

Dual Role of Wnt5a in the Progression of Inflammatory Diseases

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ABSTRACT

Wnt5a is a secreted Wnt ligand that plays a critical role in cellular pathways and inflammatory diseases. The *WNT5A* gene encodes two protein isoforms, Wnt5a-long and Wnt5a-short, which differ based on different promoter methylation and have distinct functions. However, the mechanisms of the promoter methylation are unclear. Depending on the extent of promoter methylation, Wnt5a exerts both anti-inflammatory and pro-inflammatory effects in inflammatory diseases, which may be involved in different Wnt5a isoforms. Therefore, the Wnt5a isoforms may be potential diagnostic markers for inflammatory diseases and the mechanisms of the *WNT5A* gene promoter methylation need to be further investigated.

Key words: Wnt5a; inflammatory diseases; promoter methylation

INTRODUCTION

Inflammatory diseases are characterized by excessive tissue inflammation, cell proliferation, and increased metabolism^[1]. Notably, Wnt proteins play a dual role in inflammatory diseases^[2]. The Wnt family of proteins are cysteine-rich secreted glycoproteins essential for various cellular functions^[3], and at least 19 members have been discovered in humans and mice^[4]. They associate with several transmembrane proteins including the G-protein-coupled Frizzled (Fzd) receptors^[5], low-density lipoprotein receptor-related protein 5/6 (LRP5/6)^[6], receptor tyrosine kinase-like orphan receptor 2(Ror2)^[7], and receptor-related to tyrosine kinase (Ryk)^[8] and activate the downstream β -catenin-dependent^[9] and -independent^[10] signaling pathways. The expressions of Wnt proteins are regulated by the promoter methylation of *WNT* genes^[11].

Wnt5a signals through both β -catenin-independent^[12] and -dependent pathways^[13] and is associated with the inflammatory response compared with different levels of promoter methylation^[14]. Aberrant Wnt5a expression and *WNT5A* gene and abnormal methyla-

tion level of *WNT5A* gene have been observed in several chronic inflammatory diseases including rheumatoid arthritis^[15], psoriasis^[16], atherosclerosis^[17], and sepsis^[18], although the underlying pathological mechanisms remain unclear.

WNT5A GENE AND WNT5A-RELATED SIGNALING PATHWAYS

The human *WNT5A* gene is located on chromosome 3p14-p21^[19] and generates two transcripts through different transcription start sites^[20] downstream of promoter A and promoter B^[21] that respectively encode the 380 amino acid Wnt5a-long (Wnt5a-L) and 365/360 amino acid precursor protein Wnt5a-short (Wnt5a-S)^[22]. The predominance of either transcript depends on the preferential hypomethylation of their respective promoters^[23]. The Wnt5a-L isoform interacts with Fzd7, and Wnt5a-S interacts with Fzd5 or Ror2^[24] to exert opposing cellular functions. While Wnt5a-S promotes cell proliferation, migration, and differentiation, Wnt5a-L has an inhibitory effect on these processes^[24].

The role of Wnt5a in the β -catenin-dependent pathway is ambiguous^[25]. In the absence of Wnt5a, phosphorylated and ubiquitinated β -catenin form a "destruction complex" consisting of Axin, glycogen synthase kinase 3- β (GSK3- β), adenomatous polyposis

coli (APC), and casein kinase 1 α (CK1 α)^[26] (**Fig. 1Aa**). Wnt5a/Fzd4 combination activates the disheveled (Dvl) protein^[27] (**Fig. 1Ab**), which degrades this destruction complex and results in the accumulation of cytoplasmic β -catenin^[28] (**Fig. 1Ab**). The latter interacts with the T-cell factor/leucocyte enhancer factor (TCF/LEF) to activate the transcription of target genes^[29] (**Fig. 1Ab**). Wnt5a-S isoform may be involved in the Wnt5a- β -catenin-TCF/LEF axis^[24]. On the other hand, Wnt5a can also inhibit the β -catenin-dependent pathway through Ca²⁺ signaling^[30]. The Wnt5a/Fzd7 complex activates Ca²⁺/calmodulin-dependent protein kinase (CAMK) II and protein kinase C (PKC)^[31] (**Fig. 1Ba**), which decreases β -catenin stabilization and inhibits TCF/LEF transcription^[32] (**Fig. 1Ba**).

Wnt5a also associates with β -catenin-independent pathways^[33]. Wnt5a/Fzd5 and Wnt5a/Ror2 complex interact with disheveled (DSH) proteins and activate them, which trigger the release of intracellular Ca²⁺ via G-protein-mediated phospholipase C activation^[34] (**Fig. 1Ba**). The Ca²⁺ efflux activates the nuclear factor of activated T cell (NFAT) through the PKC/CAMKII/calcineurin axis, eventually leading to the transcription of target genes^[35] (**Fig. 1Ba**). Wnt5a can also activate the planar cell polarity (PCP) pathway^[36]. The Wnt5a/Fzd5 complex activates the c-Jun N-terminal protein kinase (JNK) through the DSH/Rho/Rac axis^[36] (**Fig. 1Ba**) as well as by the Wnt5a/Ror2 complex^[37] (**Fig. 1Bb**), thus promoting the transcription of target genes of c-jun^[37] (**Fig. 1Ba**).

WNT5A IN THE INFLAMMATORY RESPONSE

Wnt5a is expressed in monocytes such as the peripheral blood mononuclear cells, macrophages, and microglia^[38] and can increase the secretion of both pro-inflammatory^[39] as well as anti-inflammatory cytokines^[40] in an autocrine or paracrine manner. It is upregulated in the antigen-stimulated macrophages and microglia via the toll-like receptor (TLR)-2/NF- κ B signaling pathway^[40, 41] (**Fig. 2A**). In the early stage of inflammation, the Wnt5a/Fzd7 complex induces IL-10 secretion via Ca²⁺ signaling, which blocks TLR-2/NF- κ B signaling pathway and alleviates the inflammatory response^[41] (**Fig. 2A**). However, with the development of inflammation, the same Wnt5a/Fzd5/Ca²⁺ axis increases the secretion of pro-inflammatory cytokines such as IL-6, IL-8, IL-1 β , and macrophage inflammato-

ry protein-1 β (MIP-1 β) in response to lipopolysaccharides (LPS) and fatty acid stimulation^[42] (**Fig. 2B**). Wnt5a also induces CCL2 and IL-8 secretion in T cells to recruit neutrophils, lymphocytes, and macrophages^[43] (**Fig. 2C**). Furthermore, Wnt5a/Fzd5 and Wnt5a/Ror2 stimulate the neutrophils to secrete interferon (INF)- γ , which in turn recruits macrophages and lymphocytes, eventually leading to the inflammatory response^[44] (**Fig. 2C**). In addition, Wnt5a is known to induce the pro-inflammatory cyclooxygenase 2 (COX-2) in microglia^[45] (**Fig. 2B**), as well as inhibit its upregulation via the Fzd7/IL-10 axis^[46] (**Fig. 2A**). Inflammatory cytokines, in turn, regulate Wnt5a expression. For instance, TNF- α induces Wnt5a expression in adipocytes, bone marrow stromal cells (BMSCs), mesenchymal stem cells (MSCs), and macrophages^[47] (**Fig. 2C**).

Inflammation is also characterized by aberrant tissue function and metabolism^[48]. Wnt5a/Fzd5 and Wnt5a/Ror2 complexes secreted from the activated macrophages target peripheral tissues via Wnt-PCP signaling, leading to cellular hyperproliferation and dysfunction^[49] (**Fig. 2D**). For instance, high levels of Wnt5a in the macrophage-rich atherosclerotic lesions of mice induce the cholesterol accumulation in smooth muscle cells^[50] and the proliferation of atrial endothelial cells^[51]. In the mouse model of sepsis, macrophage-derived Wnt5a can induce the damage of capillary endothelial cells^[52].

WNT5A IN INFLAMMATORY DISEASES

Wnt5a can affect the progression of inflammatory diseases by regulating the immunocytes activity and the metabolism and proliferation of abnormal cells. In inflammatory diseases, research on *WNT5A* gene has been focused on rheumatoid arthritis (RA), psoriasis (PsO), atherosclerosis (AS), diabetes, sepsis, and chronic obstructive pulmonary disease (COPD). The role of *WNT5A* in these diseases is bidirectional, except in RA. (**Fig. 3**)

Wnt5a in autoimmune inflammatory diseases

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial inflammation^[53] and osteoclast-osteoblast imbalance^[54]. Wnt5a can aggravate the progression of RA by increasing synovial secretion of IL-6, IL-8, IL-15, and nuclear factor-kappa B ligand (RANKL)^[55] (**Fig. 3A**). Compared to the normal

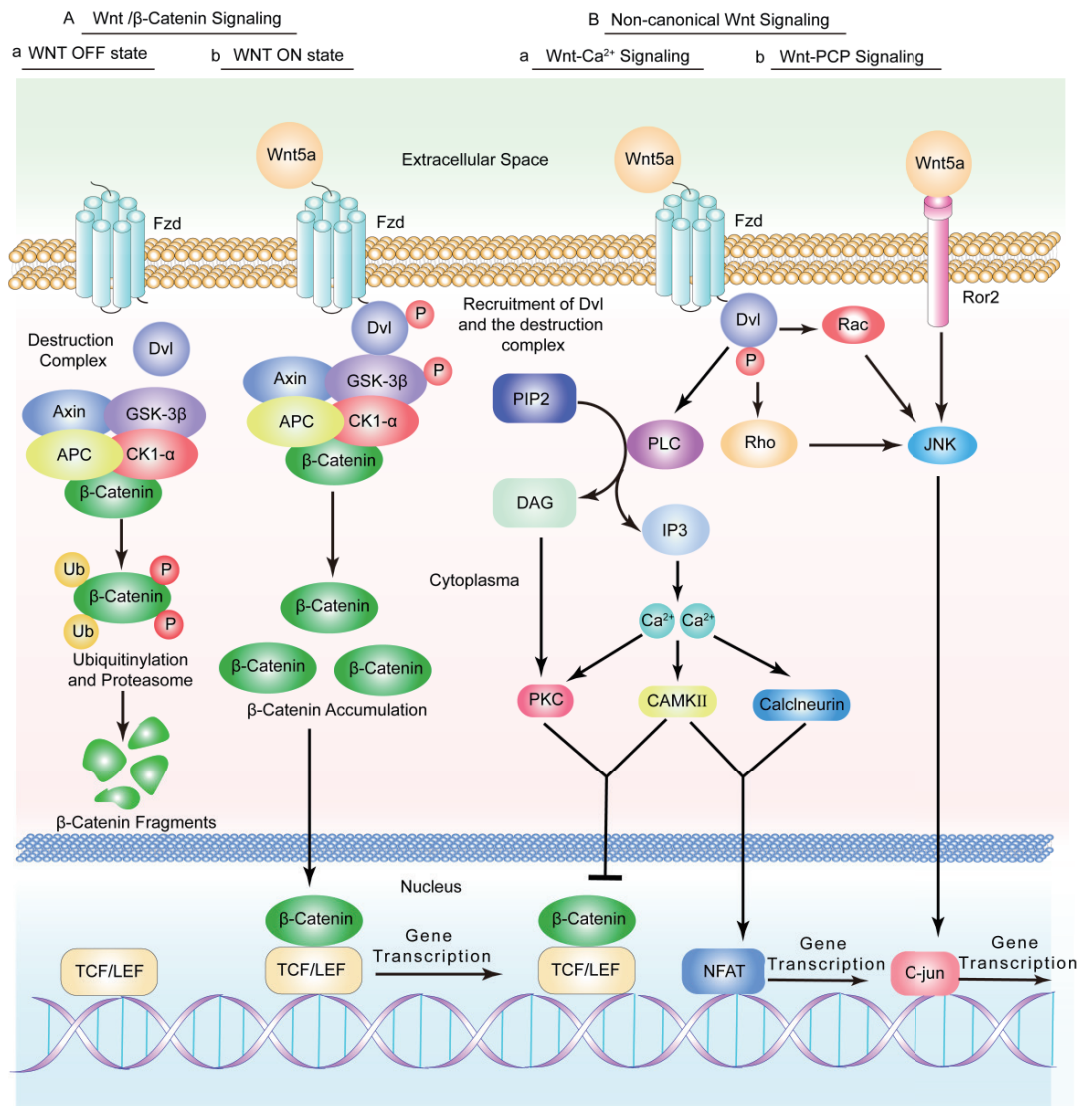


Figure 1. Wnt5a-related signaling pathways. (A) Wnt/β-catenin signaling pathway. (a) In the “off” state, the frizzled protein is not bound to Wnt5a. β-catenin is phosphorylated by GSK3β/Axin/APC/CK1-α and then degraded by the ubiquitin-proteasome. (b) Wnt5a binds to the receptor Frizzled and switches the signaling pathway to the “on” state. Phosphorylation of Dvl disrupts the GSK3β/Axin/APC/CK1-α complex, which dephosphorylates β-catenin and increases its cytoplasmic accumulation. It eventually translocates to the nucleus and binds to TCF/LEF, leading to the transcription of Wnt-responsive genes. (B) Non-canonical Wnt signaling pathways. (a) Wnt-Ca²⁺ signaling pathway. The Wnt5a-Frizzled interaction phosphorylates Dvl, which breaks down PIP2 to IP3 and DAG. IP3 triggers Ca²⁺ efflux, which activates PKC, CAMK II, and calcineurin. The latter activates NFAT and the transcription of downstream target genes. Activated PKC and CAMK II inhibit the binding of β-catenin and TCF/LEF by blocking the Wnt/β-catenin signaling pathway. (b) Wnt-PCP signaling pathway. Wnt5a binds to Frizzled receptor and phosphorylates Dvl, which activates Rac and Rho, leading to JNK translocation into the nucleus and transcription of c-jun target genes.

synovial tissues, the arthritic tissues had upregulated Wnt5a mRNA level, which correlates positively with IL-6, IL-8, and IL-15^[15]. Wnt5a can also induce synovial cell proliferation *in vivo* and *in vitro* via the Wnt5a-Ca²⁺ pathway (Fig. 3A)^[56]. In the RA mouse model, Wnt5a secreted from osteoblasts can enhance RANKL-induced

osteoclast formation via Wnt5a/JNK signaling pathway, which aggravates the disease (Fig. 3A)^[57]. Wnt5a-deletion, on the other hand, attenuates osteoclast degeneration in the RA mice^[58]. Furthermore, promoter B hypomethylation of the *WNT5A* gene was observed in synovial cells and osteoblasts in RA patients^[59]. There-

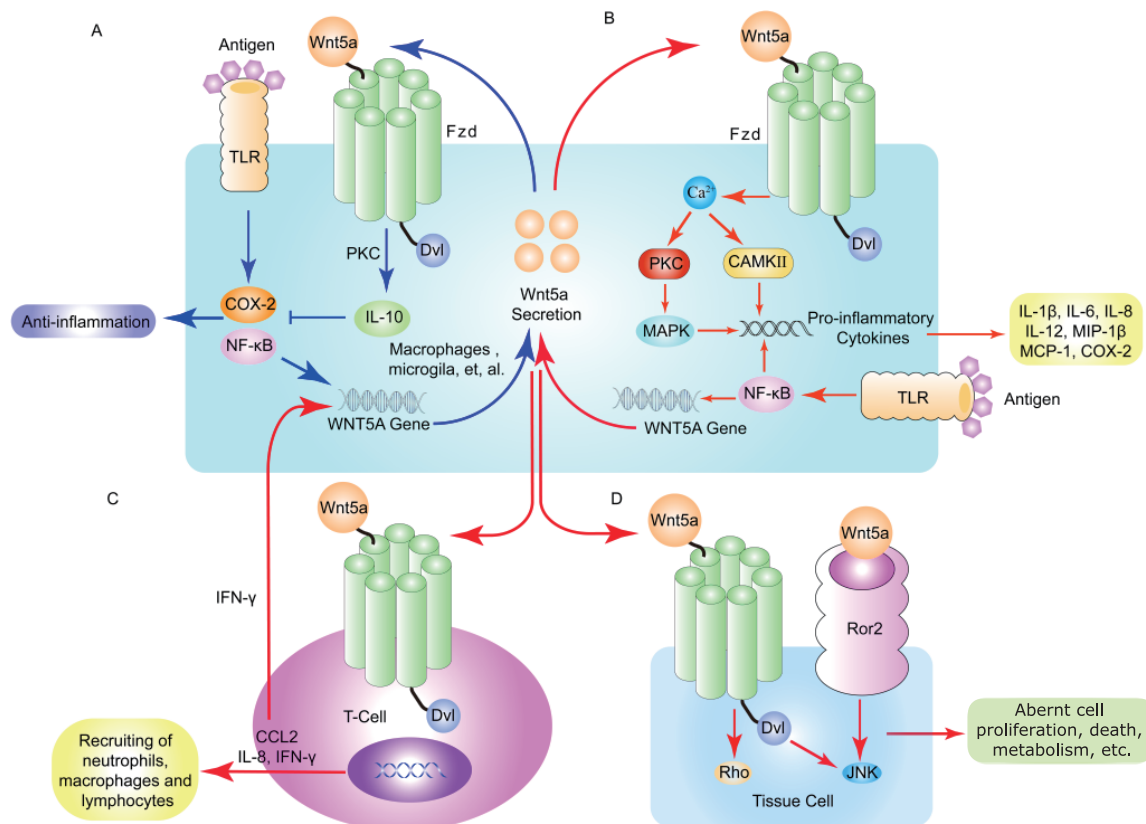


Figure 2. The dual role of Wnt5a in the inflammatory response. (A) Antigen stimulation of macrophages and microglia activate NF-κB/COX-2 pathway via TLRs, leading to Wnt5a upregulation. Wnt5a binds to the receptor Frizzled 5 and induces IL-10 secretion, inhibiting the NF-κB inflammatory pathway. (B) Wnt5a and Frizzled 5 binding activates Ca²⁺ signaling, leading to IL-6, IL-8, IL-1β, IL-12, MIP-1β, MCP-1, and COX-2 secretion. (C) Wnt5a/Frizzled 5 complex stimulates T-cells to secrete CCL2, IL-8, and IFN-γ, which recruits macrophages, lymphocytes, and neutrophils. (D) Macrophage-derived Wnt5a induces aberrant proliferation, death, and metabolism in the peripheral tissues via PCP signaling.

fore, Wnt5a can aggravate RA progression by stimulating synovial inflammation, synovial cell proliferation, and osteoclast-osteoblast imbalance, which may involve aberrant promoter methylation of *WNT5A* genes.

Psoriasis

Psoriasis (PsO) is a chronic autoimmune skin disease involving the aberrant proliferation and differentiation of keratinocytes^[60]. Wnt5a overexpression has been observed in psoriatic skin lesions compared to normal skin tissues^[61]. Correspondingly, *WNT5A* silencing in keratinocytes triggered their apoptosis by repressing the Wnt5a/Ca²⁺ pathway (**Fig. 3B**)^[62], and a low expression level of Wnt5a was associated with milder disease in the PsO mouse model^[63]. However, *WNT5A* knockdown can induce keratinocyte proliferation *in vitro* (**Fig. 3B**)^[64]. The Wnt5a activity during PsO progression depends on its epigenetic regulation^[63]. Verma *et al.* found that the *WNT5A* promoter B was hypomethylated and promoter A was hypermethyl-

ated in PsO lesions compared to normal skin tissues, and the extent of methylation was correlated with the progression of PsO^[65]. Demethylation of the *WNT5A* promoter in keratinocytes induced their proliferation *in vitro* by activating Wnt5a/CAMK II/β-catenin signaling pathway^[65]. Thus, Wnt5a plays a dual role in PsO, depending on the promoter methylation status.

Wnt5a in metabolic inflammatory diseases

Atherosclerosis

Atherosclerosis (AS) is a chronic inflammatory condition characterized by the gradual build-up of plaques in the arterial walls due to endothelial cell dysfunction, macrophage overactivity, and aberrant cholesterol metabolism^[66]. In the AS mouse model, Wnt5a levels were upregulated in the endothelial cells and macrophage-rich atherosclerotic lesions^[67]. Besides, Wnt5a overexpression in endothelial cells correlated with TLR-4 upregulation and increased proliferation via the Wn-

t5a/Ror2 signaling pathway^[68]. In the plaque lesions, elevated Wnt5a expression coincided with that of macrophage markers and TLR-2, promoting the proliferation of macrophages via the Wnt5a/Ror2 signaling pathway (**Fig. 3C**)^[69]. Wnt5a overexpression impairs cholesterol metabolism by reversing its transportation, which leads to cholesterol accumulation in the macrophages and smooth muscle cells (**Fig. 3C**)^[68, 70]. In the *in vitro* AS model, Wnt5a silencing reduced inflammatory response by inhibiting the mitogen-activated protein kinase (MAPK) signaling pathway^[71]. In intracranial atherosclerotic stenosis patients, promoter A of the *WNT5A* gene was hypomethylated in the peripheral blood, whereas promoter B was hypermethylated^[72]. Thus, Wnt5a triggers the inflammatory progression in AS, and the methylation level of the promoter might influence the *WNT5A* gene function.

Diabetes

Inflammation is a crucial mechanism underlying the progression of diabetes^[73], wherein Wnt5a plays a dual role^[74, 75]. Wnt5a increases the proliferation of pancreatic islet β -cells via the JNK signaling pathway and alleviates diabetic progression in mice (**Fig. 3D**)^[76, 77]. Furthermore, Wnt5a alleviated renal inflammation in a mouse model of diabetic neuropathy by inhibiting lymphocyte proliferation in the renal tubes via the CaMKII / β -cat-

enin axis (**Fig. 3D**)^[78]. However, Relling *et al.* showed that Wnt5a promoted infiltration of monocytes into the pancreatic islets and renal interstitium of diabetic mice, thereby aggravating disease progression and its ensuing complications^[79]. Likewise, Li *et al.* found that Wnt5a increased monocyte infiltration into the renal tubules in diabetic mice by activating the JNK signaling pathway (**Fig. 3D**)^[80]. Furthermore, hypomethylation of *WNT5A* promoter B has been observed in the mouse model of diabetes nephropathy^[80], whereas *WNT5A* promoter A was hypomethylated in the early stage of diabetes in mice^[75]. Therefore, Wnt5a has a bidirectional role in diabetes, possibly depending on promoter methylation.

Wnt5a in other inflammatory diseases

Sepsis

Sepsis is characterized by a systemic inflammatory response driven by activated macrophages^[81]. Wnt5a protein is elevated in septic patients^[82] and associated with severe disease and poor prognosis^[83]. In the septic mouse model, Wnt5a stimulated macrophage proliferation via the CaMKII/NFAT signaling pathway, aggravating the inflammatory response (**Fig. 3E**)^[84]. Wnt5a also stimulated the secretion of pro-inflammatory cytokines (e.g., IL-6, IL-8, IL-1 β , and MIP-1 β) from the activated macrophages (**Fig. 3E**)^[84]. Moreover,

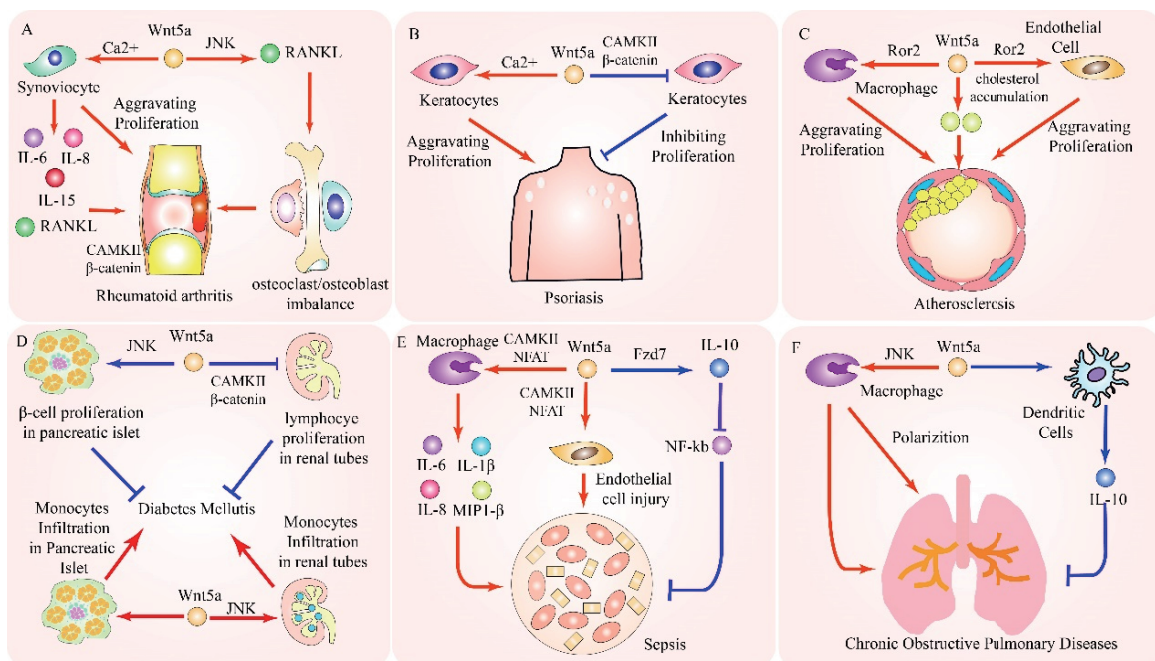


Figure 3 The role of Wnt5a in inflammatory diseases. (A) Wnt5a aggravates rheumatoid arthritis. (B) Wnt5a regulates psoriasis via bi-direction. (C) Wnt5a aggravates atherosclerosis. (D) Wnt5a regulates diabetes mellitus via bi-direction. (E) Wnt5a regulates sepsis via bi-direction. (F) Wnt5a regulates chronic obstructive pulmonary diseases via bi-direction.

Wnt5a induced capillary endothelial cell injury in the murine sepsis model by activating CaMKII/NFAT signaling, which aggravated the disease (**Fig. 3E**)^[52]. However, in the early stage of sepsis, Wnt5a alleviated inflammation by inhibiting NF- κ B signaling and macrophage autophagy via the Fzd7/IL-10 axis (**Fig. 3E**)^[85]. Promoter A hypomethylation of *WNT5A* gene improved the overall survival time of septic patients via attenuated NF- κ B activation^[86], whereas promoter B hypomethylation of the *WNT5A* gene promoted sepsis progression via Wnt/JNK signaling pathway^[87]. Therefore, Wnt5a regulated the progression of sepsis in a bidirectional manner, possibly depending on the methylation site of the *WNT5A* gene.

Chronic obstructive pulmonary disease (COPD)

COPD is characterized by localized inflammation in the airway, which obstructs airflow and causes difficulty in breathing^[88]. Wnt5a regulates the activity of macrophages and dendritic cells (DCs) during COPD progression^[89]. In the COPD mouse model, Wnt5a-overexpressing DCs secreted IL-10 that mitigates the inflammatory response (**Fig. 3F**)^[89]. However, Wnt5a might promote macrophage-mediated COPD by activating the Wnt-JNK signaling pathway (**Fig. 3F**)^[90]. In addition, Wnt5a polarized macrophages to the inflammatory M1 phenotype in both humans and mouse models via the JNK signaling pathway, which aggravated COPD symptoms (**Fig. 3F**)^[89]. In COPD mice models, promoter A hypomethylation of *WNT5A* triggered Dcs activation to alleviate inflammatory response in COPD mice models^[91], whereas promoter B hypomethylation of *WNT5A* stimulated macrophages to secrete pro-inflammatory cytokines, which aggravated inflammatory response^[92]. Therefore, the role of Wnt5a in COPD is complex and is based on regulating the balance between pro-inflammatory and anti-inflammatory cells, also possibly depending on the *WNT5A* gene methylation.

CONCLUSIONS

Wnt5a plays a dual regulatory role in inflammatory diseases. It can mitigate inflammation by increasing anti-inflammatory cytokines secretion through NF- κ B inhibition, whereas Wnt5a overexpression following continuous antigen stimulation can activate pro-inflammatory cytokine secretion via Ca^{2+} signaling. It can also trigger aberrant cellular proliferation and metabolism in peripheral tissues via JNK signaling. This bidirectional activity of Wnt5a may be due to differential

promoter demethylation. Promoter A hypomethylation increases the levels of the Wnt5a-L-encoding transcript (**Fig. 4A**). Wnt5a-L interacts with Fzd7 and augments the secretion of IL-10 by inhibiting NF- κ B signaling, which can attenuate the progression of inflammatory diseases (**Fig. 4B**). In addition, the Wnt5a-L/Fzd7 complex inhibits β -catenin activity via the CAMKII/ β -catenin axis, which decreases cell proliferation (**Fig. 4B**). Promoter B hypomethylation results in Wnt5a-S as the dominant transcript (**Fig. 4A**). The Wnt5a-S isoform combines with Fzd5 and Ror2 to stimulate Wnt5a/CAMK II/NFAT and Wnt5a/Ror2-JNK signaling pathways, which augments the secretion of pro-inflammatory cytokines and results in aberrant cell proliferation and metabolism (**Fig. 4C**). Thus, the Wnt5a isoform may be a potential prognostic marker of inflammatory diseases, although the underlying mechanisms of *WNT5A* gene promoter methylation need to be further

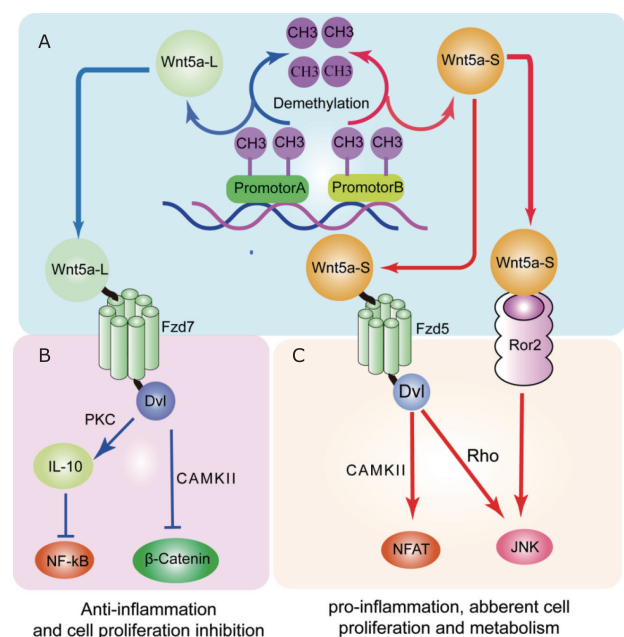


Figure 4. Possible mechanisms of the bidirectional role of Wnt5a in inflammatory diseases. (A) Promoter A demethylation leads to the production of Wnt5a-L, whereas promoter B demethylation predominantly results in Wnt5a-S. (B) Wnt5a-L combines with Fzd7 and inhibits NF- κ B and β -catenin, stimulating the Wnt5a/Fzd7/IL-10 and Wnt5a/CAMKII/ β -catenin pathways, and attenuates pro-inflammatory cytokines secretion and cell proliferation. (C) Wnt5a-S binding to Fzd5 and Ror2 stimulate the Wnt5a-CAMKII-NFAT and Wnt5a-PCP signaling, resulting in inflammatory cytokines secretion, abnormal cell proliferation and metabolism.

elucidated.

Conflict of interests

The authors disclosed no conflicting interest.

Authors' contributions

Zhao FH conceived and designed the study. Chen X drafted the manuscript, and Chen X and Li DH revised the draft. Liu HL searched relevant literature. Wang JS made critical revisions. All authors approved the final version.

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综述

Wnt5a 在炎症疾病中具有双向调节性

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摘要

Wnt5a 是一种分泌性的 Wnt 蛋白，在细胞通路及炎症疾病中扮演重要作用。*WNT5A* 基因可编码形成 Wnt5a 长链蛋白和 Wnt5a 短链蛋白，这两种蛋白的形成取决于 *WNT5A* 基因启动子甲基化的部位，具有不同的功能。然而，*WNT5A* 基因启动子甲基化的机制目前仍然不清楚。在炎症疾病中，因为 *WNT5A* 基因甲基化的部位不同，Wnt5a 具有抑制炎症和促进炎症的双面功能，这或许涉及 Wnt5a 蛋白不同的亚型。因此，Wnt5a 蛋白的不同亚型或许是潜在的炎症疾病诊断标记，*WNT5A* 基因甲基化的具体机制也需要深入研究。

关键词：Wnt5a；炎症疾病；启动子甲基化

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