Role of Wnt5a in inflammatory diseases

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Abstract

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Abstract

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Wnt is a family of secretory glycoproteins that regulates a series of cellular behaviors through receptor-mediated signaling pathways on the cell surface (1). Recent studies have demonstrated that Wnt signaling pathway plays an important role in regulating cell proliferation, embryonic development, differentiation, polarity, migration, and inflammation (2-6). Wnt5a, a member of the highly conserved Wnt protein family, has been reported in the development and maturation of tissues and organs and is closely related to various

diseases, such as malignant tumors, metabolic disorders, fibrosis. In particular, recent studies have shown that Wnt5a signaling is also involved in the inflammatory diseases (7). In this paper, the Wnt family and the signaling pathway, the relationship between Wnt5a and inflammatory factors, and the relationship between Wnt5a and inflammatory signal transduction pathway is expounded. Meanwhile, the latest results of Wnt5a protein in sepsis, bronchial asthma, Chronic obstructive pulmonary disease (COPD), tuberculosis, rheumatoid arthritis, atherosclerosis, psoriasis Vulgaris and other inflammatory diseases in recent years are reviewed. It means to clarify the mechanism of action of Wnt5a rotein in the pathogenesis of inflammatory diseases, to provide the basis for the prevention and

treatment of inflammatory diseases with Wnt5a as a target in the future.

1. Wnt family and signaling pathways

Wnt is a large family of secreted glycoproteins rich in cysteine residues, which

was initially found in mouse breast cancer and is widely expressed in various tissues (8,9). There are 19 kinds of Wnt protein subtypes in mammals, mainly including Wnt1, Wnt2, Wnt3, Wnt4, Wnt5a, Wnt6, Wnt7b, Wnt10b, etc. The Wnt protein signal transduction pathway is a complex protein action network. Most of them can bond to a variety of Frizzled (FZD) receptors, which belong to the G protein-coupled transmembrane protein family (10,11); Part of Wnt protein combines with common receptors, such as low-density lipoprotein receptor-related protein (LRP) 5 and 6, receptor tyrosine kinase-like orphan receptor 2 (Ror2), and receptor tyrosine kinase (Ryk), etc to mediate the signaling pathways of different cells (11,12). Mingyi Li et al. have also shown that FZD receptors are required for Tiki inhibition of cell-surface Wnt signaling. Tiki binds to the Wnt-FZD complex and clears the N-terminus of Wnt3a or Wnt5a, preventing the recruitment and activation of the co-receptors LRP6 or ROR1/2 by the Wnt-FZD complex without affecting the stability of the Wnt-FZD complex (13). Bowin C-F's team studied the dynamic changes in FZD5-Dishevelled (DVL) 2 interactions induced by Wnt3a and Wnt5a. The discovery of ligand-induced bioluminescent resonance energy transfer changes between FZD5 and DVL2 or the FZD-binding DEP domain isolated by DVL2 shows a complex response in the FZD5-DVL2 complex consisting of DVL2 recruitment and conformational dynamics (14).

Wnt protein subtypes are generally divided into two types: canonical Wnt proteins (such as Wnt3a, Wnt7a) and non-canonical Wnt proteins (such as Wnt5a, Wnt11) (15). They activate different downstream signaling pathways respectively, the canonical Wnt signaling pathway (Wnt/ β-catenin pathway) and the non-canonical Wnt signaling pathway (16). Canonical Wnt/ β-catenin pathway, also known as the β-catenin signaling pathway, mainly refers to a series of reactions after the combination of Wnt protein and the FZD receptor family on the cell surface, so that the "β-catenin degradation complex" is inhibited and the intracytoplasmic β-catenin is stable. Part of the β-catenin enters the nucleus and interacts with the nuclear transcription factor T-cell factor/lymphoid enhancing factor (TCF/LEF) family to promote the expression of specific genes, which are mainly involved in regulating cell proliferation and differentiation (11,17-19). The other non-canonical Wnt signal pathway, also known as non-dependent on the β-catenin signal pathway, is mainly divided into Wnt/Ca2+ signal transduction pathway and Wnt/Planar cell polarity (PCP) signal transduction pathway. These two pathways bind different receptors, including FZD-3, FZD-4, FZD-5, and receptor tyrosine kinase-like orphan receptor 2 (Ror2), etc (20,21), and are mainly involved in regulating cytoskeletal recombination, cell adhesion, migration, and tissue separation (22). Wnt/Ca2+ signal transduction pathway is activated by Wnt11 or Wnt5a. It can promote the release of intracellular Ca2+ to activate protein kinase C through the action of calmodulin-dependent kinase and calcineurin phosphatase, which can increase the intracellular Ca2+ concentration and activate T nuclear factors, to play a role in cancer inhibition (23). In Xenopus laevis and zebrafish, Wnt5a activates the Wnt-Ca2+ signaling pathway to regulate contraction and extension (24,25). The Wnt/PCP signal transduction pathway is the Wnt/JNK (c-Jun N-terminal kinase) kinase pathway, which is activated by GTPase Rho A protein. The activated JNK phosphorylates by binding to the transcription factors c-jun and ATF2 amino-terminal region, thereby regulating gene expression and participating in some important processes, such as gastrula formation and localization cell repair (11,26). There is also a cross-interaction between the canonical Wnt signaling pathway and the non-canonical Wnt

signaling pathway, such as Wnt-Ca2+ channel which can inhibit the β-catenin pathway, Wnt-Ca2+ signaling pathway activating Protein kinase C (PKC), blocking the Disheveled (Dsh) Protein phosphorylation of the canonical β-catenin upstream channel (27).

2. Wnt5a and its receptors

As a member of the Wnt family protein and a representative of the non-canonical Wnt pathway, Wnt5a is expressed in monocytes and macrophages (28). It was discovered by Clark et al. of Thomas Jefferson University in the 1990s. It is composed of 1,172 adenines, 884 cytosines, 946 guanines, and 1,172 thymidines, and plays an important role in embryo formation, organ homeostasis and cell maturation (9,29,30). It has been reported in the literature that the Wnt5a gene encodes for two subtypes by selecting promoters 1A and 1B, and is closely related to several signaling pathways including Nuclear factor-kappa B (NF-ϰB), Transforming growth factor-beta (TGF-β), Notch and Hedgehog (31). Like other Wnt proteins, Wnt5a goes through two important modifications after translation to become a full-functional protein finally. In the process of binding to specific receptors and secretion, Wnt5a needs to be modified by lipids and glycation, and secretory Wnt5a can be modified by lipids to obtain hydrophobicity (9,32–34).

Wnt5a binds to the cellular transmembrane receptor, which can transmit signals into the cell to produce a series of reactions. In different cells, Wnt5a can bind to different types of receptors, forming complex regulatory networks through canonical and non-canonical Wnt pathways, and participate in the regulation of cell response. The most common receptor is the FZD receptor (a seven-fold transmembrane receptor protein). At present, FZD2, FZD3, FZD4, FZD5, FZD7, and FZD8 receptors are involved in the Wnt5a signaling pathway at least. Among them, FZD2 can mediate wnt5a-dependent cells to increase calcium ion concentration. FZD4 receptor can activate the β-catenin pathway (canonical pathway) through binding to Wnt5a. The combination of FZD5 receptor and Wnt5a can regulate the expression of IL-12 in antigen-presenting cells induced by micro-organisms, to regulate the inflammatory response of human monocytes stimulated by micro-organisms. Besides, FZD7 is involved in Wnt5a-induced AP-1 activation and Dv1 activation in mouse fibroblasts (35). Another receptor that binds to Wnt5a, Ror2, is a single transmembrane receptor protein containing tyrosine kinases with only one tyrosine kinase domain (36), which can be used as a receptor or coreceptor of Wnt5a to regulate non-canonical Wnt signaling pathways (37-42). Wnt5a mediates Wnt-Ca2+ and Wnt-PCP pathways by binding to Ror2 receptor while inhibiting the β-catenin pathway (canonical pathway). The Wnt-Ca2+ transduction signaling pathway regulates cell proliferation, migration, and adhesion by activating CaMKII (Calmodulin dependent protein kinase II) and PKC; while Wnt-PCP transduction signaling pathway plays a role in regulating cell localization through small G protein or JNK (43). In the osteoblastic lineage, the Wnt5a/Ror2 signaling pathway can promote the occurrence of osteoclasts during the transformation of cells into osteoclast precursors, providing a new therapeutic direction for related diseases. Moreover, two other receptors have been proved to bind to Wnt5a. Receptor-like tyrosine kinase (Ryk) is involved in the regulation of axial growth, and tyrosine kinase-like receptor (PTK) is closely related to cell polarity. Nishita et al. have also shown that Wnt5a can bind the Ror2 receptor and FZD7 receptor to form a complex, thus acting on the Wnt signaling pathway (39). The diversity of the receptors that bind to Wnt5a leads to complex signaling pathways and dual regulation. For example, not only can it activate the β-catenin pathway with FZD receptors, but it also can inhibit the β-catenin pathway through Ror2 receptors (43-45). In another experiment, Okamoto's team had demonstrated that the Wnt5a signaling pathway regulates osteoblasts and bone formation, however, it was indicated that plays an important role in osteoclast formation as well (46).

3. The relationship of Wnt5a and inflammatory factors.

Wnt5a has been recognized as a proinflammatory factor widely based on its

induction of proinflammatory cytokines and chemokines in different cells such as macrophages, endothelial cells, pulp cells , marrow stroma cells, synovioblasts, and other cell types (47). Upon lipopolysaccharide (LPS) stimulation, increased production of Wnt5a in macrophages has been found, which induces the expression of intracellular IL-1β, IL-6, IL-8, macrophage inflammatory protein-1b (MIP-1b) and other proin-

flammatory factors (48). Wnt5a can also induce chemokines such as CCL2 and IL-8, which can recruit macrophages and neutrophils and amplify the inflammatory reaction (5,48-52). Besides, Wnt5a Has been reported to induce Cyclooxygenase (COX)-2 production; and knocking out or blocking Wnt5a can reduce the production of COX-2 (52), so Wnt5a can be a target of the inhibition of COX-2. Furthermore, Wnt5a is upregulated after mycobacterium infection and regulates the inflammatory response of IL-12 in human monocytes with binding to the FZD5 receptor (48,53). Similarly, Valencia et al. have shown that Wnt5a gene knockout leads to a significant decrease in IL-12 expression in mature dendritic cells (54). Kim et al. confirmed in another study that Wnt5a upregulates IL-1α、IL-3, and other cytokines in cultured endothelial cells by activating the NF-ϰB signaling pathway (5). The comprehensive analysis of the Wnt signaling pathway mediated by cytokines and the proinflammatory signaling pathways further support the role of Wnt5a as a biomarker in the diagnosis, severity assessment, and prognosis of inflammatory diseases. In addition, studies have shown that Wnt5a increases the invasiveness of melanoma cells through activating PKC signaling pathway (43). To further support the proinflammatory signaling function of the non-canonical Wnt signaling pathway, Catalan et al. have demonstrated that activation of non-canonical Wnt signaling through Wnt5a can activate the inflammatory response of visceral adipose tissue in obese subjects(55,56). Similarly, the Wnt5a-mediated non-canonical Wnt signaling pathway has been shown to increase inflammation in adipose tissue through activating the JNK pathway by promoting the expression of macrophage proinflammatory cytokines (56). Interestingly, Wnt5a not only increases the expression of proinflammatory cytokines, but also acts on cells to induce the increase of Wnt5a production. For example, Rauner et al. showed that Wnt5a expression in human marrow stromal cells was significantly increased. Other experiments have confirmed that TNF-α can also regulate Wnt5a overexpression in mesenchymal stem cells, fat cells, and human pulp cells. Moreover, it has been found that the stimulation of IL-6 on melanoma cells can also induce Wnt5a overexpression in a dose-dependent manner (51-52,55,57-58). In conclusion, the interaction between Wnt5a and proinflammatory cytokines can be enhanced and amplified in different cells.

Although a large number of literatures have reported that Wnt5a can promote the expression of inflammatory cytokines, but some studies have also shown that Wnt5a can induce the expression of anti-inflammatory factors in some special conditions. Bergenfield et al. reported that Wnt5a, which is highly expressed in proinflammatory M1-type macrophages of sepsis patients, can promote the expression of IL-10, and inhibit the production of IL-6, IL-8, and IL-12, which plays an anti-inflammatory role (59).

In conclusion, the above studies confirmed the proinflammatory function of Wnt5a, suggesting that Wnt5a pathway may be a potential candidate target for therapeutic intervention in inflammatory diseases, however, Wnt5a's inflammatory signal transduction pathway is complex, and there are actions and reactions between Wnt5a and proinflammatory factors, so its mechanism of action in inflammatory diseases needs to be further studied (Figure 1). Studies in recent years have shown that Wnt5a is involved in a variety of inflammatory diseases including bronchial asthma, chronic obstructive pulmonary disease, sepsis, rheumatoid arthritis, atherosclerosis, psoriasis Vulgare, and tuberculosis. Here we review the mechanism of Wnt5a in the pathogenesis in these inflammatory diseases (Table 1).

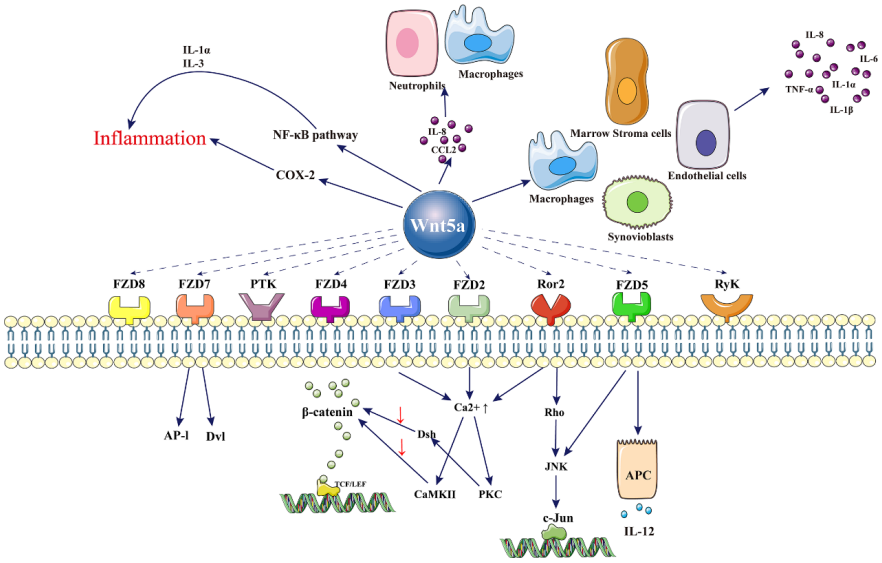

Figure 1 The relationship of Wnt5a and inflammatory factors

Tabel 1

Wnt5a and Inflammatory Diseases

Diseases	Wnt Trend	Activated Cells	Proinflammatory Cytokines	Signal
Sepsis	Increased	Macropages	IL-1β/IL-6/ IL-8/MIP-1b	Wnt5a/
Asthma	Increased	Airway SMCs	TGF-β1	Wnt5a/
COPD	Increased	Alveolar epithelial cells	IL-6/IL-8	Wnt5a/
Tuberculosis	Increased	Macrophages	IL-6/IL-12/ TNF-α/IL-1β	FOXO1
Rheumatoid Arthritis	Increased	Macrophages/ Synovial Fibroblasts	IL-6/IL-8/ IL-15	Wnt5a/
Atherosclerosis	Increased	Macrophages/ Endothelial cells/SMCs	COX-2/MCP-1/MMP-2/MMP-9	Wnt5a/
Psoriasis Vulgaris	Increased	Epidermal Keratinocytes	Non-specific	Wnt5a/

SMC: smooth muscle cell; LDL: low-density lipoprotein

4.Wnt5a and inflammatory diseases

4.1 Wnt5a and sepsis

Sepsis is a complicated and severe disease characterized by infection of the systemic inflammatory response, leading to diffuse intravascular coagulation and shock (60). The researchers confirmed the role of Wnt5a in sepsis and found that the level of Wnt5a protein in patients are significantly increased, and the serum concentration of Wnt5a in patients with sepsis was positively correlated with the severity of the disease; its decrease or increase positively correlated with the improvement or deterioration of the disease (48,61-62). Pereira et al. also reported a significant increase in Wnt5a levels in serum and bone marrow macrophages in patients with sepsis, and confirmed that the inflammatory signaling axis (Wnt5a/FZD5/CaMKII) played a crucial role in the inflammatory reaction of macrophages. Their study also found that Wnt5a recombinant protein stimulated the release of proinflammatory cytokines in macrophages such as IL-1β, IL-6, IL-8 and MIP-1b, which were inhibited in cells pretreated with activated protein C (APC) (55). In another study, Bergenfield et al. also found that Wnt5a induces immunosuppressive macrophages in a proinflammatory state, and that the phenotype of these immunosuppressive cells are similar to that of recombinant monocytes in patients with sepsis. It was also found that Wnt5a-induced feedback inhibition was closely related to

IL-10-induced inhibition of the classical TLR4-NF-ϰB signaling pathway in macrophages of patients with gram-negative bacteria or LPS induced sepsis (58). Results from Jungho Shin's team showed that Wnt5a levels were significantly elevated in patients with urinary sepsis, and assessing Wnt5a levels may help predict the occurrence of major renal adverse events and renal recovery in these patients (63). Ye, J et al. also found that miR-23a-3p inhibited sepsis-induced kidney epithelial cell injury by suppressing Wnt/β-catenin signaling by targeting wnt5a (64).

4.2 Wnt5a and asthma

Asthma is a chronic airway disease characterized by chronic airway inflammation, airway hyperresponsiveness, and irreversible airway remodeling (65). Katharina Dietz et al. found that the expression of Wnt5a, transglutaminase 2 and leukotriene in asthmatic airway inflammation, was age-related and correlated with age-related hormone resistance in asthmatic patients, which may be a potential new therapeutic target for airway inflammation and remodeling (66). Besides, studies have shown that Wnt5a is abundant in airway smooth muscle cells, and there is also a significant rise of TGF-β1, which promotes the expression of collagen protein and fiber connections. It is suggested that Wnt5a may be involved in airway remodeling of asthmatic patients, and Wnt5a is also involved in regulating airway smooth muscle, which may suggest a relationship of airway hyperresponsiveness in asthma (67). Andrius Januskevicius et al. have shown that eosinophils enhance the expression of Wnt5a, TGF-β1, fibronectin, and collagen genes in airway smooth muscle cells of asthmatic patients, suggesting Wnt5a may be involved in eosinophil-mediated airway remodeling (68). Studies have also confirmed that the expression of Wnt5a/JNK signaling pathway-related molecules in the lung tissues of asthmatic rats are enhanced, and the expressions of Wnt5a mRNA、p-JNK、p-c-Jun proteins are significantly increased, which may be related to the inflammatory response of bronchial asthma (69). Furthermore, studies on peripheral blood mononuclear lymphocytes of asthmatic patients have verified that Wnt5a, thymus, and activation-regulated chemokines, macrophage-derived chemokines and eosinophil activated chemokines 3 can be used as potential biomarkers for anti-IL-13 therapy (70). Liu Na's team found that, in the asthma group of mice, worsened subepithelial fibrosis was associated with increased TGF-β1 and Wnt5a compared with the control group, which may be related to airway remodeling in asthma (71). Xiaoshun Ai et al. have also proposed a diagnostic model of 10 macrophage-related genes, including Wnt5a, to predict asthma risk. The expression of Wnt5a in the control group was lower than that in the asthma group (72).

In conclusion, Wnt5a is associated with eosinophil effect, airway hyperresponsiveness, and airway remodeling in the pathogenesis of bronchial asthma, which can provide a new idea for the treatment of asthma.

4.3 Wnt5a and COPD

COPD is a preventable and treatable disease of airway inflammation characterized by continuous airflow limitation (73). Hoeke a. Baarsma et al. showed that the Wnt5a signaling pathway impaired endogenous pulmonary repair in COPD and the overexpression of pulmonary-specific Wnt5a in vivo experiments aggravated the air expansion of elastase-induced emphysema (74). Thus, a new and important mechanism of impaired mesenchymal-epithelial cross-linking has been identified for the treatment of COPD. Studies by Diana Feller's team have shown that Wnt5a and proinflammatory cytokines can be transported in lipid bilayer enclosed extracellular vesicles that can reach every organ in patients with COPD, indicating the underlying systemic mechanism of this disease and also the difficulty in controlling COPD (75). Additionally, studies have shown that inhibition of the Wnt5a/JNKl pathway by Sfrp5 can combat the inflammatory response in the rat model of insulin resistance combined with COPD, which may be a new target for the treatment of COPD (76). Recently, Xiuli Zhang et al. have shown that microRNA-149-3p can regulate the expression of Wnt5a, causing changes in the expression of alveolar inflammatory factors, and further affecting the development of COPD (77).

4.4 Wnt5a and tuberculosis

Tuberculosis, a pulmonary infectious inflammatory disease caused by Mycobacterium

tuberculosis, is one of the leading causes of infectious death in the world (78). The Wnt signaling pathway has been shown to play an immunoregulation role in a variety of inflammatory and infectious diseases, including tuberculosis. Blumenthal et al. found that Wnt5a and its putative receptor FZD5 exist in lung biopsies of tuberculosis patients. Mycobacterium induces the expression of macrophage Wnt5a in a TLR-NF-κB-dependent way, and Wnt5a has an immunoregulation function on immune cells (53). Junwei Cui et al. have shown that Wnt5a overexpression can reverse the effects of liver kinase B1 on the intracellular survival of mycobacterium and the release of inflammatory cytokines, and plays an important role in controlling mycobacterium and cellular inflammation (79). In addition to human and mouse cells, increased Wnt5a expression was observed in adult zebrafish infected with Mycobacterium saltwater, suggesting that Wnt5a induction after infection is a conserved mechanism (80). By activating innate immune cells, Wnt5a plays an important regulatory role in the host's response to Mycobacterium tuberculosis infection, thereby directly affecting the function of adaptive immune cells. Interestingly, however, Deming Chen's latest study reveals the opposite idea that Wnt5a is reduced in both humans and mice during Mycobacterium tuberculosis infection and the effect of Wnt5a reduction on Mycobacterium tuberculosis infection in mice and its biological significance. Wnt5a deficiency in Mycobacterium tuberculosis-infected macrophages regulates the secretion, polarization, and apoptosis of inflammatory cytokines, thereby shielding the macrophages themselves from multidrug-resistant tuberculosis infection (81).

Thus, the expression of Wnt5a in the pathogenesis of tuberculosis and its mechanism are still unclear, and further experimental studies are needed to verify.

4.5 Wnt5a and rheumatoid arthritis

Rheumatoid arthritis is a chronic autoimmune disease of unknown origin that is associated with inflammation of the joints and causes gradual destruction of articular cartilage and bone (82). The inflammatory response of the synovial membrane induces changes in macrophages and synovial fibroblasts derived from bone marrow cells, leading to the secretion and expression of various inflammatory mediators (83,84). For example, Sen et al. used Western-Blot analysis to show that the RNA levels of Wnt5a and FZD5 in synovial tissue of rheumatoid arthritis were increased compared with the normal adult control group. Results show that compared with the normal synovial fibroblasts, IL-6, IL-8, IL-15 expression level is higher in the cultured fibroblasts, rheumatoid arthritis synovial cells, and the expression pattern of cytokines was replicated in normal fibroblasts transfected with Wnt5a expression vector, suggesting that the Wnt5a/FZD5 signaling pathway in the synovial membrane of rheumatoid arthritis may be a new target for therapeutic intervention (85). By inhibiting the Wnt5a/FZD5 signaling pathway, the activation of fibroblasts in the rheumatoid synovial was inhibited, and the expression of IL-6, IL-15 and NF-κB ligand (RANKL) receptor activators in the cells were down-regulated, which further confirmed that Wnt5a participated in the inflammatory response in the pathogenesis of rheumatoid arthritis (86). Angela Rodriguez-Trillo et al. indicated that Wnt5a contributes to the enhanced migration and invasiveness of rheumatoid arthritis fibroblast-like synoviocytes through Ryk and the specific activation of Ras homolog gene family member A leads to Rho-Kinase and downstream kinases (87). Results from Dorra Elhaj Mahmoud's team showed that Wnt5a-induced inflammation was significantly activited in the presence of SFRP5, stimulating the expression of pro-inflammatory targets in tissue-derived fibroblast-like synoviocytes from patients with

rheumatoid arthritis (88).

4.6 Wnt5a and atherosclerosis

Atherosclerosis lesions are based on lipid deposition caused by lipid metabolism disorders, characterized by the fact that the lesion of the involved artery starts from the intimal layer and is the main cause of coronary heart disease, cerebral infarction, and peripheral vascular disease. In the late 20th century, Ross proposed that atherosclerosis is an inflammatory disease characterized by the aggregation of macrophages in the intima (89). Immunohistochemical analysis showed that Wnt5a was highly expressed in human and mouse atherosclerotic lesions, especially in the macrophage filling area, consistent with the expression of TLR-4 (90,91). The induction of Wnt5a may be related to oxidized low-density lipoprotein, which can stimulate

the expression of Wnt5a in human macrophages in vitro (92). Adipose tissue-derived Wnt5a regulates obesity vascular redox signaling through USP17/RAC1-mediated Nicotinamide adenine dinucleotide phosphate oxidase activation (93). Similarly, Malgor et al. found that Wnt5a, TLR-2, and TLR-4 were increased in advanced human atherosclerotic lesions (87). Besides, Wnt5a stimulates proliferating and calcifying endothelial cells, both of which are involved in the pathogenesis of atherosclerosis (94-97). Some research teams have found that the Wnt5a protein level is positively correlated with the calcification degree of smooth muscle cells, which is mediated by the Wnt5a/Ror2 signaling mechanism (97). Qin also showed that Wnt5a can reduce cholesterol accumulation by regulating the reverse transport of cholesterol in macrophages (98). Consistent with these in vitro results, silencing Wnt5a inhibits NF-ϰB and mitogen-activated protein kinase (MAPK) signaling pathways to attenuate atherosclerotic inflammation in vivo experiments in mice (99). Moreover, studies have shown that the Wnt5a level of serum in atherosclerosis patients is significantly higher than that in healthy people, and it is related to the severity of atherosclerosis (90,91). Moreover, Wnt5a has been verified to be involved in vascular calcification, which is a marker of advanced atherosclerosis and can be used as a biomarker to reflect the stages of atherosclerosis (96). Another major finding was that anti-Wnt5a therapy inhibited the development of atherosclerosis in mice of apolipoprotein e deficiency and reduced the expression of inflammatory cytokines (99). The results of Futao Zhang's team showed that Wnt5a was verified as the target of miR-141-3p in vascular smooth muscle cells in an In Vitro Model of Atherosclerosis. PcDNA3-Wnt5a partially reversed the action of miR-141-3p mimic in oxidized- stimulated low-density lipoprotein vascular smooth muscle cells (100). Sara Awan's team found that Wnt5a senses changes in dietary cholesterol supply and promotes lysosomal cholesterol export to the endoplasmic reticulum, thereby avoiding the formation of atherosclerosis through increasing lysosomal acid lipase expression, reducing the metabolic signal of mTORC1 kinase, and binding to Niemann–Pick C1 (NPC1) and NPC2 (101). Shi, Y et al. also fund that the Wnt5a/Ror2/PKC signaling pathway may be a potential and promising therapeutic target for the prevention and treatment of vascular proliferative diseases (102). Studies have shown that the dedicator of cytokinesis 9-AS2 promoted the proliferation and migration of vascular smooth muscle cells in atherosclerosis through regulating Wnt5a by targeting LIN28B (103).

These results indicate that Wnt5a is involved in the inflammatory response inatherogenesis and calcification, the level of Wnt5a in serum can reflect the severity and stage of atherosclerosis, it can also inhibit the inflammatory response of atherosclerotic plaque formation by regulating the expression of Wnt5a. Therefore, anti-Wnt5a targeted therapy may become a new therapy for atherosclerosis.

4.7 Wnt5a and psoriasis Vulgaris

Psoriasis Vulgaris is a chronic inflammatory skin disease that affects 1 to 3 percent of the population (104). The cellular response includes neutrophils, macrophages, dendritic cells, epidermal keratinocytes, and a group of T lymphocytes (105). Studies have shown that Wnt5a is significantly increased in psoriatic plaques (106,107). Similarly, Romanowska et al. reported that Wnt5a and FZD5 were overexpressed in human psoriasis skin lesions and redistributed in the psoriasis epidermis, which was related to the disorder of keratinocytes differentiation (108). Wnt5a functionally enhances the proinflammatory signaling pathway of interferon, it synergistically increases the expression of type 1 interferon target genes nedd8, ubiquitin-like protein, and amyloid precursor proteins by reducing the concentration of interferon required to induce these target genes in stimulated keratinocytes (108,109). Gene expression profiles of patients who responded to treatment without significant scarring, some genes associated with psoriasis, including Wnt5a, did not return to baseline after 3 months of treatment with etanercept, this indicates that even if the epidermal response to psoriasis is completely resolved, there is still an inflammatory gene consisting of a "residual disease gene" (110). Therefore, it is suggested that the histological resolution of psoriasis lesions should be accompanied by gene map analysis to prevent recurrence, which will provide some evidence for the clinical management of psoriasis. Xiaoying Ning's team found that Wnt5a was highly expressed in psoriasis lesions and was positively correlated with the severity of psoriasis, which may be one of the immunohistochemical predictors of the severity of psoriasis (111).

5. Prospect

This paper reviews Wnt5a and it signaling pathways, its relationship with inflammatory factors, and its role in the pathogenesis of inflammatory diseases. Wnt5a has a variety of signal transduction modes and signaling pathways in cells, and there are different cross-regulations in each signal transduction mode and signaling pathway. Wnt5a mainly induces cells to secrete inflammatory factors in proinflammatory process. But in a few cases, it also participates in process of inhibiting inflammation. Meanwhile, inflammatory factors can also react on Wnt5a to regulate its expression level, which maintains a whole regulatory balance. Therefore, Wnt5a plays a bothway role in the transduction of inflammatory signaling pathways and inflammatory diseases. Its specific function varies according to the type of the receptors or cells it binds to. Excessive activation and inhibition of the Wnt5a signaling pathway may lead to the occurrence of various inflammatory diseases. In this paper, the Wnt family and it signaling pathways, Wnt5a and its relationship with inflammatory factors were systematically demonstrated; the role of Wnt5a in inflammatory diseases such as sepsis, bronchial asthma, COPD, tuberculosis, rheumatoid arthritis, atherosclerosis, psoriasis Vulgare were also reviewed. According to the current research results, Wnt5a pathway is a potential candidate target for therapeutic intervention in inflammatory diseases. For example, COX-2 prevents the production of inflammatory prostaglandins to achieve anti-inflammatory, analgesic and antipyretic effects; inhibiting Wnt5a/JNKl pathway to reduce inflammation in patients with chronic obstructive pulmonary disease through Sfrp5; blocking of Wnt5a/ FZD5 signaling pathway to treat rheumatoid arthritis; Upregulation of miR-23a-3p may alleviate LPS-induced cell injury by targeting wnt5a and inactivating Wnt/β-catenin pathway, which may serve as a novel therapeutic target for sepsis-associated acute kidney injury; Genetic analysis of patients with psoriasis Vulgaris has a very positive effect on the prevention and treatment of relapse and strengthening clinical management. Thus, further studies on the specific receptors Wnt5a bounded and specific signaling pathways involved are needed to find new targets for the treatment of related diseases, which may be helpful to the clinical treatment and prevention.

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Conflicts of Interest

The authors declare no potential competing interests with respect to the research, authorship, and/or publication of this article.

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