue and the establishment of the tumor microenvironment by regulating processes such as fibroblast activation, extracellular matrix deposition, cell proliferation, and migration. TGF-β plays a dual role in tumorigenesis, inhibiting cell proliferation while promoting tumor invasion and immune evasion. SMAD3, as a key transcription factor, plays a central role in regulating fibrotic gene expression and tumor cell behavior. PAI-1, by influencing the fibrinolytic system and angiogenesis, participates in tissue sclerosis and tumor progression. Clinical and experimental studies have demonstrated that factors associated with this pathway have potential biomarker value and therapeutic target significance. Future efforts should strengthen multi-omics integrated analysis and the development of targeted intervention strategies to promote precise diagnosis and treatment of thyroid diseases and their mechanism of action.***

Keywords: TGF-β, SMAD3, PAI-1, Thyroid fibrosis, Thyroid tumors, Signaling pathways, Targeted therapy, Biomarkers.

1. Introduction

As a common endocrine system disease, the incidence of thyroid disease has been increasing year by year in recent years, seriously affecting the quality of life and health level of patients. In addition to traditional functional abnormalities, fibrosis and tumorigenesis of thyroid tissue have gradually become the focus of clinical attention [1]. Thyroid fibrosis can not only lead to organ structural destruction and functional impairment, but may also be closely related to the formation of the tumor microenvironment, thereby promoting the occurrence and progression of thyroid cancer [2]. Among the many signaling pathways, the transforming growth factor-beta (TGF-β) signaling pathway has attracted much attention due to its key regulatory role in cell proliferation, differentiation, apoptosis and extracellular matrix remodeling [3]. Maternal effect defect protein 3 (SMAD family member 3, SMAD3) is the main downstream transcription factor of TGF-β signaling and plays a core role in mediating the expression of fibrosis and tumor-related genes [4]. Plasminogen Activator Inhibitor-1 (PAI-1), as one of the target genes of SMAD3, is not only involved in the regulation of the fibrinolytic system during fibrosis, but is also closely related to the migration, invasion and angiogenesis of tumor cells [5].

In recent years, the research on the TGF-β/SMAD3/PAI-1 signaling axis in thyroid diseases has gradually deepened, revealing its multiple mechanisms of action in the pathological process. This article aims to systematically review the research progress of this signaling pathway in thyroid fibrosis and tumorigenesis, explore its potential intervention targets and clinical application prospects, and provide theoretical basis and research direction for the prevention and treatment of related diseases.

2. Basic Structure and Function of the TGF-β/SMAD3/PAI-1 Pathway

The TGF-β family is a class of cytokines with a wide range of biological functions, which are widely involved in processes such as cell proliferation, differentiation, apoptosis, immune regulation and tissue remodeling. This family mainly includes three subtypes: TGF-β1, TGF-β2 and TGF-β3. Among them, TGF-β1 has been the most deeply studied in fibrosis and tumorigenesis [6]. TGF-β binds to its membrane surface receptors TGF-βRI and TGF-βRI to form a heterodimer complex, initiating downstream signal transduction [7]. After receptor activation, it can phosphorylate SMAD proteins, thereby mediating gene expression regulation. This receptor mechanism is highly conserved and is a key link in the function of the TGF-β signaling pathway. SMAD proteins are the core transduction factors of the TGF-β signaling pathway and are divided into three categories: R-SMAD, Co-SMAD, and I-SMAD [8]. After TGF-β signal activation, SMAD3 is phosphorylated and forms a complex with SMAD4, translocates into the cell nucleus, and regulates the transcriptional expression of target genes [9]. SMAD3 is particularly important in the process of fibrosis, promoting the expression of matrix-related genes such as collagen and fibronectin, and is also involved in the proliferation, migration, and immune escape mechanisms of tumor cells [9]. The activity of SMAD proteins is affected by multiple regulatory factors, including phosphorylation status, nuclear translocation efficiency, and interaction with other transcription factors. PAI-1 is one of the important target genes downstream of the TGF-β/SMAD pathway. Its main function is to inhibit tissue plasminogen activator and urokinase plasminogen activator, thereby inhibiting the activity of the fibrinolytic system and promoting extracellular matrix deposition. PAI-1 expression is significantly increased in fibrotic tissue and is one of the important markers of tissue fibrosis [10]. In addition, PAI-1 also plays multiple roles in the tumor microenvironment. It can promote tumor cell survival by inhibiting cell apoptosis and affect the adhesion and migration ability of tumor cells. Its expression is regulated by TGF-β/SMAD3 signaling and is also affected by various stimuli such as oxidative stress and inflammatory factors [11].

TGF-β, SMAD3 and PAI-1 form a highly coupled signaling regulatory network. After TGF-β activates SMAD3, it can directly induce PAI-1 gene expression, and the overexpression of PAI-1 can affect the persistence and intensity of TGF-β signaling through a feedback mechanism. For example, PAI-1 can indirectly affect the active release and receptor binding efficiency of TGF-β by regulating the degradation and remodeling of the extracellular matrix [12]. In addition, SMAD3 has cross-regulatory effects with other signaling pathways such as MAPK and PI3K/Akt, resulting in complex dynamic changes in the TGF-β/SMAD3/PAI-1 pathway under different pathological conditions. This interaction and feedback regulation mechanism not only plays a key role in thyroid fibrosis, but also has important significance in the occurrence and development of thyroid tumors [13].

3. The Role of the TGF-β/SMAD3/PAI-1 Pathway in Thyroid Fibrosis

Thyroid fibrosis is a common pathological manifestation of various thyroid diseases. It is commonly seen in chronic lymphocytic thyroiditis such as Hashimoto's thyroiditis, thyroid changes after radiation damage, and interstitial reactions of some thyroid tumors [14]. Its main characteristics are fibroblast proliferation, collagen deposition, extracellular matrix remodeling, and glandular structure destruction. Fibrosis not only affects the normal function of the thyroid gland, but also may interfere with drug absorption, aggravate the progression of the disease, and is even closely related to tumor development [15].

The TGF-β signaling pathway plays a core regulatory role in the occurrence and development of thyroid fibrosis and has become an important research target. Its expression is elevated in the local microenvironment of the thyroid gland and can activate fibroblasts through autocrine or paracrine pathways. Activated fibroblasts show enhanced expression of α-SMA, improved migration ability, and the ability to secrete large amounts of collagen, thereby accelerating the formation of fibrous tissue [16]. TGF-β can also inhibit the expression of matrix metalloproteinases, reduce ECM degradation, and further promote collagen deposition and tissue sclerosis. In the state of chronic inflammation or damage of the thyroid gland, the continuous activation of TGF-β is considered to be the key driving factor for the irreversible progression of fibrosis. As the main downstream transduction factor of the TGF-β signaling pathway, SMAD3 plays an important role in thyroid fibrosis [17]. After activation of the TGF-β receptor, SMAD3 is phosphorylated and forms a complex with SMAD4 to enter the cell nucleus, regulating the expression of multiple fibrosis-related genes, such as COL1A1, FN1, ACTA2, etc. SMAD3 not only promotes the phenotypic transformation of fibroblasts, but also enhances their responsiveness to inflammatory factors, forming an inflammation-fibrosis positive feedback loop [18]. In addition, SMAD3 synergizes with other transcription factors to enhance its binding ability in the promoter region of fibrosis genes, making the fibrosis process more persistent and extensive [19]. PAI-1 is one of the important target genes of the TGF-β/SMAD3 pathway, and its expression is significantly increased in thyroid fibrotic tissue. As an inhibitor of the fibrinolytic system, PAI-1 blocks fibrin degradation by inhibiting the activity of tPA and uPA, thereby promoting ECM accumulation. PAI-1 can also affect cell adhesion and migration, and regulate the distribution and activity of fibroblasts in tissues. Studies have shown that the sustained high expression of PAI-1 is positively correlated with the degree of thyroid tissue sclerosis, and its expression level can be used as a potential biomarker for the progression of fibrosis [20]. In addition, PAI-1 may also participate in the immune regulation process of thyroid fibrosis by regulating the infiltration of immune cells and the release of inflammatory factors [21].

Currently, a variety of animal models have been used to study the role of the TGF-β/SMAD3/PAI-1 pathway in thyroid fibrosis, including mouse thyroiditis models, radiation damage models, and transgenic models [22-23]. Animal experiments have found that targeted intervention of TGF-β signaling can significantly reduce the degree of thyroid tissue fibrosis, verifying the key role of this pathway in the pathological process [24]. Clinical studies have confirmed that the expression levels of TGF-β1, SMAD3, and PAI-1 in tissues of patients with thyroid fibrosis are significantly higher than those in normal controls, and are positively correlated with the degree of fibrosis. Some studies have also explored the therapeutic potential of anti-TGF-β antibodies, SMAD3 inhibitors, and PAI-1 interfering agents, providing new ideas for targeted intervention of thyroid fibrosis [25].

4. The Relationship Between the TGF-β/SMAD3/PAI-1 Pathway and Thyroid Tumors

Thyroid tumors are common endocrine system tumors in clinical practice, mainly including papillary thyroid carcinoma, follicular carcinoma, undifferentiated carcinoma, and medullary carcinoma [26]. Different types of thyroid tumors have significant differences at the molecular level. For example, papillary thyroid carcinoma is often accompanied by BRAF V600E mutation, while follicular carcinoma is more common with RAS mutation and PAX8/PPARγ fusion. These molecular characteristics not only affect the biological behavior of the tumor, but are also closely related to the activation state of the signaling pathway [27]. Recent studies have found that the TGF-β/SMAD3/PAI-1 pathway is abnormally activated in a variety of thyroid tumors, participating in tumor cell proliferation, migration, immune escape, and microenvironment remodeling [28].

TGF-β has a complex dual role in the occurrence and development of tumors. In the early stages of tumor development, TGF-β can inhibit tumor growth by inhibiting cell cycle progression and inducing apoptosis. However, in the progression stage of tumor development, TGF-β often transforms into a pro-oncogenic factor, promoting epithelial-mesenchymal transition of tumor cells, enhancing invasiveness, and inducing immunosuppression [29]. In thyroid tumors, the expression level of TGF-β is closely related to the degree of tumor differentiation, invasive ability, and metastasis risk. In the tumor microenvironment, it can activate fibroblasts, regulate immune cell function, and form an immunosuppressive environment that is conducive to tumor development [30]. SMAD3, as a key transcription factor in the TGF-β signaling pathway, plays multiple

regulatory roles in thyroid tumor cells. Studies have shown that SMAD3 can affect the proliferation and migration ability of tumor cells by regulating the expression of cell cycle proteins, apoptosis-related genes, and EMT markers. In some thyroid cancer cell lines, high expression of SMAD3 is closely associated with enhanced cell migration ability and inhibition of apoptosis [31]. In addition, SMAD3 can also cross-regulate with other signaling pathways such as Wnt, Notch, PI3K/Akt, and jointly participate in the occurrence and development of tumors. Its activity in the nucleus of tumor cells is positively correlated with the invasiveness of the tumor, suggesting that it may serve as a potential prognostic indicator and therapeutic target. The increased expression of PAI-1 in the tumor microenvironment has been widely reported, and its role in thyroid tumors has also gradually attracted attention [32]. As an inhibitor of the fibrinolytic system, PAI-1 not only participates in the stability and reconstruction of the extracellular matrix, but also regulates the adhesion, migration and invasion ability of tumor cells. Studies have found that PAI-1 can promote tumor angiogenesis (angiogenesis) by affecting integrin signaling and regulating vascular endothelial cell function, providing nutritional support for tumor growth and metastasis [33]. In thyroid cancer tissue, high expression of PAI-1 is closely related to tumor grade, lymph node metastasis and poor prognosis, suggesting that it plays an important role in tumor progression.

Dysregulation of the TGF-β/SMAD3/PAI-1 pathway has been shown to be closely related to the occurrence and development of thyroid cancer. Clinical studies have shown that the expression levels of factors related to this pathway are significantly correlated with the degree of tumor differentiation, depth of infiltration, risk of metastasis and patient survival [34]. For example, TGF-β1 and PAI-1 expression are significantly elevated in anaplastic thyroid cancer, suggesting that they are closely related to the malignancy of the tumor [35]. In addition, the nuclear localization of SMAD3 is positively correlated with the invasiveness of thyroid cancer cells, and some studies have incorporated it into prognostic scoring models. Targeted intervention strategies for this pathway, such as TGF-β receptor inhibitors, SMAD3 inhibitors, and PAI-1 antibodies, have shown certain anti-tumor potential in in vitro experiments and animal models, providing new ideas for the precision treatment of thyroid cancer [36].

5. Clinical and Experimental Research Progress on the TGF-β/SMAD3/PAI-1 Pathway in Thyroid Fibrosis and Tumorigenesis

With the development of molecular diagnostic technology, factors related to the TGF-β/SMAD3/PAI-1 pathway have gradually been included in the biomarker screening system for thyroid diseases. The expression levels of TGF-β1, SMAD3 and PAI-1 are significantly increased in thyroid fibrosis and tumor tissues [37], which have potential diagnostic and prognostic value. Studies have found that serum TGF-β1 concentration is positively correlated with the degree of thyroid fibrosis, the nuclear localization of SMAD3 can predict tumor aggressiveness [38], and the expression level of PAI-1 is closely related to the risk of lymph node metastasis. Detection of these factors by immunohistochemistry, real-time quantitative PCR, ELISA and other methods can help achieve early screening, disease assessment and efficacy monitoring [39]. In the future, multi-factor joint analysis combined with artificial intelligence algorithms is expected to improve the sensitivity and specificity of markers. Targeted treatment strategies for this pathway have been explored in various disease models. Drugs such as anti-TGF-β monoclonal antibodies, TGF-β receptor inhibitors, SMAD3 small molecule inhibitors, and PAI-1 interfering agents have shown good anti-fibrosis and anti-tumor effects in in vitro experiments and animal models [40]. Some studies have also attempted to combine these drugs with traditional treatments, such as radiotherapy, chemotherapy, or immunotherapy, to enhance efficacy and reduce side effects [41]. In addition, the application of nanocarriers and targeted delivery systems has also provided new ideas for the precise treatment of pathway inhibitors. Although there are currently no clinically approved drugs for this pathway, related research has entered the preclinical stage and has high translational potential.

With the maturity of gene editing technologies such as CRISPR/Cas9, precise regulation of key genes in the TGF-β/SMAD3/PAI-1 pathway has become possible. In animal models, knocking out the SMAD3 or PAI-1 gene can significantly reduce the degree of thyroid fibrosis and inhibit the migration and invasion of tumor cells [42]. In addition, RNA interference, antisense nucleic acids, and miRNA regulation have also been used to inhibit pathway activity, showing good intervention effects. In terms of drugs, some natural products such as curcumin and quercetin have been found to have the ability to inhibit TGF-β signaling, providing a new direction for the development of low-toxicity treatment options [43]. In the future, a comprehensive strategy combining gene editing and drug intervention is expected to achieve precise treatment of thyroid diseases. Multi-omics technologies such as transcriptomics, proteomics, metabolomics and single-cell omics provide powerful tools for in-depth analysis of the mechanism of action of the TGF-β/SMAD3/PAI-1 pathway in thyroid diseases [44]. By integrating different omics data, pathway regulatory networks can be constructed, key nodes and synergistic factors can be identified, and their dynamic changes under different pathological conditions can be revealed [45]. For example, single-cell RNA sequencing can reveal the differences in the response of different cell types to TGF-β signals in the thyroid microenvironment, and proteomics can explore pathway-related upstream and downstream regulatory factors [46]. These data not only enrich the depth of mechanism research, but also provide a theoretical basis for the formulation of personalized treatment plans.

6. Conclusion

The TGF-β/SMAD3/PAI-1 signaling pathway, as a key molecular mechanism regulating extracellular matrix remodeling, cell proliferation, and migration, plays a crucial role in thyroid fibrosis and tumorigenesis. This pathway not only participates in fibroblast activation and collagen deposition but also influences the development and progression of thyroid tumors by regulating the tumor microenvironment, promoting angiogenesis, and facilitating

immune evasion. In recent years, advances in molecular biology and omics technologies have led to a continuous in-depth understanding of both basic and clinical research on this pathway, providing new insights and strategies for the early diagnosis, prognosis, and targeted treatment of thyroid diseases. Despite significant progress, further elucidation of the mechanisms underlying the TGF-β/SMAD3/PAI-1 pathway in thyroid disease remains crucial, particularly in terms of the spatiotemporal specificity of pathway regulation, cross-integration with other signaling networks, and personalized treatment. Future research should strengthen multicenter, large-sample clinical validation and integrate emerging technologies such as gene editing and nano-delivery to promote the translational application of pathway intervention strategies. At the same time, leveraging multi-omics data and artificial intelligence analysis, it is hoped that precise modeling and dynamic regulation of this pathway will be achieved, providing a more scientific and systematic basis for the comprehensive prevention and treatment of thyroid fibrosis and tumors. In summary, the TGF-β/SMAD3/PAI-1 pathway is not only an important molecular basis for the development and progression of thyroid diseases, but also represents a key direction for future precision medicine and targeted therapies. In-depth research into the biological functions and clinical significance of this pathway will help improve the diagnosis and treatment of thyroid diseases, improve patient prognosis, and promote the continued development of personalized medicine.

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