Journal of Carcinogenesis
Covering Genesis to Therapeutics
Journal of Carcinogenesis ISSN: 1477-3163
2025; Vol 24: Issue 10s, https://carcinogenesis.com/

CLINICAL IMPLICATIONS OF WNT5A: A MULTIFACETED PLAYER IN CELLULAR SIGNALING AND IMMUNE REGULATION

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ABSTRACT

Wnt proteins, a family of highly modified cysteine-rich proteins, play vital roles in embryonic development and tissue homeostasis. This review focuses on Wnt5a, a classical non-canonical Wnt ligand, and its diverse functions in various cellular processes and diseases. Emphasizing its association with the NF-κB pathway, the review explores Wnt5a's impact on immune cells, atherosclerosis, rheumatoid arthritis, psoriasis vulgaris, and sepsis. Wnt5a regulates convergent extension, planar cell polarity, and epithelial-mesenchymal interactions during embryonic development and is implicated in pathological conditions, especially cancer. Its dysregulation is linked to the onset and progression of various diseases. The review details Wnt5a's involvement in signaling cascades and its interaction with receptors, such as ROR1 and 2, Ryk receptor tyrosine kinase, and Frizzled 7-transmembrane receptors. It also discusses Wnt5a expression regulation, emphasizing its upregulation in response to stimuli like pathogens and cytokines, and its role in inducing pro-inflammatory cytokines, linking it to inflammatory disorders' pathogenesis. The review delves into Wnt5a's impact on immune cells, its regulatory effect on dendritic cells, and its influence on macrophage polarization. It addresses Wnt5a's potential as a therapeutic target in inflammatory conditions and cancer. In summary, this comprehensive review provides insights into Wnt5a's multifaceted roles in signaling pathways, immune regulation, and disease pathogenesis, highlighting its potential as a therapeutic target.

1. INTRODUCTION

Wnt proteins form an extensive group of cysteine-rich and significantly modified proteins that play a vital role in embryogenesis and adult tissue equilibrium, controlling polarity, cell division and differentiation, adhesion, and movement. Being extracellular ligands, they bind to various receptors such as Frizzled (FZD) 7-transmembrane domain receptors, low-density lipoprotein-related proteins (LRP5 and LRP6), receptor tyrosine kinase-like orphan receptors (ROR1 and 2), and receptor tyrosine kinase-related molecules (RYK). The interaction of Wnt with its receptors induces phosphorylation and activation of Dishevelled (Dvl) cytoplasmic phosphoprotein [1,2]. At this level, Wnt signaling divides into branches: a canonical or Wnt/β-catenin-dependent pathway and several non-canonical or β-catenin-independent pathways. The β-catenin-dependent pathway is primarily activated by Wnt1, Wnt3a, or Wnt8 and has been extensively studied. In summary, Wnts binding to their receptors, primarily LRP and FZD, results in the suppression of the β-catenin destruction complex, leading to β-catenin accumulation and nuclear migration, which subsequently enhances transcription by transcription factors from TCF/LEF family (T cell factor/lymphoid enhancing factor) [3-5]. Conversely, in non-canonical pathways a broad range of intracellular proteins are activated in response to Wnts like Wnt4, Wnt5a, or Wnt11, as will be described below. The β-catenin-independent pathways are less explored, and some factors remain unclear, for example, what regulates the activation of one pathway over the others or the extent of overlap between them. Also unclear is why certain Wnts can trigger different signaling pathways and govern various aspects of cell functions in different systems [6-8]. Indeed, the investigations have been complicated by the large number of involved genes and the diversity of receptors. In mammals, 10 FZD genes and 19 Wnt genes have been described, along with an unusually high number of extracellular regulators, among them Wnt inhibitory factor 1 (WIF1), secreted frizzled-related proteins (sFRP, five genes), and Dickkopf (Dkk, four genes). The situation is further exacerbated by considerable diversity of Wnt ligands and frizzled receptors. These and other findings have led to the understanding that the capacity to activate a specific non-canonical pathway and exert a particular biological effect depends not only on the Wnt ligand but also on the array of receptors and modulators in the cellular expression [9,10]. It means that Wnt signaling is closely dependent on the cellular type and context, and caution must be exercised when generalizing findings from a specific system. This review concentrates on Wnt5a and its newly identified

immunoregulatory role in cancer, including recent findings on the activation of NF-κB by Wnt5a and the impacts of abnormal Wnt5a expression on the tumor microenvironment [11].

2. THE WNT5A SIGNALING PATHWAY

Much of our understanding of non-canonical pathways comes from Wnt5a research, making it the classical non-canonical Wnt ligand. Wnt5a is an evolutionarily conserved Wnt member crucial for regulation of developmental pathways in embryogenesis and maintenance of post-natal homeostasis. In embryonic organogenesis, Wnt5a is a key regulator of convergent extension, planar cell polarity (PCP), and epithelial-mesenchymal interactions (EMI). By modulating the Wnt/Calcium pathway and the PCP pathway, Wnt5a mediates significant cytoskeletal reshaping, including the initiation of lamellipodia and filopodia and the repositioning of the microtubule-organizing center, which are vital for polarized cell movement [12,13]. Beyond its essential role in embryogenesis, Wnt5a deregulation has been linked to several pathological conditions, most notably cancer. Research using cells from adult subjects has shown that Wnt5a can activate numerous signaling pathways beyond those identified in embryonic cells. It has been determined that Wnt5a can signal via a variety of different receptors, including ROR1 and 2, Ryk receptor tyrosine kinase, and Frizzled 7-transmembrane receptors, and can mobilize and induce Dvl, the key protein of the signalosome complex, and other proteins, e.g., of casein kinase I family [14,15]. This interaction activates various pathways, including protein kinase A and C, Src, c-Jun N-terminal kinase, Cdc42, Rho and its subfamily Rac, Akt, CAMKII, calcineurin, phosphodiesterase, and phospholipase C, leading to both transcriptional (by activating transcription factors like ATF2, c-Jun, and NFAT) and non-transcriptional reactions to Wnt5a stimulation. Additionally, Wnt5a has been shown to impact the canonical pathway. Typically, Wnt5a inhibits β-catenin target gene expression, however, β-catenin activation has also been observed [16].

3. REGULATION OF WNT5A EXPRESSION

Reflecting its significant role during embryogenesis, Wnt5a is abundantly expressed in various embryonic organs and tissues. While its expression generally diminishes in adult tissues, in adult organs this pathway has been demonstrated to control tissue maintenance and self-renewal of stem cells. Notably, deregulation of Wnt5a signaling, often caused by the increased expression of Wnt5a, has been linked to the onset of various pathologies in humans, including cancer, fibrosis, metabolic conditions, and inflammations [17,18]. Consequently, there is considerable attention to the mechanisms and environments leading to Wnt5a upregulation. It has been clearly shown that Wnt5a expression grows in immune cells upon exposure to pathogens and conserved bacterial structures such as lipoteichoic acid or lipopolysaccharides. Additionally, Wnt5a expression is stimulated in immune and non-immune cells by certain cytokines, including tumor necrosis factor alpha, interferon-γ, interleukin1β, and interleukin-6. This increased expression can be inhibited by prior incubation with either NF-κB or STAT3 transcription factor, which seems to indicate that these pathways are involved in Wnt5a transcription [19,20].

Conversely, cancer cells behave quite differently as they independently increase Wnt5a levels without external stimuli. Wnt5a has long been known to be excessively expressed in various tumors in contrast with the corresponding healthy tissues. The increase in Wnt5a levels in human malignant tumors is not associated with either gene rearrangement or gene amplification, but is probably a result of gene expression reprogramming that develops due to the major genetic and epigenetic changes characteristic of cell transformation. Expression of Wnt5a typically intensifies together with the tumor growth and even more so in tumors that acquire resistance to BRAF-targeted treatment. Thus, Wnt5a upregulation is not merely a byproduct of the transformation process, but a significant driver of cancer development [21,22].

4. WNT5A AND INFLAMMATION

Wnt5a levels are elevated after mycobacterial infection and, after coupling with its receptor Frizzled-5, Wnt5a modulates the inflammatory reaction of microbial interleukin-12 in mononuclear cells in humans. Valencia and colleagues also demonstrated that knocking down the Wnt5a gene considerably reduces the expression of interleukin-12 in mature dendritic cells. Furthermore, Wnt5a is increased in macrophages activated by endotoxin (LPS) and provokes in them the expression of pro-inflammatory cytokines, including interleukins1β, 6, and 8, and macrophage inflammatory protein-1β (MIP-1β) [23,24]. Besides the ability of upregulated Wnt5a to boost the expression of pro-inflammatory cytokines, the stimulation of melanoma cells with interleukin-6 also triggers Wnt5a excessive expression in a dose-related fashion. Additionally, supporting the regulating impact of inflammatory cytokines on Wnt5a expression, Rauner and colleagues found that upon stimulation with tumor necrosis factor alpha, Wnt5a expression is significantly higher in bone marrow stromal cells in humans [25-27]. These findings indicate the existence of interaction between Wnt signaling and inflammatory pathways, consequently connecting inflammation and metabolic regulatory pathways in inflammatory disorders. Moreover, cytokine-mediated association of Wnt signaling and pro-inflammatory pathways means that Wnt5a can potentially be used to predict or diagnose inflammatory disorders [26,28].

Quite a few researchers have explored the function of Wnt non-canonical signaling in the inflammatory reaction. Kim and colleagues found that Wnt5a triggers inflammatory responses by activating NF-κB signaling and upregulating cytokines such as interleukins -1α and 3 in cultured endothelial cells. Processing of endothelial cells with a protein kinase C inhibitor or a calcium chelating agent blocks inflammatory reactions activated by Wnt5a, indicating that the Wnt/Calcium non-canonical signaling pathway governs Wnt5a-induced inflammation in these cells. Additionally, it has been shown that Wnt5a enhances melanoma cells intrusion and aggressiveness that was independent of nuclear translocation or β-catenin overexpression and regulated by the induction of the protein kinase C signaling pathway [8,29]. Catalan and colleagues reported that the induction of non-canonical Wnt signaling via Wnt5a stimulates inflammatory responses in the visceral adipose tissue (VAT) of obese individuals, which further proves the pro-inflammatory signaling role of the non-canonical Wnt pathway [30]. Likewise, it was shown that non-canonical Wnt signaling mediated by Wnt5a enhances VAT inflammation by stimulating the macrophage expression of pro-inflammatory cytokines in a JNK-dependent fashion. In conclusion, the pro-inflammatory signaling function of Wnt5a is complicated, and additional research is necessary to elucidate its pathological role in inflammatory disorders [31,32].

Over the past few decades, Wnt5a has been linked to various inflammatory disorders, such as sepsis, atherosclerosis, plaque-like psoriasis, and rheumatoid arthritis. Supporting its pro-inflammatory signaling functions, the Wnt5a pathway has been proposed as a promising target for medical treatment in inflammatory conditions. Below, the impact of Wnt5a will be reviewed in the development of these inflammatory disorders [33].

5. THE NF-KB PATHWAY

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a family of transcription factor protein complexes composed of Rel proteins including c-Rel, RelA (or p65), and RelB, as well as NF-κB1 (or p105 to p50), and NF-κB2 (or p100 to p52). All of them share an N-terminal Rel homology domain crucial for dimerization and DNA binding [34-36]. Stimulation of these transcription factors causes significant gene transcription of proteins that govern immune response, cellular survival and apoptosis. In unstimulated cells, NF-κB is sequestered in the cytoplasm by IκB inhibitor proteins. Three distinct mechanisms for NF-κB activation have been identified. In the canonical pathway, tumor necrosis factor-alpha or interleukin-1β cause the recruitment of TNF receptor-associated factor 2 and receptor-interacting protein kinase 1 to the membrane, resulting in the IκB kinase complex assembly and phosphorylation [37,38]. This complex, consisting of NEMO (NF-κB essential regulator or IKKgamma), IKKalpha, and IKKbeta, facilitates nuclear translocation of the p50/p65 heterodimer, IκBα phosphorylation and degradation, and processing of p105 precursor to generate p50. The non-canonical pathway is activated by different ligands, such as RANKL or CD40. They stimulate the recruitment of TNF receptor-associated factor to the membrane and consequent triggering of NF-κB inducing kinase, which leads to IKKalpha phosphorylation [39,40]. This, in turn, causes p100 phosphorylation, ubiquitination, and partial proteolysis to p52 followed by binding with RelB. The resulting RelB/p52 dimers migrate to the nucleus. An alternative NF-κB activation route, where casein kinase 2 promotes IκBα phosphorylation and degradation, is triggered by external stimuli, like genotoxic stress and ultraviolet radiation. Regardless of the activation mechanism, NF-κB activation leads to substantial gene expression modifications [41-43].

6. THE ACTIVATION OF NF-KB BY WNT5A

Wnt5a-dependent activation of NF-κB signaling has been documented for a variety of healthy cells, such as macrophages, monocytes, endothelial cells, fetal lung fibroblasts, granulosa cells, carotid cells, bone marrow stromal cells, dental pulp cells, and chondroprogenitor cells. The researchers identified the NF-κB activation by various processes, such as enhanced cytokine synthesis, phosphorylation of p65 and IkB kinase, p65 migration, or elevated NF-κB-dependent luciferase activity. In more complicated environments, Wnt5a has been demonstrated to mitigate NF-κB activation provoked by other pathways [44]. In 2018, Wnt5a-dependent activation of NF-κB was reported for cancer cells. Lee and colleagues demonstrated that the BAY11-7082 (IkB kinase inhibitor) completely suppressed Wnt5a-mediated BMP-6 mRNA elevated levels in LNCaP cells [45]. Additionally, Han et al. reported that Wnt5a is involved in NF-κB transcriptional initiation and MMP7 upregulation caused by Forkhead box C1 excessive expression in breast cancer cells [46].

7. REGULATION OF IMMUNE CELLS BY WNT5A

Because our immune system is adept at eliminating cancer, one of the more formidable challenges for tumor cells is evading immune detection. To achieve this, they initially attract immune cells to the tumor microenvironment and then co-opt their functions by altering the balance between suppressor and effector cells, activating inhibitory pathways, and suppressing traditional cytotoxic and phagocytic immune activities [47]. Part of the immune cells mediated by Wnt5a is professional and most effective antigen-presenting dendritic cells (DCs). They are crucial for initiating and regulating cytotoxic T lymphocyte reaction against tumors, and their impaired function significantly compromises anti-tumor immune reaction and the effectiveness of immunotherapy [48]. It has been repeatedly demonstrated that Wnt5a exerst a negative regulatory

effect on DC function. Oderup and colleagues found that Wnt5a stimulates interleukin-10 secretion and facilitates a tolerogenic DC phenotype that fosters the formation of FOXP3-positive regulatory T (Treg) cells, a specialized T cells subset which inhibits immune responses [49]. Addressing the same matter, Valencia and colleagues focused on the Wnt5a impact during human DCs differentiation from monocytes [50]. They found that Wnt5a, when added during monocyte development, stimulates the production of TNFα and interleukins 6 and 10, leading to DCs with reduced antigen presentation capability and impaired ability to T cell-mediated killing—an effect mediated by NF-κB activation and calcium-dependent non-canonical signaling. Likewise, Zhou and colleagues reported how upregulation of forkhead box transcription factor M1 inhibits DC function and maturation via the Wnt5a signaling pathway in colorectal and pancreatic cancer [51]. Moreover, Wnt5a derived from melanoma cells was found to reprogram local dendritic cells by increasing the activity and expression of indoleamine 2,3-dioxygenase-1 and inhibiting interleukins 6 and 12. This results in the differentiation of regulatory T cells and the suppression of tumor immunosurveillance. It was also demonstrated that Wnt5a pathway suppression by shRNA against either Wnt5a or PORCN (an O-acyl transferase essential for Wnt secretion) arrested cancer progression in murine models [52]. Suppression of Wnt5a signaling via shRNA increased PD-L1 levels in tumor tissues, thereby increasing the efficacy of both anti-CTLA-4 and anti-PD-1 antibody-based immunotherapy. Consistent with the proposed role of Wnt5a in regulating dendritic cells and T cells, tumors with PORCN knockdown exhibited higher numbers of infiltrating CD8+ T cells. Similarly, in a model using a PORCN suppressor, increased CD8+ T cell activation and an expanded population of tumor antigen-specific CD8+ T cells were observed amid infiltrating cells. Notably, it was demonstrated that Wnt5a acted as a facilitator of these events through activation of the β-catenin signaling pathway. One possible explanation for this unconventional signaling could be the total absence of ROR1 receptor expression in DCs [53,54].

Wnt5a signaling plays a crucial role in almost all aspects of macrophage differentiation and functioning. Macrophages are a pivotal component of the tumor microenvironment, influencing various facets of antitumor immune responses. Wnt5a was demonstrated to stimulate macrophage activation and chemotaxis through JNK- and NF-κB-dependent pathways. Additionally, Wnt5a-transfected conditioned cell culture media from gastric cancer cells induced macrophage chemotaxis and cytoskeletal modifications via monocyte chemoattractant protein-1 (MCP-1/CCL2) [55,56]. A similar Wnt5a impact was observed in human neutrophils. In reaction to microenvironmental cues, macrophages can change their phenotype, which affects their function. Macrophages polarize into classically activated M1macrophages and alternatively activated M2 macrophages. M1 type secretes pro-inflammatory cytokines and is crucial for effective immune responses against infections and tumors. In contrast, M2 type secretes anti-inflammatory cytokines and also supports tumor progression and suppression of the immune system. Wnt5a was demonstrated to foster polarization of M2 macrophages, a process implicated in kidney fibrosis. It was also found that Wnt5a inhibited M1 polarization but did not affect M2 polarization, resulting in an M2-like phenotype characterized by immunosuppressive traits linked molecularly to IL-10 induction [57,58]. Another publication substantiated that Wnt5a facilitates M2 polarization and established that its impact is mediated through IL-10, as evidenced by its blockade with neutralization of IL-10 antibodies [59]. Within tumors, infiltrating M2 macrophages form the subset known as tumor-associated macrophages (TAMs), which are indicative of poor prognosis and promote tumor growth. TAMs suppress inflammatory reactions and hinder the function and generation of antitumor T lymphocytes, thereby fostering tumor tolerance. Liu et al. demonstrated high expression of Wnt5a in TAMs within the tumor stroma of colon cancer [60]. These Wnt5a+ TAMs stimulate CCL2 secretion, thus supporting tumor cell proliferation and relocation, as well as macrophage infiltration. These findings were corroborated in a tumor model using Wnt5a knockout mice. The study revealed that these animals exhibited reduced expression of CCL1, 2 and 12, as well as CXCL10 and 12, along with higher levels of INFγ protein as opposed to the control tumor group. Furthermore, tumors developed in Wnt5a knockout animals showed higher cytotoxic T cells and M1 macrophages, and reduced M2 macrophages, evidencing that host Wnt5a facilitates an immunosuppressive microenvironment [61].

Consistent with the aforementioned studies, another investigation examined the impact of inhibiting Wnt5a using a decoy protein and its synergy with immunogenic cell death induced by doxorubicin. This research revealed that mice treated with the Wnt5a inhibitor exhibited elevated levels of TNFα, IL-12α, and IFN-γ, indicative of a shift from a Th-2 toTh-1 phenotype in the immunostimulatory tumor microenvironment. Correspondingly, the treated mice demonstrated increased numbers and a restored function of dendritic cells, improved activation and infiltration of effector T cells, and decreased presence of immunosuppressive myeloid-derived suppressor cells, M2 type macrophages, and PD-L1-expressing cells. Furthermore, after a period of over two months, a significant rise in memory CD4+ T cells was observed within both the tumor microenvironment and in lymph nodes, while splenic CD4 cells exhibited enhanced proliferation in Wnt5a trap-treated mice, demonstrating the development of memory CD4 immune responses [62,63].

8. WNT5A IN ATHEROSCLEROSIS

Atherosclerosis (ASVD), a common inflammatory condition, stands as a significant risk factor for cardiovascular diseases. The condition is characterized by atherosclerotic plaques forming within the walls of large- and medium-sized arteries causing their hardening and narrowing as a result of gradual buildup of macrophages, cellular waste products, fatty substances, and calcium [64,65]. Upon rupture of these plaques, blood supply to various organs decreases, resulting in conditions like stroke, heart attack, and peripheral artery disease. Wnt5a shows high expression in areas rich in macrophages within atherosclerotic plaques in mice and humans, and this expression coincides with the presence of inflammatory Toll-like receptor-4 (TLR-4) [66]. Likewise, Malgor and colleagues demonstrated elevated expression of Wnt5a, TLR-2, and TLR-4 in lesions of patients with advanced ASVD [67]. Additionally, Wnt5a promotes endothelial cell proliferation and calcification, both processes linked with the development of ASVD. Similarly, Xin and colleagues observed a direct correlation between Wnt5a levels and the degree of calcification in smooth muscle cells (SMC), facilitated by the Wnt5a/Ror-2 signaling pathway [68]. Further supporting Wnt5a participation in atherosclerotic plaque development, Qin and colleagues demonstrated that Wnt5a decreases cholesterol accumulation by modulating reverse cholesterol transport in macrophages and vascular SMC [69]. In line with these laboratory findings, silencing Wnt5a using siRNA has been shown to mitigate inflammatory responses in vivo during atherosclerosis by suppressing the NF-κB and mitogen-activated protein kinase signaling pathways. These findings strongly indicate that Wnt5a influences inflammatory processes at various stages of atherosclerotic plaque formation, underscoring the potential clinical relevance of targeting Wnt5a in ASVD management.

9. WNT5A IN RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder of unknown origin characterized by joint inflammation that results in progressive degradation of joint tissue lining and bone. Although the exact cause of RA remains unidentified, it has commonly been assumed that hereditary disposition and environmental conditions contribute to its onset. Several studies have implicated Wnt5a in the development of RA [70]. For example, Sen and colleagues with the help of Northern blotting demonstrated elevated RNA levels of Wnt5a and Frizzled-5 in RA synovial tissues as against normal adult synovial tissues [71]. Additionally, the study revealed that RA fibroblast-like synoviocytes cultured from synovial tissue express higher levels of interleukins 6, 8, and 15 compared to normal synovial tissue, and this expression pattern of the cytokines was reproduced in normal fibroblasts upon introduction of a Wnt5a expression vector. These findings propose that Wnt5a/Fzd5 signaling in the synovial membrane of RA patients could represent a novel target for medical intervention [72]. Supporting this notion, inhibition of Wnt5A/Fzd5 signaling with Wnt5a antisense and antibodies to Frizzled-5 was shown to hinder the activation of RA synovial fibroblasts and decrease the expression of IL-6 and IL-15 cytokines, and receptor activator of nuclear factor-kappa B ligand in these cells. At the same time, the research also highlighted that the significance of Fzd5 might be exaggerated because of a potential non-specific blockade of other frizzled receptors by the antiserums described. These findings demonstrate the significance of receptor antagonists targeting Wnt5A/Fzd5 signaling pathways in RA development [73].

10. WNT5A IN PSORIASIS VULGARIS

Psoriasis vulgaris is a chronic inflammatory skin condition that afflicts approximately 1 to 3 per cent of people. It is impossible to predict the continuance and intensity of psoriasis which involves responses from various types of white blood cells, including subsets of T lymphocytes, immune cells, and epidermal cells. Studies have demonstrated a considerable rise in Wnt5a expression in psoriatic plaques [74,75]. Romanowska and colleagues noted over-expression of Wnt5a and Fzd5 in psoriatic plaques in humans, where they redistributed within the epidermis, affecting keratinocyte differentiation [76]. The function of Wnt5a is to enhance the pro-inflammatory interferon (IFN) signaling and synergetically boost the expression of type 1 IFN target genes, such as amyloid-beta precursor protein and the ubiquitin-like protein nedd8, thereby reducing the IFN concentration needed to induce these genes in activated keratinocytes. Gene expression analysis in subjects who had undergone etanercept therapy for three months and got rid of visible scarring revealed that certain psoriasis-related genes, Wnt5a among them, were still above the baseline. This assumes that despite complete epidermal resolution of psoriatic lesions, there persists a "residual disease genomic profile" characterized by elevated expression of pro-inflammatory genes like Wnt5a in treated plaques. Therefore, it is recommended to combine histological analysis of cleared psoriatic skin lesions with gene expression profiling to prevent the disease relapse and enhance clinical management of psoriasis [76].

11. WNT5A IN SEPSIS

Sepsis is a serious and life-threatening condition marked by inflammation, which occurs as the body’s extreme response to infection leading to disseminated intravascular coagulation and circulatory shock. Sepsis is often accompanied by multiple organ dysfunction syndrome contributing to a high morbidity and death rate among subjects in the intensive care unit (ICU).

The impact of Wnt5a in sepsis has been explored in several studies that have proved its increased levels in septic patients [77,78]. For example, Schulte et al. demonstrated that the serum concentration of Wnt5a in septic subjects upon their transfer to the ICU correlates with the condition severity and shows direct association with the condition improvement or worsening [79]. Pereira et al. documented elevated Wnt5a levels in the sera and bone marrow-derived macrophages of septic subjects, highlighting the crucial role of the inflammatory Wnt5a/Fzd5/calmodulin kinase II signaling axis in macrophage induction during inflammation [80]. They further detected that recombinant Wnt5a triggers the discharge of pro-inflammatory cytokines such as MIP-1β, interleukins 1β, 6 and 8 in macrophages, an effect mitigated by pretreatment with Activated Protein C (APC). APC was previously used in severe sepsis therapy, but was discontinued due to its failure to reduce mortality in a clinical study. In another investigation, Bergenfelz et al. demonstrated that in inflammation-provoking conditions, Wnt5a triggers immunosuppressive macrophages resembling those observed in reprogrammed monocytes in septic subjects [81]. They also noted that the feedback inhibition stimulated by Wnt5a correlates with IL-10 induction and suppression of the classical TLR4-NF-κB signaling pathway in macrophages, particularly in subjects with sepsis initiated by LPS, endotoxin of gram-negative bacteria.

Table 1. Implication of Wnt5a in various diseases

Disease/Condition	Role of Wnt5a	Involved Receptors	Signaling Pathways Activated	Effects on Immune Cells	Therapeutic Implications
Cancer	Dysregulation linked to tumor progression and microenvironment.	ROR1, ROR2, Frizzled receptors	NF-κB, JNK, non-canonical Wnt signaling	Alters dendritic cell function; promotes M2 macrophage polarization.	Targeting Wnt5a may enhance immunotherapy effectiveness.
Atherosclerosis	High expression in plaques; promotes endothelial proliferation and calcification.	Frizzled-5, Ryk, TLR-4	NF-κB, Wnt/Ca^{2+} pathway	Modulates macrophage inflammatory response.	Targeting Wnt5a signaling may mitigate plaque formation.
Rheumatoid Arthritis	Elevated levels in synovial tissues; promotes inflammation.	Frizzled-5	NF-κB, MAPK pathways	Enhances cytokine production (IL-6, IL-15) in fibroblasts.	Blocking Wnt5a may reduce inflammation in synovial tissues.
Psoriasis Vulgaris	Increased expression in psoriatic plaques; enhances pro-inflammatory signaling.	Frizzled receptors	Wnt/β-catenin, NF-κB, STAT3 pathways	Affects keratinocyte differentiation and immune response.	Combination therapies targeting Wnt5a may prevent relapse.
Sepsis	Correlated with severity; promotes pro-inflammatory cytokine release.	Frizzled-5, ROR2	NF-κB, IL-10 signaling	Induces immunosuppressive macrophage phenotype.	Targeting Wnt5a may restore immune function in sepsis.
Inflammatory Disorders	Elevated levels during inflammation; links to NF-κB signaling.	ROR1, Ryk, Frizzled receptors	NF-κB, JNK, potential crosstalk with other pathways	Influences dendritic cell maturation and T cell response.	Wnt5a as a prognostic marker and therapeutic target in diseases.

CONCLUSION

In conclusion, the diverse functions of Wnt5a in cellular processes, immune regulation, and disease pathogenesis underscore its significance as a pivotal player in various physiological and pathological conditions. The intricate involvement of Wnt5a in signaling cascades, epithelial-mesenchymal interactions, and its regulatory impact on immune

cells illuminates its potential as a therapeutic target in diseases such as cancer, inflammatory disorders, and atherosclerosis. Understanding Wnt5a's complex role in modulating the NF-κB pathway, its crosstalk with multiple receptors, and its regulatory effects on immune cells provides valuable insights for developing targeted therapeutic interventions. Moreover, the dysregulation of Wnt5a in disease states emphasizes the need for further research to decipher its precise mechanisms of action and to explore its potential as a prognostic and diagnostic marker. Moving forward, elucidating the intricate mechanisms underlying Wnt5a's functions will be crucial for harnessing its therapeutic potential and developing innovative treatment strategies for a broad spectrum of diseases. Additionally, the exploration of Wnt5a-based therapeutic interventions holds promise for addressing unmet clinical needs in conditions characterized by dysregulated immune responses and aberrant cellular signaling. In essence, this review underscores the importance of continued research into the multifaceted roles of Wnt5a, paving the way for novel therapeutic approaches and personalized medicine strategies aimed at targeting Wnt5a-associated pathways in various disease conditions.

Author Contributions: Writing—original draft preparation, A.V.P.; writing—review and editing, V.N.S., T.V.K., T.I.K., I.A.S., D.F.B., A.N.O, A.V.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Russian Science Foundation, grant number 22-15-00134

Conflicts of Interest: The authors declare no conflict of interest.

Ethics Approval: Not applicable.

Consent to Participate: Not applicable.

Consent to Publish: Not applicable.

Data Availability Statement: Not applicable.

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