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The multifaceted role of SMAD4 in immune cell function

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ABSTRACT

The Transforming Growth Factor-beta (TGF-β) signaling pathway, with SMAD4 as its central mediator, plays a pivotal role in regulating cellular functions, including growth, differentiation, apoptosis, and immune responses. While extensive research has elucidated SMAD4's role in tumorigenesis, its functions within immune cells remain underexplored. This review synthesizes current knowledge on SMAD4's diverse roles in various immune cells such as T cells, B cells, dendritic cells, and macrophages, highlighting its impact on immune homeostasis and pathogen response. Understanding SMAD4's role in immune cells is crucial, as its dysregulation can lead to autoimmune disorders, chronic inflammation, and immune deficiencies. The review emphasizes the significance of SMAD4 in immune regulation, proposing that deeper investigation could reveal novel therapeutic targets for immune-mediated conditions. Insights into SMAD4's involvement in processes like T cell differentiation, B cell class switch recombination, and macrophage polarization underscore its potential as a therapeutic target for a range of diseases, including autoimmune disorders and cancer.

1. Introduction

The signaling pathways that govern cellular functions are pivotal to understanding the complexities of both normal physiology and disease states [1,2]. The Transforming Growth Factor-beta (TGF-β) pathway stands out due to its extensive role in regulating cellular, with SMAD4 as its central mediator, is essential in regulating cellular functions, including growth, differentiation, apoptosis, and immune responses [3]. Despite extensive research on SMAD4's role in tumorigenesis, its functions in immune cells remain comparatively underexplored, leaving significant gaps in understanding its role in immune homeostasis and pathogenesis [4].

Understanding the diverse roles of SMAD4 in immune cells is crucial due to its significant impact on immune homeostasis and response to pathogens [5]. Dysregulation of SMAD4 can contribute to immune-related diseases, including autoimmune disorders, chronic inflammation, and immune deficiencies [6]. Consequently, exploring the functions of SMAD4 within the immune system can uncover novel therapeutic targets and strategies, potentially leading to innovative treatments for a variety of immune-mediated conditions [7].

This review seeks to synthesize current knowledge regarding SMAD4's roles in various immune cells, emphasizing how its signaling pathways influence immune regulation and disease outcomes. We aim to provide new insights by interpreting existing findings and proposing potential mechanisms and experimental approaches to bridge gaps in the field. By evaluating the dual role of SMAD4 in immune regulation, we also highlight its clinical implications, particularly as a therapeutic target in autoimmune diseases and cancer.

Research on SMAD4 in immune cells is not as prolific as in tumor cells, yet the findings so far suggest profound implications. For instance, SMAD4's role in the differentiation of T cells into regulatory T cells (Tregs) or Th17 cells, its involvement in B cell class switch recombination, and its influence on macrophage polarization highlight the diverse and critical functions it serves [8]. These roles are integral to maintaining immune balance and responding to immunological challenges, suggesting that deeper investigation into SMAD4 within immune cells could reveal novel therapeutic targets for a range of immune-related diseases [9].

Understanding the importance and potential of SMAD4 research in immune cells is crucial. Delving into its mechanisms can uncover new insights into immune regulation and the pathogenesis of autoimmune and inflammatory diseases [10]. Moreover, this research holds significant clinical implications, as modulating SMAD4 activity could lead to innovative treatments for conditions such as autoimmune disorders, chronic inflammation, and immune deficiencies [11].

In summary, this review seeks to highlight the underappreciated yet

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vital roles of SMAD4 in immune cells, advocating for increased research in this area. By doing so, we aim to underscore the potential clinical benefits that such research could yield, paving the way for novel therapeutic approaches in immunology [12].

2. Molecular characteristics of SMAD4

SMAD4, an essential component of the TGF-β signaling pathway, exhibits several key molecular characteristics integral to its function. Structurally, SMAD4 contains two conserved MAD homology domains: the MH1 domain at the N-terminus, responsible for DNA binding and nuclear localization, and the MH2 domain at the C-terminus, critical for protein-protein interactions and mediating associations with other SMAD proteins and cell membrane receptors [13]. The linker region between these domains is a phosphorylation target that regulates SMAD4's activity and stability (Fig. 1) [14].SMAD4 forms a complex with phosphorylated receptor-regulated SMADs (R-SMADs) to translocate to the nucleus, where it regulates gene transcription by binding to SMAD-binding elements (SBEs) and interacting with various transcriptional co-factors and co-repressors [15]. Its activity is modulated through phosphorylation, ubiquitination, and controlled subcellular localization [16].

Genetic mutations and epigenetic modifications affecting SMAD4 can lead to its dysregulation, contributing to various diseases such as cancer, fibrotic disorders, and immune dysfunctions [17]. Specific genetic mutations in SMAD4 have been identified in multiple cancers, including pancreatic and colorectal cancers [18]. For instance, mutations in the MH2 domain can impair SMAD4's ability to form functional complexes with R-SMADs, disrupting downstream signaling and leading to uncontrolled cell proliferation and survival [19]. In immune cells, such mutations can alter the balance of cell differentiation and function, potentially contributing to autoimmune diseases and impaired immune responses [20].

Epigenetic changes, such as DNA methylation and histone modifications, also play a significant role in regulating SMAD4 expression and function [21]. Hypermethylation of the SMAD4 promoter region can lead to reduced expression of SMAD4, as observed in some cancer types [22]. In the context of immune cells, reduced SMAD4 expression due to epigenetic silencing can affect T cell differentiation, skewing the balance between regulatory T cells (Tregs) and Th17 cells, and impacting immune tolerance and inflammation [6].

One notable example is the impact of SMAD4 mutations on T cell behavior. Mutations that inhibit SMAD4 function can lead to a decrease in Treg differentiation and an increase in Th17 cell differentiation [9]. This shift can result in heightened inflammatory responses and contribute to the development of autoimmune diseases such as multiple sclerosis and rheumatoid arthritis [23]. Similarly, in B cells, mutations that disrupt SMAD4 signaling can impair class switch recombination, affecting antibody production and immune responses [24].

Additionally, SMAD4's role in macrophage polarization is influenced by its molecular characteristics. Mutations or epigenetic changes that diminish SMAD4 function can hinder the transition of macrophages to the M2 phenotype, leading to a predominance of pro-inflammatory M1 macrophages [25]. This imbalance can exacerbate chronic inflammatory conditions and impede tissue repair processes [26].

Understanding these molecular characteristics and their impact on immune cell behavior provides insights into SMAD4's pivotal role in cellular processes and its potential as a therapeutic target [27]. By elucidating the specific genetic and epigenetic alterations that affect SMAD4 function, researchers can develop targeted interventions to

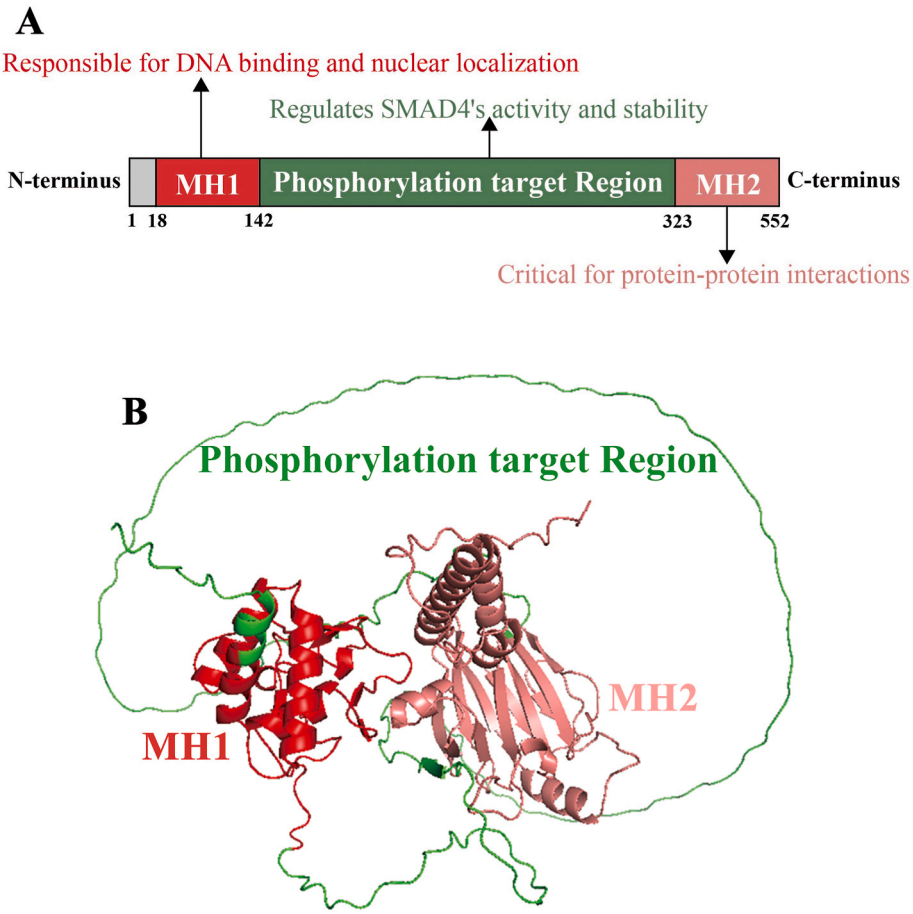

Fig. 1. Molecular characteristics of SMAD4: A The key structural domains of the SMAD4 protein; B The 3D structure of the SMAD4, date from AlphaFold.

modulate immune responses and treat various diseases [12].

3. SMAD4 in T cells

SMAD4, a critical mediator of the TGF-β signaling pathway, plays a significant role in the regulation of T cell responses, a process integral to both adaptive immunity and the pathogenesis of various diseases. TGF-β, a pleiotropic cytokine, modulates T cell differentiation, activation, and function, with SMAD4 being a key intracellular signal transducer [17].

In T cells, SMAD4 regulates differentiation through complex molecular mechanisms. Upon TGF-β binding to its receptors on the cell surface, SMAD2 and SMAD3 are phosphorylated, and they then form a complex with SMAD4. This SMAD complex translocates to the nucleus,

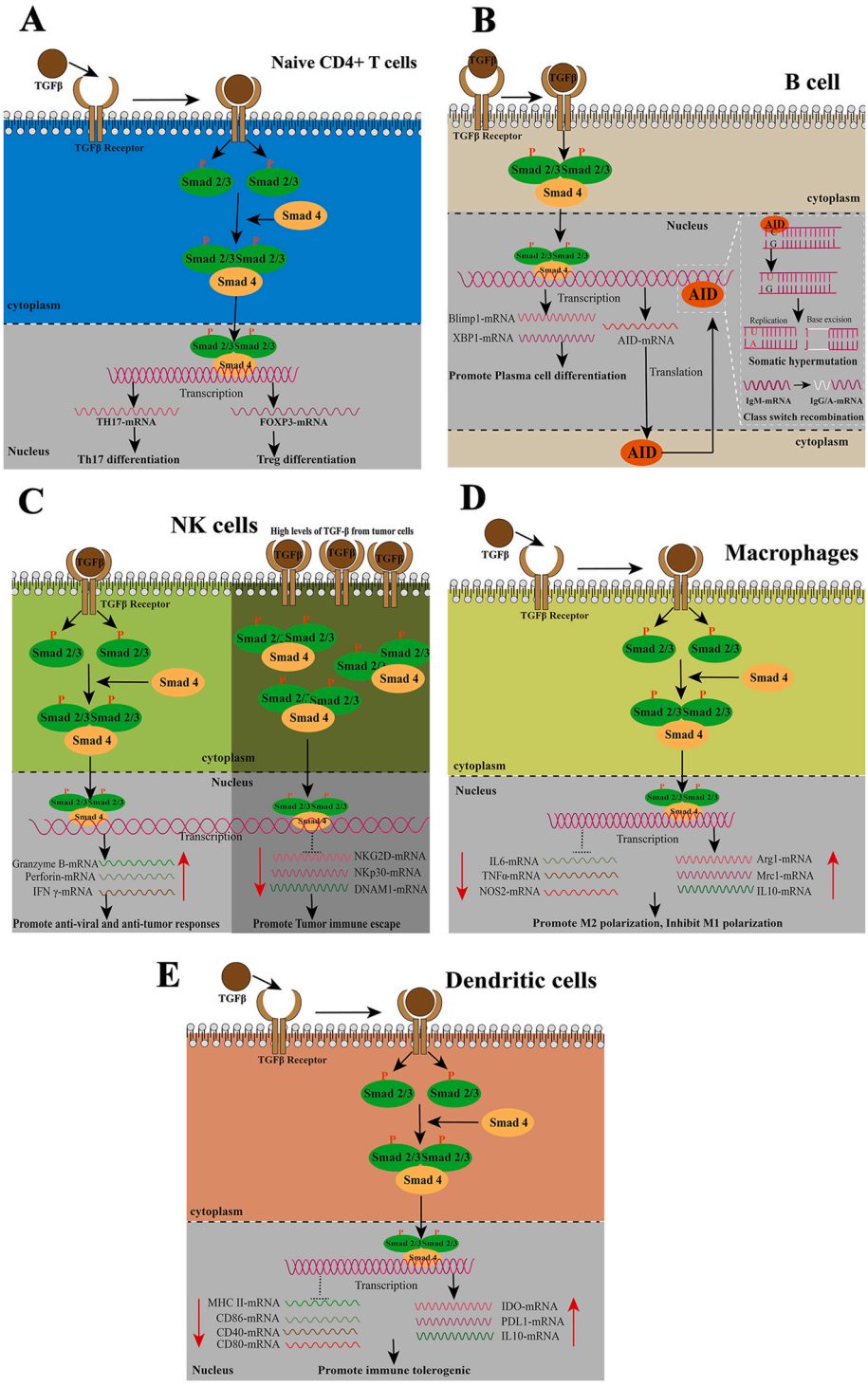

Fig. 2. The role of TGF-β/SMAD4 signaling pathway in immune cell; A The TGF-β/SMAD4 signaling pathway promote the differentiation of naive $CD4^+$ T cells into Th17 cells and regulatory T cells (Tregs). B The TGF-β/SMAD4 signaling pathway regulate class switch recombination (CSR), somatic hypermutation (SHM), and plasma cell differentiation in B cells. C Moderate TGF-β/SMAD4 signaling promote NK cell maturation and the expression of cytotoxic molecules such as perforin and granzyme. High levels of TGF-β/SMAD4 signaling inhibit NK cell cytotoxicity. D The TGF-β/SMAD4 signaling promote M2 polarization and inhibit M1 polarization in Macrophage. E The TGF-β/SMAD4 signaling inhibit DC maturation and promote the development of tolerogenic DCs.

where it binds to SMAD-binding elements (SBEs) on DNA and interacts with various transcription factors to regulate gene expression [14].

One critical aspect of SMAD4's function in T cells is its role in the differentiation of naive $CD4^+$ T cells into various T helper (Th) cell subsets, notably Th17 cells and regulatory T cells (Tregs) (Fig. 2A) [9]. For Th17 differentiation, SMAD4 collaborates with the transcription factors RORγt and STAT3 to promote the expression of IL-17 and other Th17-associated cytokines [28]. This process is tightly regulated, as excessive Th17 responses can lead to autoimmunity [29].

In Treg differentiation, TGF-β/SMAD4 signaling induces the expression of Foxp3, a master regulator of Tregs. $Foxp3^+$ Tregs are essential for maintaining immune tolerance and preventing autoimmunity. SMAD4 enhances Foxp3 transcription and stabilizes its expression, ensuring the suppressive function of Tregs.

SMAD4 also plays a role in T cell anergy, a state of unresponsiveness to antigenic stimulation. TGF-β-induced SMAD4 activation inhibits the production of IL-2 and other cytokines essential for T cell proliferation, thereby promoting anergy. This mechanism is crucial for maintaining tolerance to self-antigens and preventing overreactive immune responses [30].

In the context of T cell receptor (TCR) signaling, SMAD4 modulates the activation of downstream transcription factors such as NF-AT and AP-1. By integrating signals from TGF-β and TCR pathways, SMAD4 fine-tunes T cell activation, ensuring appropriate immune responses [31].

The regulation of T cell differentiation and function by SMAD4 has profound implications for various diseases, particularly autoimmune diseases and cancer. In autoimmune diseases such as multiple sclerosis (MS), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE), dysregulation of SMAD4 can disrupt the balance between Th17 cells and Tregs. Enhanced Th17 differentiation and impaired Treg function contribute to chronic inflammation and autoimmunity [32]. For instance, in MS, increased Th17 cell activity driven by defective SMAD4 signaling exacerbates neuroinflammation and demyelination [33].

In cancer, SMAD4-mediated regulation of T cells plays a dual role. On one hand, TGF-β/SMAD4 signaling in the tumor microenvironment can suppress anti-tumor immune responses by promoting Treg differentiation and inhibiting cytotoxic T lymphocytes (CTLs) [9]. This immunosuppressive environment enables tumor evasion [5]. On the other hand, targeting SMAD4 pathways can enhance anti-tumor immunity. For example, inhibiting TGF-β signaling to reduce Treg activity and boost CTL responses is a promising strategy in cancer immunotherapy [34].

Reflecting on the current understanding of SMAD4's role in T cells, it is evident that this molecule acts as a crucial node in the complex network of immune regulation. The modulation of T cell differentiation by SMAD4, particularly in the context of Th17 and Treg cells, underscores its potential as a therapeutic target for autoimmune diseases. The ability of SMAD4 to influence T cell anergy and cytokine production also highlights its importance in maintaining immune tolerance and preventing excessive immune responses.

Furthermore, the interplay between SMAD4 and TCR signaling suggests a broader role in the fine-tuning of T cell activation. As research progresses, it will be essential to dissect the intricate mechanisms by which SMAD4 integrates various signals to regulate T cell responses. This knowledge could pave the way for novel immunotherapies, particularly in the treatment of autoimmune conditions and possibly in enhancing anti-tumor immune responses [20].

Additionally, exploring the epigenetic regulation of SMAD4 and its impact on T cell function could reveal new layers of immune control. The translation of these findings from bench to bedside will require careful consideration of the human immune context, emphasizing the need for clinical studies that can validate the preclinical insights gained from in vitro and animal models. Ultimately, a deeper comprehension of SMAD4's role in T cells will not only enhance our fundamental understanding of immune biology but also facilitate the development of targeted therapies that could transform the treatment landscape for a multitude of diseases [12].

4. SMAD4 in B cells

SMAD4 is an integral component of the TGF-β signaling pathway and plays a critical role in regulating B cell development, differentiation, and function. Understanding the molecular mechanisms by which SMAD4 influences B cells is crucial for developing therapeutic strategies aimed at treating autoimmune diseases and other B cell-related disorders [17].

In B cells, SMAD4 regulates various processes, including class switch recombination (CSR), somatic hypermutation (SHM), and plasma cell differentiation (Fig. 2B). These processes are essential for producing high-affinity antibodies and ensuring effective humoral immunity.

CSR is a mechanism that changes a B cell's production of antibody from one type to another, such as from IgM to IgG, IgA, or IgE. TGF-β signaling via SMAD4 promotes CSR by inducing the expression of activation-induced cytidine deaminase (AID), a key enzyme required for this process. SMAD4 interacts with other transcription factors, such as NF-κB and STAT6, to enhance AID expression and facilitate CSR. This process is critical for generating diverse and specific antibody responses necessary for effective immune defense [35].

SHM introduces point mutations into the variable regions of immunoglobulin genes, leading to the production of antibodies with increased affinity for their antigens. SMAD4, through TGF-β signaling, influences SHM by regulating the expression of enzymes and factors involved in DNA repair and mutagenesis. This regulation ensures the production of high-affinity antibodies, crucial for long-term immunity [36].

SMAD4 also plays a role in the differentiation of B cells into plasma cells, which are responsible for antibody production. TGF-β/SMAD4 signaling can modulate the expression of transcription factors such as Blimp-1 and XBP1, which are essential for plasma cell differentiation and function. By regulating these pathways, SMAD4 ensures the production of efficient antibody-secreting cells [37].

Dysregulation of SMAD4 in B cells can contribute to the pathogenesis of autoimmune diseases. For instance, impaired SMAD4 signaling can lead to defective CSR and SHM, resulting in the production of autoantibodies. These autoantibodies can target self-antigens, leading to autoimmune conditions such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Additionally, abnormal SMAD4 function can affect B cell survival and differentiation, further exacerbating autoimmune responses [38].

SMAD4 influences B cell survival through its effects on apoptotic pathways. TGF-β/SMAD4 signaling can induce the expression of anti-apoptotic proteins such as Bcl-2 and inhibit pro-apoptotic factors like Bax. By regulating these pathways, SMAD4 ensures the survival of mature B cells and plasma cells, which is crucial for sustained antibody production. Dysregulation of these survival pathways can lead to increased apoptosis of B cells, impacting humoral immunity and contributing to immune deficiencies.

Targeting SMAD4 in B cells presents a potential therapeutic approach for treating autoimmune diseases. Modulating SMAD4 activity could help restore the balance between B cell activation and tolerance. For instance, enhancing SMAD4 function in B cells might promote CSR and SHM, leading to the production of high-affinity antibodies and reducing autoantibody production. Conversely, inhibiting SMAD4 in specific contexts could prevent excessive B cell activation and autoimmunity [9].

One potential strategy is the use of small molecules or peptides that modulate TGF-β/SMAD4 signaling. These agents could be designed to enhance or inhibit SMAD4 activity selectively in B cells, depending on the desired therapeutic outcome. Additionally, gene-editing technologies such as CRISPR/Cas9 could be employed to correct mutations in SMAD4 that contribute to autoimmune diseases [39].

Furthermore, targeting the epigenetic regulation of SMAD4 in B cells

could provide new avenues for therapy. Epigenetic modifiers, such as DNA methyltransferase inhibitors or histone deacetylase inhibitors, could be used to modulate SMAD4 expression and function, thereby influencing B cell behavior and improving disease outcomes [40].

The role of SMAD4 in B cells is multifaceted, encompassing critical processes such as CSR, SHM, and plasma cell differentiation. By regulating these pathways, SMAD4 ensures effective antibody production and humoral immunity. Dysregulation of SMAD4 can contribute to autoimmune diseases and immune deficiencies, highlighting the importance of understanding its molecular mechanisms. Targeting SMAD4 in B cells offers promising therapeutic potential for treating autoimmune conditions, with strategies ranging from small molecule modulators to gene-editing approaches. Continued research into the molecular characteristics and regulation of SMAD4 in B cells will pave the way for novel treatments that enhance immune function and ameliorate disease.

5. SMAD4 in NK cells

Natural Killer (NK) cells are a crucial component of the innate immune system, responsible for the rapid response to virally infected cells and tumor cells without the need for prior sensitization [41]. The TGF-β/SMAD4 signaling pathway significantly influences NK cell development, maturation, and function (Fig. 2C). Understanding the specific contexts in which this signaling pathway enhances or suppresses NK cell functions is vital for leveraging NK cells in cancer immunotherapy and other therapeutic applications [42].

In certain contexts, TGF-β/SMAD4 signaling can enhance NK cell functions. For instance, moderate TGF-β signaling can promote NK cell maturation and the expression of cytotoxic molecules such as perforin and granzyme B, which are essential for the destruction of target cells [43]. Additionally, SMAD4-mediated signaling can support the production of IFN-γ, a critical cytokine for antiviral and anti-tumor responses. This enhancement is particularly evident during the early stages of NK cell development, where TGF-β/SMAD4 signaling aids in the acquisition of functional competence.

Conversely, in other contexts, TGF-β/SMAD4 signaling can suppress NK cell activity. High levels of TGF-β can inhibit NK cell cytotoxicity by downregulating the expression of activating receptors such as NKG2D, NKp30, and DNAM-1 [44]. This suppression is often observed in the tumor microenvironment, where TGF-β is abundant and acts as an immune evasion mechanism employed by cancer cells. By inhibiting NK cell activity, TGF-β/SMAD4 signaling allows tumor cells to escape immune surveillance and promotes tumor progression [45].

The dual role of TGF-β/SMAD4 signaling in NK cells has significant implications for cancer immunotherapy. Strategies to modulate this pathway can enhance the effectiveness of NK cell-based therapies against cancer.

To enhance NK cell activity in cancer patients, therapeutic approaches aim to inhibit TGF-β signaling. This can be achieved through the use of TGF-β receptor inhibitors, neutralizing antibodies against TGF-β, or small molecule inhibitors that block the SMAD4 signaling cascade [46]. By reducing TGF-β-mediated suppression, these therapies can restore NK cell cytotoxicity and improve the elimination of tumor cells. Additionally, combining TGF-β inhibition with other immunotherapeutic strategies, such as checkpoint inhibitors, can further enhance anti-tumor responses [47].

In some cases, selectively activating certain aspects of the TGF-β/SMAD4 pathway may be beneficial. For instance, promoting SMAD4-mediated enhancement of NK cell maturation and function during the early stages of NK cell development can ensure a robust NK cell population ready to combat tumors. This approach requires a nuanced understanding of the signaling dynamics and careful regulation to avoid unwanted suppression of NK cell activity [48].

Modulating the TGF-β/SMAD4 pathway within the tumor microenvironment is another therapeutic avenue. By targeting the sources of TGF-β production or altering the tumor stroma, it is possible to reduce the immunosuppressive environment and enable NK cells to function more effectively [49]. This strategy can involve the use of stromal-targeted therapies, inhibitors of TGF-β-producing cells, or reprogramming of the tumor microenvironment to support immune activation [50].

SMAD4 plays a complex role in regulating NK cell functions through the TGF-β signaling pathway. Depending on the context, TGF-β/SMAD4 signaling can either enhance or suppress NK cell activity, with significant implications for immune responses and cancer therapy [51]. Understanding these dual roles is crucial for developing effective immunotherapeutic strategies. By modulating the TGF-β/SMAD4 pathway, it is possible to enhance NK cell-mediated anti-tumor responses, offering promising avenues for cancer treatment. Future research should focus on elucidating the precise mechanisms by which SMAD4 influences NK cell functions and exploring innovative approaches to harness this knowledge for therapeutic benefit.

6. SMAD4 in macrophages

Macrophages are versatile immune cells that play critical roles in host defense, tissue repair, and the regulation of inflammation [52]. They exhibit remarkable plasticity, adapting to various microenvironmental signals by polarizing into distinct functional phenotypes [53]. The TGF-β/SMAD4 signaling pathway is a key regulator of macrophage polarization, influencing their behavior and functions in health and disease (Fig. 2D) [54]. Understanding the molecular mechanisms by which SMAD4 regulates macrophage polarization and exploring potential therapeutic applications can provide valuable insights into treating diseases characterized by macrophage dysregulation, such as chronic inflammatory diseases and cancer [55].

Macrophages can polarize into at least two main phenotypes: classically activated (M1) macrophages and alternatively activated (M2) macrophages [56]. M1 macrophages, induced by pro-inflammatory signals such as IFN-γ and LPS, produce high levels of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and reactive nitrogen and oxygen species, contributing to pathogen clearance and anti-tumor responses [57]. Conversely, M2 macrophages, stimulated by anti-inflammatory signals like IL-4, IL-10, and TGF-β, are involved in tissue repair, wound healing, and immunoregulation through the production of anti-inflammatory cytokines (e.g., IL-10, TGF-β) [58].

SMAD4 plays a crucial role in the TGF-β signaling pathway, which influences macrophage polarization. Upon TGF-β binding to its receptors, SMAD2 and SMAD3 are phosphorylated and form a complex with SMAD4. This complex translocates to the nucleus, where it regulates gene transcription by binding to SMAD-binding elements (SBEs) on DNA [59].

TGF-β/SMAD4 signaling is a potent inducer of M2 macrophage polarization [60]. SMAD4 promotes the expression of genes associated with the M2 phenotype, including Arg1, Mrc1 (mannose receptor), and IL-10 [61]. This signaling pathway also enhances the production of extracellular matrix components and growth factors that support tissue repair and remodeling. By promoting M2 polarization, SMAD4 helps to resolve inflammation and restore tissue homeostasis [62].

SMAD4 can suppress M1 macrophage activation by inhibiting the expression of pro-inflammatory cytokines and enzymes involved in the production of reactive oxygen species (ROS) and nitric oxide (NO) [63]. This regulatory effect is crucial for preventing excessive inflammation and tissue damage [64]. Additionally, SMAD4 interacts with other transcription factors, such as NF-κB, to modulate inflammatory responses and maintain a balanced macrophage phenotype [65].

In diseases characterized by chronic inflammation, such as rheumatoid arthritis, inflammatory bowel disease (IBD), and atherosclerosis, macrophage dysregulation plays a significant role in disease pathogenesis [66]. Targeting SMAD4 to modulate macrophage polarization can offer therapeutic benefits [67].

Promoting SMAD4-mediated M2 polarization can help resolve chronic inflammation and promote tissue repair. Therapeutic strategies could include the use of TGF-β agonists or SMAD4 activators to drive the polarization of macrophages towards an anti-inflammatory M2 phenotype. This approach could reduce the inflammatory milieu and support tissue regeneration in chronic inflammatory diseases.

Inhibiting SMAD4 suppression of M1 polarization might be beneficial in certain contexts where enhanced pro-inflammatory activity is needed, such as in combating infections or certain cancers. However, careful regulation is required to prevent excessive tissue damage and chronic inflammation [68].

The role of macrophages in cancer is complex, with tumor-associated macrophages (TAMs) often exhibiting an M2-like phenotype that promotes tumor growth, angiogenesis, and immune evasion [69]. Modulating SMAD4 activity in macrophages presents a promising strategy for cancer therapy [70].

Reprogramming TAMs from an M2-like, pro-tumorigenic state to an M1-like, anti-tumorigenic phenotype can enhance anti-tumor immunity [71]. Inhibiting TGF-β/SMAD4 signaling in TAMs may reduce their immunosuppressive functions and promote a more inflammatory, tumoricidal phenotype [72]. This reprogramming could be achieved through the use of TGF-β inhibitors or SMAD4 pathway antagonists [73].

Combining SMAD4 modulation with other immunotherapeutic approaches, such as checkpoint inhibitors, could potentiate anti-tumor responses [74]. By reducing the immunosuppressive environment created by M2-like TAMs, these combination therapies could enhance the efficacy of existing cancer treatments [75].

SMAD4 is a pivotal regulator of macrophage polarization, influencing the balance between pro-inflammatory M1 and anti-inflammatory M2 phenotypes [76]. Through TGF-β signaling, SMAD4 promotes M2 polarization and suppresses M1 activation, thereby playing a critical role in maintaining immune homeostasis and regulating inflammation [77]. Dysregulation of SMAD4 in macrophages contributes to the pathogenesis of chronic inflammatory diseases and cancer [78]. Therapeutic strategies targeting SMAD4 to modulate macrophage polarization hold promise for treating these conditions, offering new avenues for restoring tissue homeostasis and enhancing anti-tumor immunity [79]. Further research into the molecular mechanisms and therapeutic applications of SMAD4 in macrophages will continue to advance our understanding and treatment of macrophage-related diseases.

7. SMAD4 in dendritic cells

Dendritic cells (DCs) are essential antigen-presenting cells (APCs) that bridge the innate and adaptive immune responses [80]. They capture, process, and present antigens to T cells, initiating and modulating immune responses [81]. SMAD4, a key mediator of the TGF-β signaling pathway, plays a significant role in regulating DC function [82]. Understanding the molecular pathways through which SMAD4 influences DCs and exploring potential therapeutic interventions can provide insights into treating diseases where DC function is compromised [83].

DC maturation is a critical process where immature DCs, which are highly phagocytic but poorly immunogenic, develop into mature DCs capable of effectively presenting antigens and activating T cells [84]. TGF-β/SMAD4 signaling modulates DC maturation through several mechanisms (Fig. 2E) [85].

TGF-β/SMAD4 signaling can inhibit DC maturation by downregulating the expression of co-stimulatory molecules (such as CD80, CD86, and CD40) and MHC class II molecules [86]. This inhibition prevents the full activation of DCs, reducing their ability to prime T cells and initiate robust immune responses [87]. This regulatory effect is crucial for maintaining immune tolerance and preventing autoimmunity [88].

TGF-β/SMAD4 signaling promotes the development of tolerogenic DCs, which are specialized in inducing immune tolerance [89]. Tolerogenic DCs produce anti-inflammatory cytokines like IL-10 and TGF-β and can induce the differentiation of regulatory T cells (Tregs) [90]. SMAD4 enhances the expression of immunosuppressive molecules such as IDO (indoleamine 2,3-dioxygenase) and PD-L1, contributing to the maintenance of peripheral tolerance and prevention of autoimmunity [5].

SMAD4 influences the antigen-presenting capabilities of DCs [91]. It regulates the expression of enzymes and proteins involved in antigen processing and presentation, ensuring efficient loading of antigens onto MHC molecules [92].

TGF-β/SMAD4 signaling modulates the expression of proteases and chaperones involved in antigen processing within the endosomal-lysosomal pathway [93]. By regulating these molecules, SMAD4 ensures the proper degradation of antigens and the generation of peptide-MHC complexes necessary for T cell activation [94].

SMAD4 affects the expression of MHC class I and II molecules on the surface of DCs [95]. TGF-β signaling can downregulate MHC class II expression, limiting the ability of DCs to present antigens to $CD4^+$ T cells. Conversely, SMAD4 can also enhance cross-presentation, a process by which DCs present extracellular antigens on MHC class I molecules to $CD8^+$ T cells, critical for antiviral and anti-tumor immunity.

In autoimmune diseases, such as multiple sclerosis (MS), type 1 diabetes (T1D), and systemic lupus erythematosus (SLE), dysregulation of DC function contributes to aberrant immune responses against self-antigens [96]. Modulating SMAD4 activity in DCs offers potential therapeutic benefits [97]. Enhancing SMAD4-mediated TGF-β signaling to promote the development of tolerogenic DCs can help re-establish immune tolerance. This approach could involve the use of TGF-β analogs or SMAD4 activators to induce DCs that produce IL-10 and TGF-β, fostering the generation of Tregs and reducing autoimmunity [98]. Inhibiting excessive TGF-β/SMAD4 signaling in pro-inflammatory DCs can prevent the overactivation of T cells and the propagation of inflammatory responses [99]. This strategy might involve the use of TGF-β inhibitors or SMAD4 pathway antagonists to reduce the expression of co-stimulatory molecules and pro-inflammatory cytokines, thereby dampening autoimmune responses [100].

In cancer, the role of DCs is often compromised due to the immunosuppressive tumor microenvironment, where high levels of TGF-β inhibit DC maturation and function [101]. Targeting SMAD4 in DCs presents opportunities for enhancing anti-tumor immunity. Inhibiting TGF-β/SMAD4 signaling in DCs can promote their maturation and enhance their ability to present tumor antigens. This approach could involve the use of TGF-β receptor inhibitors or neutralizing antibodies to block TGF-β signaling, thereby increasing the expression of co-stimulatory molecules and enhancing T cell activation [102]. Enhancing SMAD4 function selectively in pathways that improve antigen processing and presentation can improve the efficacy of DC-based cancer vaccines. This strategy could involve the use of adjuvants or molecular agents that enhance cross-presentation, thereby increasing the activation of tumor-specific $CD8^+$ T cells.

SMAD4 plays a pivotal role in regulating dendritic cell function through the TGF-β signaling pathway [95]. By modulating DC maturation, antigen presentation, and the balance between tolerogenic and immunogenic phenotypes, SMAD4 influences immune responses in health and disease [92]. Therapeutic strategies targeting SMAD4 in DCs hold promise for treating autoimmune diseases by promoting immune tolerance and for enhancing anti-tumor immunity in cancer [90]. Continued research into the molecular mechanisms and therapeutic applications of SMAD4 in DCs will advance our understanding and treatment of diseases where DC function is compromised [97].

8. SMAD4 in other immune cells

While the roles of SMAD4 in T cells, B cells, NK cells, macrophages, and dendritic cells are well-documented, its influence extends to other immune cell types as well [103]. Understanding the functions of SMAD4

in these cells can provide a comprehensive view of its role in the immune system and highlight additional therapeutic opportunities [82].

In mast cells, SMAD4 regulates development, survival, and cytokine production, which are crucial for mediating allergic reactions and host defense against pathogens [104]. Through TGF-β signaling, SMAD4 influences the expression of growth factors, receptors, and cytokines such as IL-6, TNF-α, and IL-13 [105]. This modulation affects both allergic responses and chronic inflammatory conditions, presenting potential therapeutic approaches for allergic diseases and chronic inflammation by regulating cytokine production without broadly suppressing the immune system [5].

Neutrophils, as first responders to infection, rely on SMAD4 for chemotaxis, activation, and apoptosis [106]. SMAD4 affects the expression of chemokine receptors and adhesion molecules, enhancing neutrophil migration and activation to produce antimicrobial agents [107]. Additionally, TGF-β/SMAD4 signaling regulates neutrophil apoptosis, crucial for resolving inflammation and preventing tissue damage [108]. Targeting SMAD4 in neutrophils could help manage conditions characterized by neutrophil dysregulation, such as chronic obstructive pulmonary disease (COPD) and sepsis, by balancing pathogen clearance with inflammation resolution.

In eosinophils, SMAD4 influences differentiation, activation, and survival, impacting allergic responses and defense against parasitic infections [109]. It regulates differentiation from hematopoietic progenitor cells, affecting cytokine production critical for development [110]. Through TGF-β signaling, SMAD4 modulates eosinophil activation and cytotoxic granule production, as well as apoptosis [111]. Therapeutically, targeting SMAD4 in eosinophils can address diseases such as asthma and eosinophilic esophagitis by controlling eosinophil-mediated tissue damage while maintaining protective functions [112].

Regulatory T cells (Tregs) rely on SMAD4 for development and function, essential for maintaining immune tolerance and preventing autoimmunity [113]. TGF-β/SMAD4 signaling is pivotal for Treg differentiation, promoting the expression of the transcription factor FOXP3 [114]. SMAD4 enhances Treg suppressive functions by upregulating immunosuppressive cytokines like IL-10 and TGF-β, and surface molecules such as CTLA-4 [115]. Enhancing SMAD4 activity in Tregs can be beneficial for treating autoimmune diseases and preventing graft-versus-host disease (GVHD) in transplant patients, promoting immune tolerance and reducing pathological immune responses [116].

SMAD4 plays a versatile and crucial role across various immune cell types, influencing their development, function, and responses to pathogens and diseases. Understanding the specific molecular pathways through which SMAD4 operates in different immune cells opens up new therapeutic avenues [100]. Targeting SMAD4 can help modulate immune responses, offering promising strategies for treating a wide range of immune-related diseases, from allergies and chronic inflammation to autoimmunity and cancer [89]. Further research into SMAD4's diverse roles will continue to enhance our ability to develop precise and effective immunotherapies [97].

9. Discussion

9.1. Impact on current understanding

The findings discussed in this review redefine SMAD4's function as a multifaceted regulator in immune cells. SMAD4 integrates signals from the TGF-β pathway to modulate cell-specific outcomes, such as T cell differentiation, B cell antibody production, and macrophage polarization. For example, SMAD4's role in balancing Treg and Th17 differentiation underscores its importance in maintaining immune tolerance and preventing autoimmune diseases. Moreover, the role of SMAD4 in the tumor microenvironment (TME) highlights its dual nature. On one hand, SMAD4-mediated TGF-β signaling can suppress anti-tumor immunity by promoting Treg activity. On the other, targeted inhibition of this pathway can enhance cytotoxic T cell responses, offering a promising approach for immunotherapy.

9.2. Unexplored areas

Despite progress, several questions remain unanswered. While studies hint at the impact of SMAD4 promoter methylation in immune cells, the broader implications of such epigenetic changes remain unclear. The context-dependent roles of SMAD4 in innate versus adaptive immunity need further exploration, particularly in diseases like chronic inflammation or infections. How SMAD4 interacts with pathways such as NF-κB and STAT signaling remains an area of active investigation.

9.3. Future technologies

Advances such as single-cell RNA sequencing could unravel the heterogeneity of SMAD4's roles across immune cell subsets. CRISPR-Cas9 gene editing presents an opportunity to investigate specific mutations and their functional consequences, while advanced imaging could provide spatiotemporal insights into SMAD4-mediated signaling in vivo.

9.4. Experimental limitations

While existing studies provide valuable insights, several limitations must be acknowledged. Many studies rely on in vitro models or murine systems, which may not fully capture human immune responses. For instance, the TGF-β/SMAD4 axis often exhibits species-specific differences that complicate the direct translation of findings. The TGF-β pathway involves multiple SMAD and non-SMAD effectors, making it difficult to isolate SMAD4-specific contributions. Research on SMAD4 in the TME is often confounded by the presence of other immunosuppressive factors, making it challenging to attribute observed effects solely to SMAD4 activity.

9.5. Contextual considerations

It is crucial to consider the physiological context when interpreting results. For example: SMAD4's role in balancing Treg and Th17 cells is well-documented, but the exact triggers that skew this balance remain elusive. While SMAD4 inhibition may boost anti-tumor immunity, potential off-target effects on other immune cells must be evaluated carefully. A comprehensive understanding requires integrating findings from diverse immune cell types. For example, while SMAD4 promotes M2 macrophage polarization, its role in other immune cells within the same inflammatory milieu needs further investigation.

10. Conclusion

SMAD4 serves as a pivotal regulator of immune cell functions, balancing pro- and anti-inflammatory responses depending on the context. This duality underscores the need for precision in targeting SMAD4-mediated pathways, particularly in treating diseases with immune dysregulation, such as cancer and autoimmune disorders (Table 1). By addressing the gaps in our understanding—especially through cutting-edge technologies—future research could unlock novel therapeutic strategies that modulate immune responses with high specificity.

CRediT authorship contribution statement

Xinmu Cui: Writing – original draft, Methodology, Investigation, Formal analysis. **Yu Song:** Writing – review & editing, Resources, Methodology, Investigation, Conceptualization. **Jianfeng Han:** Writing – original draft, Investigation, Formal analysis, Conceptualization. **Zhaoxin Yuan:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

Table 1
Knowledge gap and current understanding of SMAD4 in immune regulation.

	Cell	Function	Disease	Gap	References
TGFβ/SMAD4 signaling	T cell	Promoting the differentiation of naive $CD4^+$ T cells into Th17 cells and regulatory T cells Promoting T cell anergy	multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus	Direct Targets of SMAD4 in Immune Cells	[9,28]
	B cell	Regulates class switch recombination (CSR), somatic hypermutation (SHM), and plasma cell differentiation	systemic lupus erythematosus, rheumatoid arthritis	Regulation of Immune Responses by SMAD4	[35–37]
	NK cell	Promoting NK cell maturation, inhibiting NK cell cytotoxicity	Cancer	Dual Role of SMAD4	[43,44]
	Macrophages	Promoting M2 polarization, Inhibiting M1 polarization in Macrophage	rheumatoid arthritis, inflammatory bowel disease, atherosclerosis	Precision in Targeting SMAD4 Pathways	[62,63]
	Dendritic cell	Inhibiting DC maturation, Promoting the development of tolerogenic DCs	multiple sclerosis, type 1 diabetes, systemic lupus erythematosus	SMAD4 in Immune Dysregulation	[87,88]

Declaration of competing interest

All authors declare no conflicts of interest.

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