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RESEARCH PROGRESS ON TGF-B GENE FAMILY

LiJie Du and Wanlong Zhu*
School of Life Sciences, Yunnan Normal University, Kunming-650500, China,
Corresponding author's E-mail: zwl_8307@163.com

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Abstract: Since the 1970s, research on the TGF-β gene family has commenced. The history of TGF-β research represents a scientific exploration that spans several decades, beginning with the initial discovery of growth factors and evolving into a significant target for drug development. The study of TGF-β has permeated various fields, including cell biology, developmental biology, pathology, and clinical treatment. Investigating the TGF-β family is not only essential for understanding its role in physiological and pathological processes but also holds great significance for the development of new therapeutic approaches. This article provides a comprehensive review of the research history, molecular composition of signaling pathways, and biological functions of the TGF-β gene family.

Keywords: Biological functions; Molecular composition; Signaling pathways.

Postal Address: **School of Life Sciences, Yunnan Normal University, No.768 Juxian Street, Chenggong District, Kunming 650500, China Phone: +86 13754982768.**

INTRODUCTION

Transforming growth factor beta (TGF-β) is a multifunctional cytokine that plays a critical role in regulating various cellular processes, including cell survival, metabolism, growth, proliferation, differentiation, adhesion, migration, and apoptosis (David and Massague, 2018). The appropriate balance of TGF-β signaling is essential for the normal function and homeostasis of a healthy body. In contrast, abnormal TGF-β signaling can lead to issues such as abnormal embryonic development, tumor formation, tissue fibrosis, cardiovascular diseases, and immune disorders (Akhurst, 2004). The dimer of TGF-β family ligands forms complexes with the corresponding type II and type I receptors on the cell membrane, leading to the phosphorylation of the type I receptor by the type II receptor and activating its kinase activity. Subsequently, the type I receptor recruits and activates downstream Smad proteins, which aggregate in the nucleus and function as transcription factors to regulate gene expression (Shi and Massagué, 2003). TGF-β signaling plays a crucial role in early embryonic development, tissue and organ formation, immune surveillance, tissue repair, and the maintenance of homeostasis in adults. The TGF-β signaling pathway is essential for various health-related processes, including regulating cell differentiation during embryonic development, promoting inflammatory responses, facilitating re-epithelialization, angiogenesis, and fibroblast activation in wound healing, as well as inhibiting cell proliferation and inducing apoptosis to maintain tissue homeostasis (Letterio and Roberts, 1998; Leask and Abraham, 2004; Wrana 2013). With the increasing understanding of the role of the TGF-β signaling pathway in health and disease, numerous therapies targeting TGF-β have been developed and shown to be safe and

effective in clinical trials (Attisano and Wrana, 2002; Castriconi *et al.,* 2013).

RESEARCH HISTORY OF TGF-B GENE FAMILY

The research on TGF-β began in 1978 when De Larco and Todaro discovered a "sarcoma growth factor" produced by transformed mouse fibroblasts, which could convert normal fibroblasts into anchorage-independent growing cells (De Larco and Todaro, 1978). Subsequently, in 1981, Roberts et al. successfully isolated and purified TGF-β from non-tumor mouse tissues, while Moses et al. independently completed the purification and characterization of the cytokine (Roberts *et al.,* 1983). In 1983, studies using SDS polyacrylamide gel electrophoresis revealed that the human TGF-β molecule is composed of two 12,500 Dalton subunits crosslinked by disulfide bonds (Assoian *et al.,* 1983). In 1998, the crystal structure of the Smad domain binding to DNA was elucidated, providing important insights into the nuclear transcriptional regulation of TGF-β signaling (Wu *et al.,* 2001; Shi and Massagué, 2003; Ken-ichi *et al.,* 2020). In 2000, Massagué et al. reviewed how cells interpret TGF-β signaling, leading to a deeper understanding of the mechanisms underlying TGF-β signal transmission (Massagué, 2000). In 2003, Shi and Massagué elaborated on the pathway of TGF-β signaling from the cell membrane to the nucleus (Schlingensiepen *et al.,* 2011). In 2005, Feng and Derynck discussed the specificity and multifunctionality of TGF-β signaling through Smad proteins (Feng and Derynck, 2005). In 2009, research demonstrated the role of TGF-β signaling in the self-renewal of cancer stem cells and in epithelial-mesenchymal transition (EMT) (Xu *et al.,* 2009; Watabe and Miyazono, 2009). In 2010, Naka et al.'s study revealed the role of the TGF-β-FOXO signaling pathway in maintaining leukemia-initiating cells in chronic myeloid leukemia (Naka *et al.,* 2010). In 2011, research highlighted the role of TGF-β signaling in the tumor microenvironment and how it transitions from an inhibitory factor to a promoting factor in the later stages of tumor development (Flavell *et al.,* 2010).

Subsequently, it was discovered that the TGF-β ligand family in humans consists of 33 members, of which 30 are positive-acting ligands. These include TGF-β, activins, bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs), and anti-Müllerian hormones. Additionally, there are three types of ligand antagonists: Inhibin-α (INHA), LEFTY1, and LEFTY2 as shown in figure 1 (Ikushima and Miyazono, 2010).

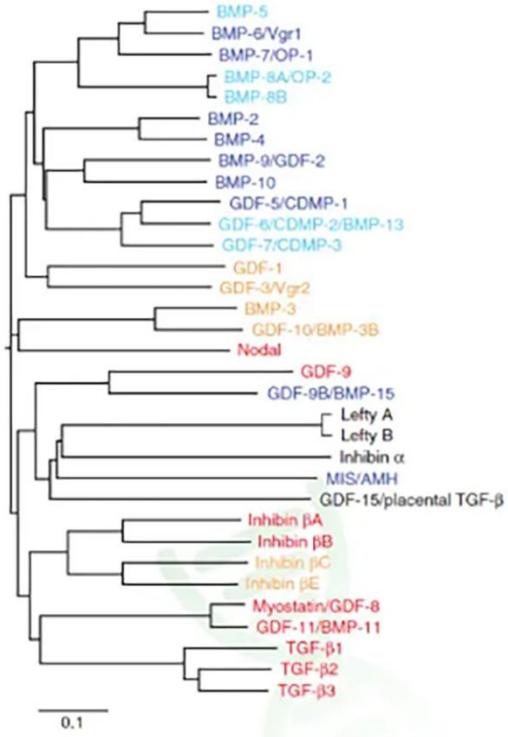

Figure 1. Cluster tree of TGF β protein family sequences

The TGF-β superfamily is highly conserved throughout evolution, with members found in both simple protozoa and humans. These molecules play a crucial role in the early embryonic development of both vertebrates and invertebrates and are essential for embryonic patterning and tissue organization (Wu and Hill, 2009). In aquatic animals, research on the TGF-β superfamily has revealed its role in regulating

physiological and biochemical processes, such as cell differentiation, embryonic development, bone formation, and immune responses. Studies have shown that the genetic sequences of TGF-β superfamily genes are widely present across various species, including mammals, bony fish, and shellfish. By comparing the amino acid sequences of TGF-β subtypes across different species for systematic evolutionary analysis, it was found that the TGF-β subtypes in mammals and fish naturally cluster into a large branch, indicating a close genetic relationship between TGF-β in these two groups (Holley and Nüsslein-Volhard, 2000). Notably, the TGF-β1 subtype is grouped into a distinct small branch across various species, while TGF-β2 and TGF-β3 cluster together in another small branch, suggesting that the genetic distance between TGF-β2 and TGF-β3 in chordates is relatively minimal. The TGF-β superfamily is highly conserved throughout evolution, with members present in both simple protozoa and humans, and it plays a crucial role in early embryonic development in both vertebrates and invertebrates. This information indicates that the TGF-β superfamily has diverse biological functions across organisms and is highly conserved evolutionarily, which is essential for maintaining the normal physiological functions of living organisms (Hinck, 2012).

MOLECULAR COMPOSITION OF TGF-B SIGNALING PATHWAY

The TGF-β Superfamily: This superfamily comprises multiple members, which can be categorized into TGF-β1, TGF-β2, and TGF-β3. The signal transduction mechanisms of the TGF-β superfamily typically involve the binding of ligands to cell surface receptors. Upon receptor activation, signals are transmitted to the nucleus through intracellular signaling molecules, such as Smad proteins, thereby regulating the expression of target genes (Tzavlaki and Moustakas, 2020). Additionally, there are non-Smad protein-dependent signaling pathways, including MAPK, Ras, and PI3K.The functional ligands of the TGF-β family are typically homodimers or heterodimers formed by the linkage of two polypeptide chains, each weighing 12-15 kDa, through disulfide bonds. The C-terminus of each monomer features a highly conserved cysteine domain, which contains seven cysteine residues that contribute to the formation of an intramolecular loop known as the cysteine junction structure. The TGF-β precursor comprises three components: a signal peptide, a long N-terminal precursor referred to as the Latent Associated Peptide (LAP), and a short C-terminal fragment corresponding to the mature cytokine. As an inactive precursor protein, TGF-β exhibits minimal activity and must bind to the TGF-β receptor (TβR) on the surface of target cells to exert its biological effects (Conidi *et al.,* 2019). There are at least five forms of TGF-β receptors, with the most extensively studied being TβR-I and TβR-II, which play crucial roles in signal transduction. Both receptors share similar structures and are classified as membrane proteins. TβR consists of four components: a signal peptide region, a cysteine-rich extracellular region, a single transmembrane region, and an intracellular region characterized by serine/threonine protein kinase activity. Notably, TβR-I features a unique core region known as GS, while the C-terminus of TβR-II contains a short tail that is rich in serine and threonine residues, facilitating the binding of TGF-β to the receptor (Derynck and Budi, 2019). During the TGF-β signal transduction process, TGF-β first binds to TβR-II on the cell membrane, leading to the phosphorylation of TβR-II. This interaction subsequently forms a complex consisting of TβR-II, TGF-β, and TβR-I. Following this, TβR-II phosphorylates and activates the CS region of TβR-I, which further transmits signals through the aggregation of intracellular Smad proteins, ultimately regulating transcription (Figure 2). Smad proteins are categorized into three groups: (1) pathway-restricted Smads (R-Smads), which include Smad-1, Smad-2, Smad-3, Smad-5, and

Smad-8. During signal transduction, these proteins can be phosphorylated by TβR-I, serving as a substrate for TβR-I kinase. (2) Universal Smads (Co-Smads), primarily Smad-4, form complexes with R-Smads and translocate to the nucleus to participate in signal transduction. (3) Inhibitory Smads (I-Smads), mainly Smad-6 and Smad-7, inhibit the phosphorylation of R-Smads and exert a negative regulatory effect on TGF-β signaling. Activated TβR-I phosphorylates Smad-2 and Smad-3, which then bind to Smad-4 to form a complex that enters the nucleus, initiating transcriptional regulation as shown in figure 3 (Hardee *et al.,* 2012).

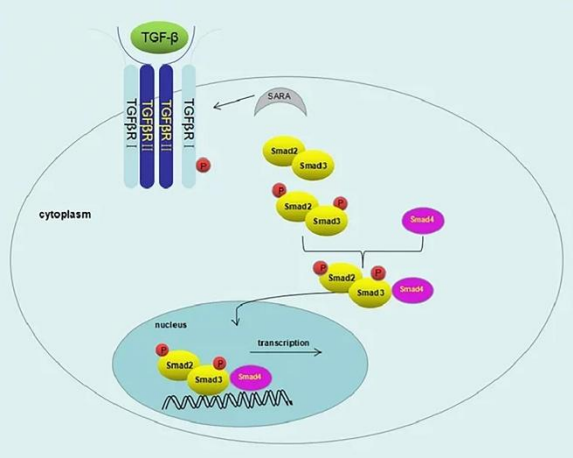

Figure 2.TGF - β Signaling Pathway

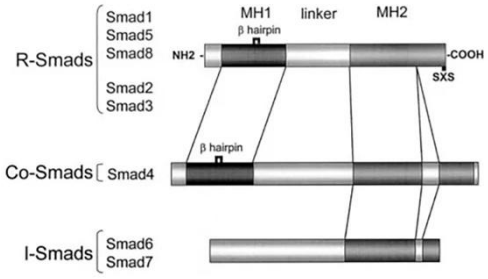

Figure 3. The Smads families and their physical structure map

The study of TGF-β superfamily members is essential for understanding their roles in various diseases, particularly in cancer treatment, tissue engineering, and regenerative medicine, where they hold significant potential for application. For example, Transforming Growth Factor Beta 1 (TGF-β1) plays a significant role in cell proliferation, differentiation, apoptosis, extracellular matrix synthesis, and immune regulation. TGF-β1 is crucial for embryonic development, tissue repair, and the onset and progression of various diseases. Bone Morphogenetic Proteins (BMPs) are involved in several cellular functions, including bone formation, cell differentiation, anterior-posterior axis differentiation, growth, and dynamic balance. Notably, BMP2 and BMP4 are essential for bone development and maintenance. Growth and Differentiation Factors (GDFs) also play vital roles in regulating cell differentiation, proliferation, and apoptosis. GDF-15, a polypeptide hormone of the TGF-β superfamily, is involved in regulating cellular responses to nutrient deprivation, oxidative stress, and endoplasmic reticulum stress, and it plays a regulatory role in aging, cancer, and metabolic processes. Activins are implicated in embryogenesis and osteogenesis while regulating various hormones, including pituitary hormones, sex hormones, hypothalamic hormones, and insulin, making them important for the survival of nerve cells (Sato *et al.,* 2000; Derynck and Zhang, 2003; Li and Flavell, 2008). The Nodal signaling pathway is critical for mesoderm differentiation during embryonic development, as it regulates the expression of target genes through transcriptional mechanisms. Myostatin (GDF8) plays an inhibitory role in muscle growth and development by regulating the proliferation and differentiation of satellite cells, thereby controlling muscle size. Anti-Müllerian hormone (AMH) is involved in gonadal development by inhibiting the formation of Müllerian ducts, which is essential for the maintenance of the male reproductive system. Transforming growth factor-beta (TGF-β) plays a crucial role in immune suppression within the tumor microenvironment by directly promoting the expansion of regulatory T cells (Treg cells) and inhibiting the production and function of effector T cells and antigen-presenting dendritic cells (DCs),

thus regulating adaptive immunity. The TGF-β signaling pathway also induces the expression of the micro-peptide NEMEP during the differentiation of mouse embryonic stem cells into the mesoderm, regulates glucose absorption, influences cell metabolism, and guides cell fate determination. Understanding the functions and regulatory mechanisms of the TGF-β superfamily is crucial for elucidating their roles in biological systems and for developing therapeutic strategies for related diseases (Massague *et al.,* 2000; Huang and Huang, 2005; Rubtsov and Rudensky, 2007; Zhang *et al.,* 2023).

SIGNALING PATHWAY

The TGF-β signaling pathway is a critical intracellular signaling pathway that plays a vital role in regulating various biological processes, including cell proliferation, differentiation, apoptosis, extracellular matrix synthesis, immune regulation, and tumorigenesis. The typical transmission process of the TGF-β signaling pathway is as follows: Ligand Binding. Ligands of the TGF-β family (such as TGF-β itself and bone morphogenetic proteins, BMPs) exist in dimeric form and bind to type II receptors on the cell surface. Formation of Receptor Complexes: After binding to ligands, type II receptors further associate with type I receptors, resulting in the formation of complexes composed of both type II and type I receptors. Receptor Phosphorylation: Upon ligand binding, type II receptors utilize their intrinsic kinase activity to phosphorylate specific regions of type I receptors. Smad Protein Activation: The phosphorylation of type I receptors activates their kinase activity, which subsequently phosphorylates and activates specific members of the Smad protein family, typically referred to as R-Smad proteins (Receptor-regulated Smads). Smad Complex Formation: Activated R-Smad proteins bind to the common mediator protein Smad4 (Co-Smad) to form Smad complexes. These complexes then translocate to the nucleus, where they bind to specific DNA sequences known as Smad binding elements (SBEs). Smad complexes can function as transcription factors, directly regulating the expression of target genes, or they can cooperate with other transcription factors to jointly modulate gene expression. Through Smad-dependent transcriptional regulation, the TGF-β signaling pathway influences various biological processes, including cell cycle inhibition, promotion of cell differentiation, synthesis of the extracellular matrix, and regulation of the immune response (Akhurst, 2002; Satya, 2005; Hu *et al.,* 2020).

The regulation of the TGF-β signaling pathway is highly complex. In addition to Smad-dependent pathways, there are also Smad-independent pathways, such as those regulated by the MAPK/ERK and PI3K/AKT signaling pathways. The TGF-β signaling pathway plays a crucial role in embryonic development, tissue repair, fibrosis, tumorigenesis, and immune regulation. Abnormal activation or inhibition of this pathway is associated with various diseases, including cancer, fibrosis, cardiovascular diseases, and immune disorders. Furthermore, the TGF-β signaling pathway interacts with other signaling pathways, such as WNT, Hedgehog, and Notch, collectively influencing cell behavior and tissue development. For example, cyclic adenosine monophosphate (cAMP) inhibits transforming growth factor-beta (TGF-β)/Smad signaling transduction and its associated gene transcription activity through protein kinase A (PKA)-dependent pathways and cAMP response element-binding protein (CREB)-mediated mechanisms. Additionally, the TGF-β/Smad signaling pathway interacts with downstream signaling pathways mediated by enzyme receptors. The mitogen-activated protein kinase (MAPK) pathway is a family of protein kinases that can be activated and translocated to the nucleus. MAPK can activate various protein kinases, nuclear proteins, and transcription factors, thereby mediating downstream signal transduction. The MAPK system has a dual regulatory effect on receptor-

regulated Smads (R-Smads): on one hand, it amplifies the biological effects of TGF-β signaling by translocating and phosphorylating ligand-dependent R-Smads; on the other hand, MAPK can phosphorylate R-Smads at the [S/T]P or PX[S/T] sites in the linker region, thereby inhibiting their translocation to the nucleus and preventing the accumulation of R-Smads within the nucleus. Furthermore, studies have shown that the phosphatidylinositol 3-kinase (PI3K) signaling pathway can be regulated by TGF-β, and blocking PI3K can reduce the activity of Smad3. Epidermal growth factor (EGF) and lipopolysaccharides are mediated through the Janus kinase/signal transducer and activator of transcription (Jak/Stat) pathway, while tumor necrosis factor (TNF) and interleukin-1 beta (IL-1β) are mediated through the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. These factors can induce the production of Smad7 and interact with the TGF-β signaling pathway. As a potential target for treating tumors, fibrosis, and other related diseases, regulating the TGF-β signaling pathway may have a positive impact on disease management. The complexity and diversity of the TGF-β signaling pathway make it a prominent topic in biomedical research, and a deeper understanding of its molecular mechanisms is essential for developing new therapeutic strategies (Derynck and Zhang, 2003; Wu and Hill, 2009; Liu *et al.,* 2018).

BIOLOGICAL FUNCTIONS

Because TGF-β receptors are widely present in various body tissues, TGF-β exerts a regulatory effect on the growth and differentiation of many cell types. Research has demonstrated that TGF-β stimulates the proliferation of mesenchymal cells, such as fibroblasts and osteoblasts. Increased collagen synthesis promotes angiogenesis, which is advantageous for tissue repair, embryonic development, wound healing, and tumor growth. Additionally, TGF-β exhibits growth-inhibitory effects on cells derived from epithelial or ectodermal origins (Jones *et al.,* 2009). The primary mechanism by which TGF-β inhibits cell proliferation is its ability to block the cell cycle. This is primarily achieved by regulating the expression levels and functional status of cyclins, cyclin-dependent kinases (CDKs), cyclin-dependent kinase inhibitors (CKIs), and the oncogene c-myc, leading to cell cycle arrest in the G1 phase. The smooth progression of chromatin replication through control points in the G1 phase is essential for the successful completion of cell division. The formation of cyclin D complexes with CDK2 or CDK4 is crucial for the transition from the G1 phase to the S phase. These complexes can phosphorylate a series of target proteins, including the retinoblastoma (Rb) protein, which dissociates from the transcription factor E2F, thereby releasing E2F and promoting cell cycle progression. Transforming growth factor-beta (TGF-β) can reduce the activity and expression levels of cyclins and cyclin-dependent kinases (CDKs) in G1 phase cells, and it can also induce cell cycle arrest by promoting the expression of cyclin-dependent kinase inhibitors (CKIs). The proto-oncogene c-Myc acts as a transcriptional activator that TGF-β utilizes to facilitate the progression of cells from the G1 phase to the S phase. In many cell types, TGF-β can also inhibit cell growth by downregulating the expression of c-Myc (Derynck *et al.,* 2001; Liu *et al.,* 2003) (Figure 4).

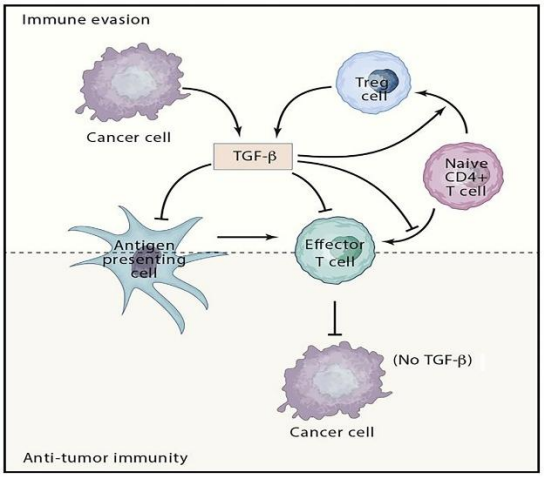

Figure 4. Key molecules of TGF - β inhibiting tumor adaptive immunity

In early embryonic development, the TGF-β signaling pathway plays a crucial role in determining cell fate and tissue formation. Additionally, TGF-β is involved in the tissue repair process, promoting the synthesis of the extracellular matrix and positively influencing wound healing. Furthermore, TGF-β serves as a key regulatory factor in the immune system, contributing to the establishment of immune tolerance and the inhibition of inflammatory responses (Zhang *et al.,* 2016). TGF-β exhibits an immunostimulatory effect during the early stages of inflammation, facilitating the recruitment of inflammatory cells and promoting the production of pro-inflammatory cytokines. However, during the resolution phase of inflammation, its immunosuppressive activity becomes more pronounced. This is characterized by the inhibition of T and B lymphocyte proliferation and activation, suppression of natural killer (NK) cell function, reduction in cytokine production, induction of cytokine antagonist expression, alterations in cell adhesion molecules, inhibition of lymphocyte-endothelial cell adhesion, decreased macrophage phagocytic ability, and suppression of immunoglobulin secretion (Castriconi *et al.,* 2013; Stewart *et al.,* 2018; Larson *et al.,* 2020).TGF-β plays a dual role in the occurrence and progression of tumors, as it can inhibit the proliferation of tumor cells while also promoting tumor invasion and metastasis. In normal cells, TGF-β inhibits cell proliferation and induces differentiation by blocking the transition from the G1 phase to the S phase. Therefore, in the early stages of tumor development, TGF-β maintains its growth-inhibitory function and acts as a tumor suppressor. However, in the later stages of tumor development, certain components of this signaling pathway may undergo abnormal changes or functional defects, including mutations or deletions of cyclin genes, TβR, and Smad genes, which can result in uncontrolled cell proliferation and resistance to TGF-β-mediated growth inhibition. When cells lose their responsiveness to the growth-inhibitory signal of TGF-β, tumor cells can feedback and increase the secretion of TGF-β. At this point, the elevated levels of TGF-β not only fail to exert their growth-inhibitory effects but also promote interactions between tumor cells and the extracellular matrix, stimulate endothelial cell proliferation, and facilitate the formation of blood vessels within tumors. Concurrently, TGF-β inhibits the activity of immune cells, allowing tumor cells to evade detection by the immune system and creating a favorable microenvironment for tumor growth and metastasis. Consequently, TGF-β plays a significant role in promoting tumor progression. Smads, which act as inhibitory factors in the TGF-β signaling pathway, help maintain a precise dynamic balance between phosphorylation activation and proteolytic degradation, ensuring normal intracellular TGF-β signal transduction. Abnormal expression of Smads can disrupt cellular responses to TGF-β, thereby contributing to the malignant transformation of cells (Quan *et al.,* 2002; Suriyamurthy *et al.,* 2019; Li *et al.,* 2020).

The functions of TGF-β are mediated through its binding to specific receptors, which activate downstream signaling molecules, such as Smad proteins, to regulate the expression of target genes. Abnormal activation or inhibition of the TGF-β signaling pathway is closely associated with the onset and progression of various diseases, including cancer, fibrosis, and autoimmune disorders. Consequently, the TGF-β signaling pathway represents a significant target for medical research and therapeutic interventions (Gordon and Blobe, 2008; Samuel, 2011). The signal transduction between cells forms the foundation of various biological activities within the body. Clarifying the mechanisms of signal transduction is of great theoretical significance for understanding the expression and regulation of cell proliferation, differentiation, metabolism, and apoptosis throughout the entire life cycle. This understanding is essential for comprehending the

essence of various biological processes. Additionally, it holds important practical value for exploring the molecular mechanisms of diseases, particularly tumors, and for discovering new diagnostic and therapeutic methods. Currently, molecular-level anti-tumor therapies targeting the cell cycle are a prominent area of research. The TGF-β/Smads signaling pathway plays a crucial biological role in body tissues and is closely associated with the onset and progression of tumors. Therefore, gaining a deeper understanding of the regulatory mechanisms of this pathway on the cell cycle, as well as the reasons for the loss of this regulation in tumors, not only aids in elucidating the mechanisms of tumorigenesis at the microscopic level but also provides valuable references and insights for clinical treatment (Zhang *et al.,* 2011; Garrison *et al.,* 2012; Hellmann *et al.,* 2017).

CONCLUSION

TGF-β is a multifunctional cytokine that plays a crucial role in various biological processes, including cell proliferation, differentiation, apoptosis, immune regulation, tissue repair, and tumorigenesis. Given TGF-β's involvement in tumor development, the development of therapeutic strategies targeting TGF-β or its signaling pathways is of significant value. Investigating the role of TGF-β in regulating the tumor microenvironment and immune cell function may contribute to the advancement of new cancer immunotherapies. Further investigation into the complexity of the TGF-β signaling pathway is essential, particularly regarding its interactions with other signaling pathways and its specific roles in various cell types. Employing gene editing technologies and animal models will enhance our understanding of the function of TGF-β in specific diseases, thereby elucidating its role in pathological processes. Studying the TGF-β signaling pathway not only aids in comprehending the pathogenesis of numerous diseases but also offers promising avenues for the development of novel therapeutic strategies. Future research should focus on exploring the biological functions of TGF-β in greater depth and on identifying safe and effective methods to regulate this signaling pathway for disease treatment.

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