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Chapter

Wnt Signaling Regulates Macrophage Mediated Immune Response to Pathogens

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Abstract

Infection with pathogenic microbes is a global threat. Macrophages play a fundamental role in promoting host resistance to deadly infections from pathogenic microbes by virtue of a well-orchestrated immune defense system. Phagocytosis and obliteration of invading pathogens by macrophages are an innate immune function that not only sustains immune homeostasis but also bolsters adaptive immune response through antigen processing and presentation. Wnt signaling, where Wnt, a secreted glycoprotein which interacts with Frizzled and ROR cell surface receptors to initiate cellular interactions, could be vital for the immune response executed and propagated by macrophages in both innate and adaptive immune responses. The goal of this chapter is to describe how Wnt signaling influences phagocytosis, autophagy, and transcriptional activation to enable the macrophage to exercise its immune response program to resist infection.

Keywords: macrophage, Wnt, phagocytosis, actin cytoskeleton, transcription, immunity

1. Introduction

1.1 Macrophages: innate and adaptive immunity

Macrophages are present as crucial members of a multitude of specialized cells that fortify our immune system by fighting against infection caused by pathogens [1]. Macrophages differentiate from tissue-infiltrated circulating monocytes, which originate from bone marrow resident myeloid precursors [2, 3]. All tissue macrophages, however, do not originate from monocytes. Although some macrophage origins have been studied carefully, the detailed molecular mechanisms toward the differentiation of different macrophage types remain mostly uncharacterized [4–7]. Irrespective of their origin, most macrophages eliminate encountered pathogens through phagocytosis (element of innate immunity) and additionally present the foreign antigens derived from pathogens via major histocompatibility complex (MHC) molecules to lymphocytes leading to lymphocyte activation (element of adaptive immunity) [2, 8]. Cytoskeletal modulations and transcriptional activation programs intrinsically associated with macrophage-mediated immune functions (e.g. phagocytosis, autophagy/xenophagy) conform to the in-built maneuvering of macrophages as they confront with different kinds of pathogens. Several lines of

evidence substantiate that Wnt signaling is important for the transcriptional programs and cytoskeletal modulations inherent to macrophages during immune surveillance and response to different kinds of infection [9–13].

1.2 Wnt signaling

Wnt signaling is an integral theme of tissue/organ morphogenesis, repair, and maintenance. Thus, it is not surprising that this central premise of life is also an important component of macrophage function [9–16]. Wnts constitute a large family of secreted glycoprotein ligands, which bind to Frizzled and/or ROR cell surface receptors during various phases of tissue and organ development, morphogenesis, and homeostasis. Frizzleds are seven transmembrane-spanning receptors bearing homology to heterotrimeric G protein-coupled receptors, and RORs bear homology to tyrosine kinase receptors [17–20]. Based on the gene database, there are about 19 Wnt ligands and about 12 and 2 Frizzled and ROR receptors, respectively [21, 22]. Whether all these gene products are expressed and functional in our system in different cellular contexts is unclear at this stage. Although there is evidence of co-receptor function by the ROR subtype receptors during Wnt-Frizzled signaling [22, 23], the degrees of coordination between the Frizzled and ROR receptors under different physiological conditions are yet to be characterized at the molecular level. Given the considerable homology among the respective members of the Wnt and Frizzled families, any one Wnt ligand may interact with multiple Frizzled receptors. Thus, the outcome of Wnt-Frizzled signaling in a particular cell type under a certain condition could be dependent precisely on the existing profile of Wnt-Frizzled stoichiometry [20].

Wnt signaling is broadly classified into two types—canonical or β-catenin-dependant and noncanonical or β-catenin-independent (**Figure 1**). The transcriptional coactivator β-catenin promotes gene expression by LEF/TCF family transcription factors in response to canonical Wnt signaling, and transcriptional activators such as NFκB, NFAT, and AP1 are associated with noncanonical Wnt signaling. Even though the ligands Wnt3A and Wnt5A are mostly considered as representatives of the canonical and noncanonical modes of Wnt signaling, respectively [21, 24], the mode of signaling is in reality governed by the receptor(s) receiving the Wnt signal as mentioned above and the associated adaptor molecule(s) transmitting it. Thus, some level of crosstalk between the two modes of signaling would not be uncommon. Interestingly, the intracellular adaptor molecule Disheveled acts as a mediator of both β-catenin-dependant and β-catenin-independent Wnt signaling. Heterotrimeric G proteins, which have been reported to couple with Frizzled receptors, add to the complexity of Wnt signaling [18, 25]. Whether heterotrimeric G proteins cooperate with Disheveled during canonical and noncanonical Wnt signaling is not known clearly. Although there is some evidence of the involvement of lipid molecules such as cholesterol in switching Disheveled between the canonical and noncanonical modes of Wnt signaling [25], the molecular details of such presumed conformational switches remain largely undefined. The reason behind the preference of cell surface coactivator receptors such as lipoprotein receptor-like protein (LRP) 5/6 for the canonical mode of Wnt signaling as opposed to the noncanonical mode also remains unclear (**Figure 1**).

1.3 Wnt signaling in immune system

Given that host cytoskeletal rearrangements encompassing phagocytosis and autophagy/xenophagy and transcriptional regulation of immune defense genes

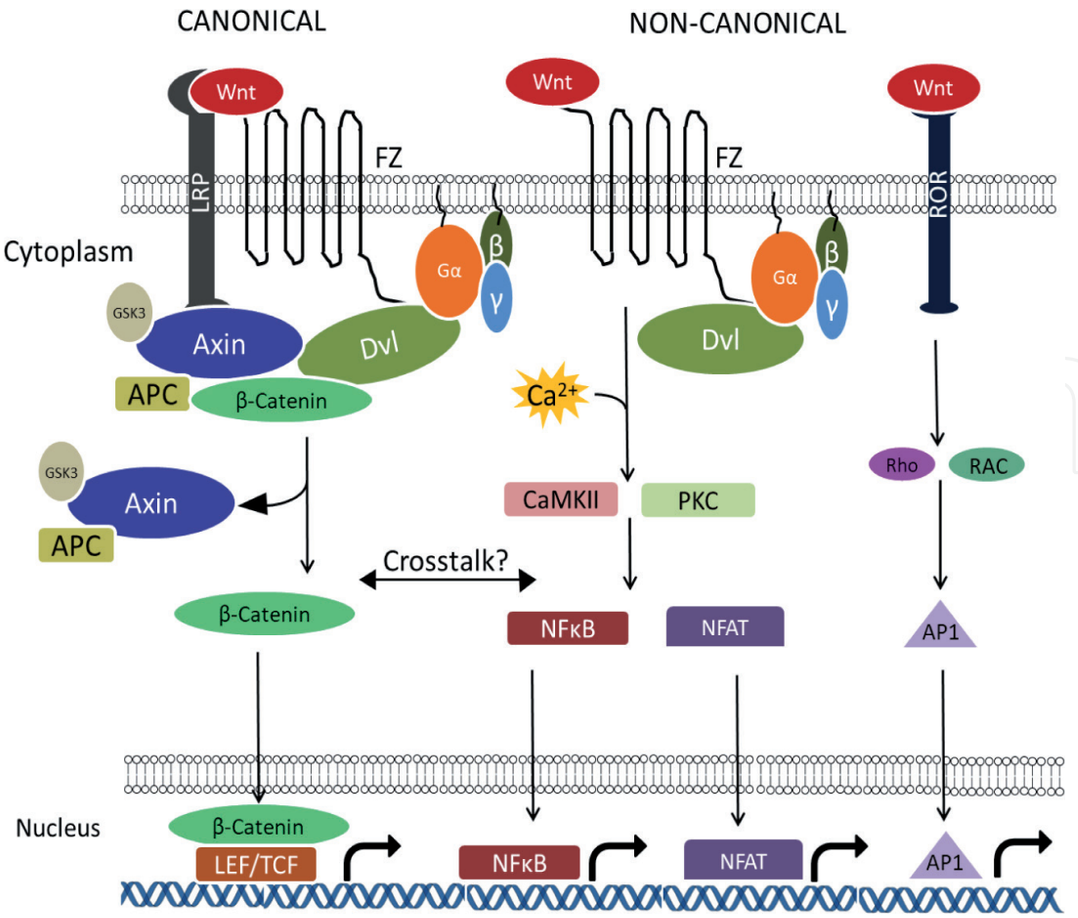


Figure 1.
An overview of Wnt signaling cascade: in canonical mode of signaling, the association of Wnt-Fz and LRP activates a signaling cascade through Dvl and/or G-proteins that leads to inactivation of a GSK3 associated destruction complex which in the absence of Wnt would phosphorylate β-catenin for terminal destruction by proteasome. Via GSK3 inactivation, β-catenin gets stabilized and translocates to the nucleus where it acts as a co-activator of LEF/TCF (transcription factor). In the non-canonical mode of Wnt signaling (often β-catenin independent) the signaling cascade through Dvl and/or G-protiens leads to activation of Ca2+ mediated signaling where protein kinase C (PKC) and CaMKII gets activated and leads to translocation of NFκB, NFAT to the nucleus. Wnt also binds to ROR leading to activation of AP1. A crosstalk between the pathways is not uncommon.

come into the direct line of control of pathogenic incursions and immune homeostasis [9–12, 26], Wnt signaling aptly associates with host-pathogen interactions of macrophages at the crossroads of innate and adaptive immunity. The attributes of Wnt signaling and the microbe world being diverse, their mutual interactions in the various host defense programs are expected to be manifold. Although Wnt3A and Wnt5A are often represented as the prototypes for the two different modes of Wnt signaling (canonical and noncanonical) in the regulation of immune response, several molecular details of the balancing act of the Wnts in relation to the interactions of macrophages with different microbes remain unclear.

The primary objective of this chapter is to briefly summarize the conceptual advancement in the context of Wnt signaling and immune defense by macrophages, focusing mainly on transcriptional activation and the actin cytoskeleton-associated phagocytosis and autophagy machineries. Our aim is to also address unanswered questions, which may prove instrumental in bridging existing gaps in our evaluation of the Wnts in the context of macrophage host defense programs.

2. Sustenance of immune defense by macrophages through a steady state of transcriptional activation by Wnt signaling

2.1 Significance of constitutive transcriptional activation in macrophages by Wnt signaling

Macrophages have long been acknowledged for executing immune defense against microbial pathogens through diverse means of signaling that include several transcription factors including NFκB, AP1, and NFAT [27–30]. The ability of macrophages to recognize and engulf pathogens, deliberate NADPH oxidase activity, and process antigens for presentation to MHC molecules and T cell activation place macrophages quite aptly at the crossroad of innate and adaptive immune defense programs [31–33]. Surely, macrophages have in-built mechanisms to execute innate immunity and translate it to adaptive immune response. However, not much is known about the molecular details of how macrophages are naturally geared to operate in such innate and adaptive modes of immune defense. We recently demonstrated that NF-κB (p65) [34], a transcription factor functioning at the core of our immune system, remains activated at a basal level in macrophages through a steady state of Wnt5A signaling. Administration of inhibitor of Wnt production2 (IWP2) to macrophages in culture or depletion of Wnt5A or Frizzled5 (putative Wnt5A receptor) gene expression in macrophages by silencing gene transcription through small interfering RNA blocks constitutive p65 activation and the steady-state immune activity of macrophages [10]. Sustained presence of the Wnt5A-p65 axis can potentially bridge innate and adaptive immune responses through regulation of the expression of immune response genes, such as CD14, interferons (IFN)s, and MHC, and elaboration of immune signaling networks that involve major immune response molecules such as the Toll-like receptors (TLR) and nucleotide-binding oligomerization domain-containing proteins (NOD) during challenge by pathogens [13, 35, 36]. The interrelation of this basal level Wnt5A-p65 signaling with other major transcription factors and coactivators of Wnt signaling that mediate immune response by macrophages remains to be deciphered at the molecular level.

2.2 NF-κB transcription factors

NF-κB transcription factors comprise a family of five members: p52, p50, p65 (RelA), c-Rel, and RelB, which regulate gene transcription as combinatorial dimers [34, 37, 38]. These dimers remain or become activated through different modes depending on the physiological context of cell signaling. In the classical mode of activation, the homo and heterodimers are translocated to the nucleus for gene expression after being released from the IκB-bound states in the cytoplasm in response to different stimuli that lead to proteasome-assisted IκB degradation through activation of the IκB kinase IKK2/β [34]. The p65 homo and heterodimers while being responsible for inflammatory gene expression are also significantly involved in the sustenance of innate immune response gene expression in a context-dependent manner [10]. Some of the NF-κB (p65) responsive immune response genes include CD14, MHC, and IFNs. A schematic of NF-κB activation is shown in **Figure 2**.

2.3 Wnt5A signaling-mediated activation of transcription

As mentioned earlier in this chapter, Wnt5A is one of several members of the large family of Wnt glycoprotein ligands. Frizzled-5, Frizzled-4, and ROR1 are putative receptors for Wnt5A. It is to be noted that although modified versions of selective Wnt-Frizzled complex structures have been solved [39], none of the ligand-receptor

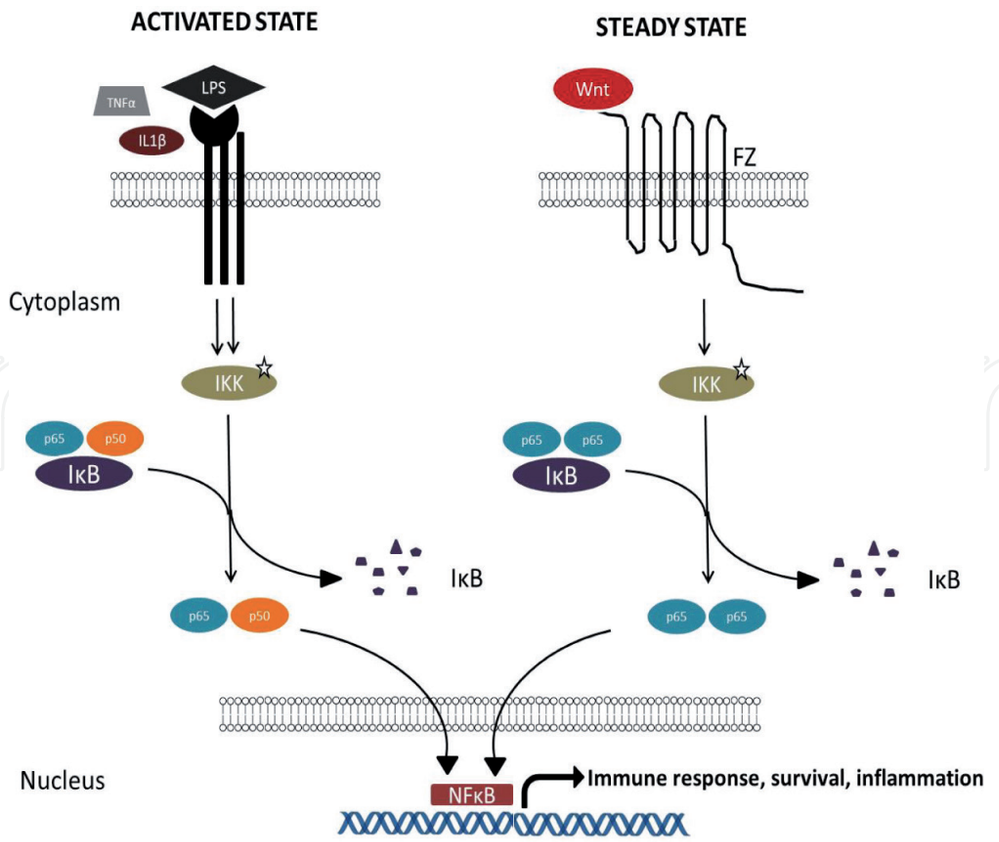


Figure 2.
An overview of NFKB activation pathway in the macrophage: During steady state a basal level of stimulus by Wnt signaling keeps IKK enough activated to result in inactivation of IκB and translocation of a certain pool of NFκB transcription factor (p65 homodimer) to the nucleus. A minimum pool of transcription factors contributes to survival and vigilance for immune response. In the activated state, during inflammation and chronic infection, stimuli (TNFα, LPS, IL1β) lead to an increase in NFκB combinatorial dimers in the nucleus.

complexes have been truly biochemically characterized in their physiological contexts. In the noncanonical mode of Wnt signaling of which Wnt5A is a representative, Wnt5A-Frizzled-ROR or Wnt5A-Frizzled-initiated signaling alters the activity of Rho/Rac family GTPases through differential activation of Disheveled [10, 40]. Within the Frizzled family of cell surface receptors, Frizzled2, Frizzled5, and Frizzled4 are some of the putative receptors for Wnt5A [17, 41, 42]. It is not known if Disheveled activation by Wnt5A signaling acts in concert with or is regulated by heterotrimeric G proteins, given that Frizzled receptors are homologous to heterotrimeric G protein-coupled receptors. The involvement of β-catenin by Wnt5A signaling is governed by the availability of receptors and cytoplasmic signaling intermediates [20, 43]. The subsequent activation of transcription factors such as AP1, NFAT, and NF-κB through complex signaling networks and crosstalk, either dependent or independent of nuclear translocation of β-catenin (explained in **Figures 1** and **2**), could lead to elaboration of context-dependent immune responses (**Figure 3**).

The basal Wnt5A-Frizzled5 signaling-dependent NF-κB (p65) activity in macrophages that we observed is at least partly accountable for the steady-state expression of CD14/IFNβ, the promoter sequence of which at the genome level contains p65 binding elements [10, 13] (**Figure 3**). The constitutive p65 activity in the nucleus also contributes to sustaining Wnt5A expression [10]. Accordingly, the self-sustaining Wnt5A-p65 axis responsive CD14 and IFNβ expression helps to initiate and coordinate several aspects of macrophage function including interaction of pathogen recognition with TLR signaling, thus enabling adaptation to protective immune responses to bacteria, bacterial LPS (lipopolysaccharide), and virus as explained in **Figure 3**. The Wnt5A-NF-κB (p65) responsive gene expression declines upon

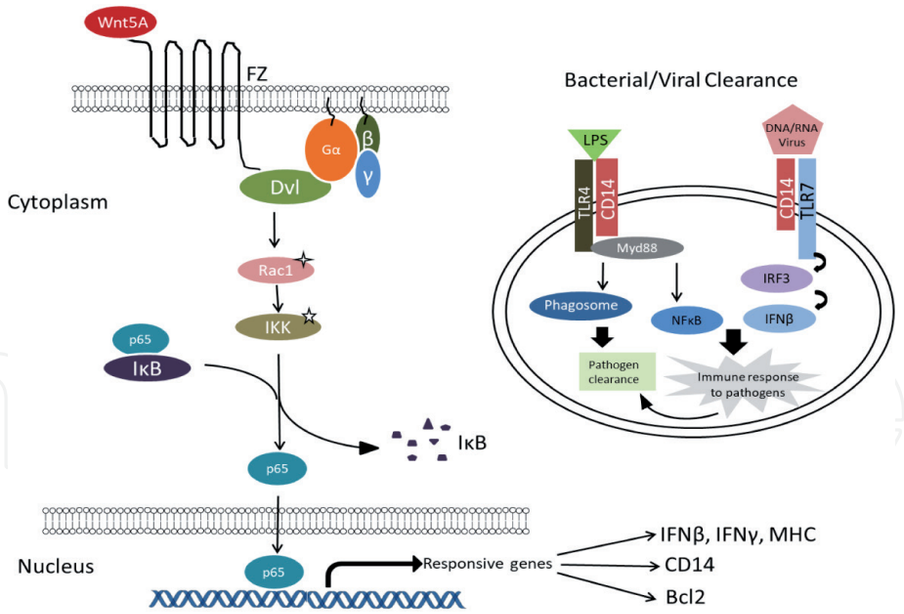


Figure 3.
A schematic of Wnt5A-p65 axis: Wnt5A binds with it's putative receptor Frizzled5 (FZ) and transmits signal through intermediates like Disheveled (Dvl), trimeric G-proteins (Gα, β, γ) activating Rac1. Activated Rac1 helps in translocation of NFκB from cytosol to nucleus via activation of IKK and proteasomal degradation of IKK-phosphorylated IκB. The translocated p65 in the nucleus helps to maintain expression of proteins such as CD14, IFNγ, IFNb, MHC, needed for pathogen detection and clearance, and Bcl2, needed for cell survival. Amplification of signals by CD14-assisted molecules such as TLRs facilitate pathogen recognition and clearance.

exposing macrophages to an IKK2-specific inhibitor [10]. Wnt5A signaling is also responsible for a basal level of secretion of IFN-γ, another important regulator of innate immune signaling in macrophages. The steady-state Wnt5A signaling and NF-κB activity also promote macrophage survival through the expression of NF-κB-responsive survival genes such as Bcl2 [10]. These data are consistent with the dearth of survival of NF-κB-deficient mice due to different kinds of infection and apoptotic cell death [44]. The Wnt5A-Frizzled5 signaling-assisted constitutive p65 activity is dependent on Rac1 activation, which lies upstream of IKK2 activity [10]. The detailed mechanism of how the Rac1 GTPase activates IKK in a Wnt5A signaling-dependent mode is yet to be explored. It also remains to be tested how Wnt5A-responsive innate immune functions in macrophages relating to pathogen recognition and activation of several intracellular signaling pathways translate to adaptive immune responses encompassing antigen processing/presentation and lymphocyte activation.

2.4 Signaling and transcriptional activation by other Wnts

In light of the fact that Wnts comprise a large family of glycoprotein ligands sharing considerable amino acid sequence homology and bind to cell surface receptors that are equally homologous [21], the schemes of regulation and sustenance of immune responses in macrophages by Wnt signaling are likely to be manifold. Several reports have outlined the importance of canonical Wnt signaling and β-catenin in the development, sustenance, and elaboration of memory and effector T cells that comprise a crucially important component of immunity to infectious pathogens [45]. The role of the TCF family of transcription factors in this respect has generated considerable interest in our understanding of the importance of Wnt signaling in immune homeostasis. However, the precise role of canonical Wnt signaling by β-catenin and TCF transcription factors in macrophages in the generation and sustenance of T cell-mediated immunity remains unclear.

3. Role of Wnt signaling in macrophage phagocytosis: involvement of the actin cytoskeleton

3.1 Significance of phagocytosis

Phagocytosis of pathogens is one of the most important features of the host-pathogen communications and interactions mediated by macrophages. This element of host defense by macrophages not only operates toward host protection at the onset of infection but also makes room for the initiation and amplification of intracellular signals that can potentially mature to the generation of antigen-specific T cell responses and creation of immunological memory (explained in **Figure 4**).

As described earlier in this chapter, Wnt5A signaling aids in maintaining a steady-state expression of CD14 and IFNβ, two of the many molecules involved in innate immune defense. Although it is not exactly clear how CD14 and IFNβ fit into the program of phagocytosis in exact molecular terms, it is documented that while CD14 is instrumental in the recognition of structural motifs like lipopolysaccharide (LPS) intrinsic to certain pathogens, both CD14 and IFNβ facilitate pathogen clearance through the initiation and propagation of macrophage TLR signaling during phagocytosis and activation of immune responses [10, 13] (**Figure 3**). Following pathogen engulfment and phagosome formation during phagocytosis, macrophages rely mostly on endosomal and lysosomal proteases and NADPH oxidase-generated reactive oxygen species for both pathogen clearance as well as processing and presentation of antigenic peptides to MHC molecules for presentation to T lymphocytes [31, 46] and translation to memory.

3.2 Need for Wnt5A signaling-assisted actin rearrangement/assembly

At the core of all phagocytosis-related processes lies the involvement of the actin cytoskeleton through its influence on protein sorting/trafficking and intracellular organelle fusions that are crucial for the activation of phagosomal enzymes such as

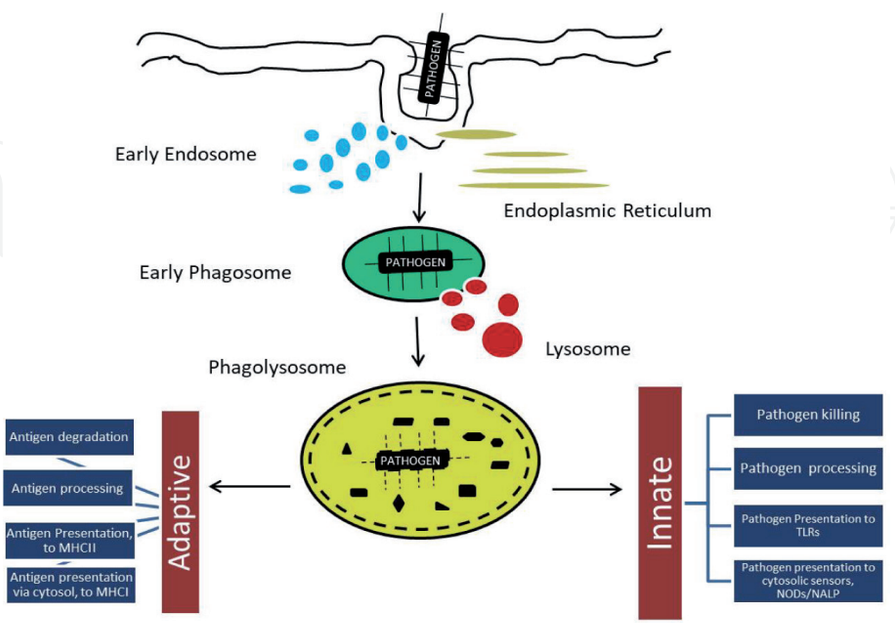


Figure 4.
A schematic of maturation of pathogen containing vesicle and its outcome: After phagocytosis of pathogen there is fusion of early endosome and endoplasmic reticulum (ER) with the phagosome which helps in the maturation of the phagosome and fusion with lysosome. This is important for both innate and adaptive immunity.

NADPH oxidase and phagosome maturation [31, 47]. Several cytoskeletal GTPases such as Rac1 and Disheveled, lipid rafts, and actin-nucleating proteins such as Arp2/3 and formins partake of the cytoskeletal actin modulations that accompany macrophage phagocytosis and phagosome maturation [47–50]. There is evidence that Wnt5A signaling is important for such rearrangements of the actin cytoskeleton. Accordingly, Wnt5A signaling facilitates Rac1- Disheveled-lipid raft-dependent phagocytosis of bacteria and other foreign matter through modulations of the actin cytoskeleton [9]. Blockers of any of the cytoskeletal actin-associated signaling intermediates—Rac1, Disheveled, or lipid raft and cytochalasin-D, an inhibitor of actin assembly—are antagonistic to the effect of Wnt5A signaling on phagocytosis [9]. The influence of Wnt5A signaling on phagocytic uptake is usually dependent on the microbe under consideration, because while most bacterial species tested undergo facilitated phagocytic uptake by Wnt5A signaling in macrophages, phagocytic uptake of *Leishmania donovani* remains unaffected by it [11]. Perhaps Wnt5A-facilitated internalization encompasses distinct membranous domains depending on the availability of cognate receptors, which are not equally compatible with all microbes. That Wnt5A signaling also facilitates phagosome-lysosome fusion during phagosome maturation which is evident from the augmented appearance of lysosomal markers such as cathepsins in Wnt5A-induced phagosomes of bacteria-infected macrophages [12]. Wnt5A-facilitated alteration in cytoskeletal actin assembly that correlates with phagosome-lysosome fusion is concomitant with the killing of several microbes including bacterial pathogens (*Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, etc.) and even *Leishmania donovani*, although it gets internalized independent of Wnt5A signaling [11, 12]. The mechanism of microbial killing is discussed at greater length in the following section of this chapter. Microbial killing is furthermore facilitated by Wnt5A-responsive NADPH oxidase activity, which is associated with cytoskeletal actin-dependent assembly of NADPH oxidase subunits [11]. Interestingly, nonpathogenic laboratory strains of bacteria that are engulfed by macrophages in increased numbers by Wnt5A signaling are not necessarily killed by it like the pathogenic bacterial strains [9, 12]. Such discrepancy in the fate of internalized microbes may be an outcome of notable differences in the interaction of different microbial components with Wnt5A-regulated cytoskeletal actin rearrangements. The interrelation between Wnt5A signaling and Ehrlichia infection is especially noteworthy in this context [51].

In light of the fact that the cytoskeletal actin-assisted phagosome is the originator and communicator of many signals generated by phagocytozed cargo-recognizing molecules such as TLR, NOD1, and NOD2 [35, 52, 53] (**Figure 4**), it is quite likely that the consequences of Wnt5A-assisted phagocytosis are numerous. Association of Wnt5A signaling with TLRs has already been reported [54]. Careful analysis of the consequences of such associations is important.

3.3 Role played by other Wnts and costimulatory molecules of Wnt signaling

Wnts other than Wnt5A are known to regulate macrophage phagocytosis as well. For example, the Drosophila Wnt has been reported to stimulate phagocytic uptake in the S2 cell, a macrophage-like line [55]. Moreover, Wnt1, Wnt7A, and Wnt3A have been reported as phagocytic modulators [56, 57]. The association or relation of these different modes of phagocytosis with Wnt5A signaling and cytoskeletal actin rearrangements is yet to be explored. At this point of our understanding of Wnt signaling with respect to phagocytosis, regulatory roles played by LRP5/6 and ROR, which act as co-receptors to Wnts [22, 58], remain unclear. It also remains to be seen if the influence of Wnt5A signaling on phagocytosis is in the canonical or noncanonical mode or is in fact an intermediary between the two depending on the context of infection, the available receptors, and coactivators.

4. Wnt signaling-induced actin-dependent autophagy-assisted xenophagy by macrophages and the potential link with antigen processing/presentation

4.1 Autophagy-assisted xenophagy

Several pathogenic microorganisms try to adapt to the intracellular milieu of macrophage creating a niche for their survival [59–61]. Nevertheless, as described earlier in this chapter, the host macrophage tries maneuvering elimination of infection by pathogens by several means. It has been reported that following phagocytosis of microbes by macrophages, the host autophagy machinery comes into play in the ultimate event of clearance of bacteria and other engulfed microbes (xenophagy) through coordinated alterations of the actin cytoskeleton. Autophagy involves the turnover and clearance of damaged organelles and proteins by the cell under both normal conditions as well as under stress in the maintenance of cellular homeostasis [62, 63]. During infection with pathogens, the autophagy program is often utilized for the incapacitation and eradication of engulfed pathogens [26, 64].

4.2 Role of Wnt signaling and cytoskeletal actin in autophagy-assisted xenophagy

Wnt signaling has been reported to play a significant role in the autophagy-assisted xenophagy of engulfed microbes by macrophages. Wnt5A signaling, for instance, has been documented to be an integral component of this theme in the killing of several bacterial pathogens through utilization of a Rac1-Disheveled-actin cytoskeleton circuit that involves interactions among several autophagy-associated proteins like microtubule-associated protein 1B-light chain 3B (LC3B), autophagy-related 5 (ATG5), ATG7, and Unc-51-like autophagy-activating kinase 1 (ULK1) [12]. The different nuances of Wnt5A signaling in connection with the actin cytoskeleton are depicted in **Figure 5**. Pathogen killing through autophagy machinery is blocked with the use of cytochalasin-D, an inhibitor of actin assembly as well as with inhibitors to Rac1 and Disheveled [12]. Although Wnt5A-assisted killing of *L. donovani* in macrophages has not been shown to directly involve autophagy, electron micrographs of *L. donovani* harboring parasitophorous vacuoles, which display distinct membranous aggregates, suggest that *L. donovani* containing parasitophorous vacuoles may be subjected to lysis by the host autophagy circuit activated by Wnt5A signaling [11]. The inactivation or lysis of microbe-carrying vacuoles, which happens in due course through fusion of autophagy-destined phagosome or autophagosome with the lysosome, may also be facilitated by Wnt5A signaling [12]. Although cholesterol and other lipids are known to partake of both Wnt5A signaling and actin dynamics [65, 66], at this stage much remains unknown about the specific roles of cholesterol and other lipids in the process of actin modulation during phagocytosis and autophagic clearance of bacteria and other microbes. It also remains to be seen if Wnt5A signaling during autophagy belongs strictly to the noncanonical mode or canonical mode based on the involvement of β-catenin.

4.3 Potential link with antigen presentation/adaptive immunity

In view of the fact that the autophagic or rather xenophagic removal of pathogens by macrophages involves reorganization and fusion of intracellular vesicles associated with at least partial lysis of pathogens, the processing and presentation of pathogen antigens to MHC molecules are a likely event during xenophagy in infected macrophages [67, 68]. Thus, autophagosome formation, autophagosome lysosome fusion, and T cell activation by the presentation of processed pathogenic

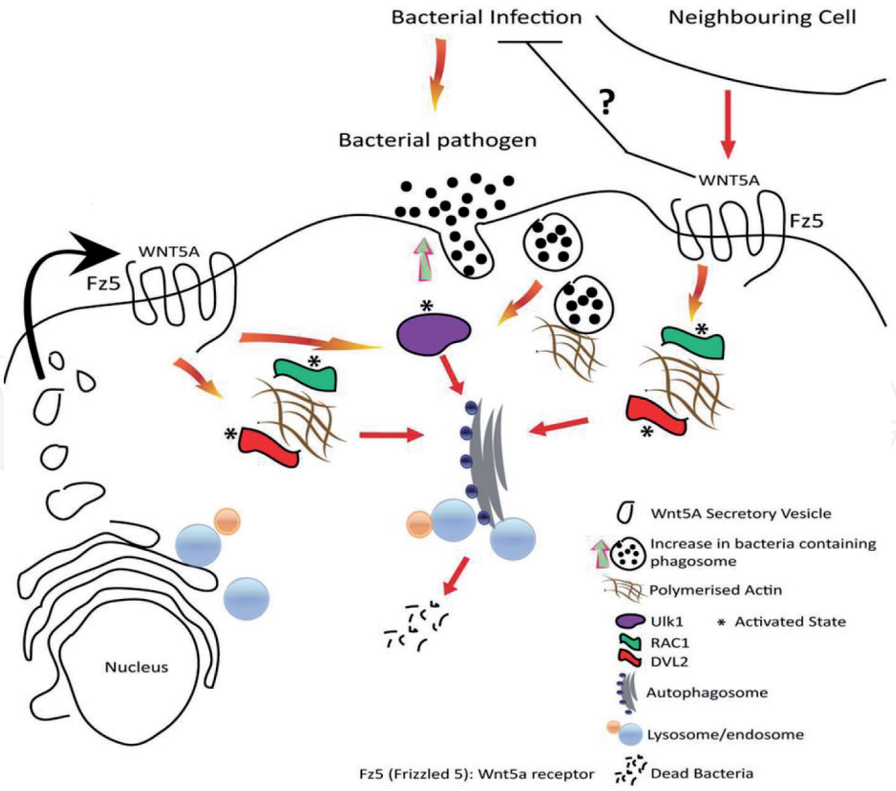


Figure 5.
Schematic of Wnt5A signaling aided bacterial killing: Both autocrine and paracrine modes of Wnt5A signaling can lead to increase in phagocytosis of pathogenic bacteria. After phagocytosis, the Wnt5A mediated cytoskeletal modulation leads to fusion of early endosome and lysosome with the pathogen containing phagosome. Wnt5A signaling also activates Rac1 and Unc like kinase 1 (Ulk1) for initiation of autophagy. The subsequent steps of maturation lead to killing of pathogen in an autophagy dependent process (xenophagy).

antigens may prevail as a continuum during immune defense depending on the nature and degree of the infection. Given the intrinsic association of Wnt signaling with cytoskeletal dynamics and autophagy [11, 12], it is quite likely that Wnt signaling will influence the antigen processing and presentation linked with autophagy in infected macrophages. Detailed investigation in this respect, although important, remains to be documented.

5. Concluding remarks

Given the important role played by Wnt ligands in the transmission of signals associated with cytoskeletal modulation and transcriptional regulation which are part and parcel of host-pathogen communications [27–29, 69], a combination of Wnt signal transduction cascades is expected to hold a fundamental standing in the immune defense program operated by macrophages in both innate and adaptive immunity. Phagocytosis, autophagy/xenophagy (intracellular microbial killing), and a steady-state expression of immune defense molecules through transcriptional regulation appear as some of the major players of the immune defense program operated by Wnt signaling.

In respect of transcriptional regulation of immune defense molecules by steady-state Wnt5A-signaling as described in this chapter [10], it is not understood exactly what dictates the nuclear translocation of p65 and not the other NFκB isoforms for specific modes of gene expression. Additionally, how this regulation fits in with the activity of other major transcription factors like NFAT and AP1 in the macrophage is also not clearly understood. Moreover, details of the context dependence of

Wnt5A signaling, wherein a certain level and mode of signal transmission will be beneficial for immune response, but excess will cause inflammation and disorder [70–72], remain largely unclear. Besides, a clear concept of how actin cytoskeleton-associated proteins such as Rac1 promote both NFκB activity as well as cytoskeletal rearrangements for phagocytosis and autophagy is yet to be achieved [10, 12]. Whether nuclear translocation of NFκB is a natural function of actin assembly or is executed by a separate pool of Rac1 associated cytoskeletal proteins is an important matter that deserves investigation.

With regard to phagocytosis and autophagy-assisted xenophagy, the molecular details of the actin rearrangements with actin binding proteins and the processing and presentation of antigens remain to be deciphered. This brings into question how different host-pathogen interactions within macrophages are guided by modulations of the actin cytoskeleton. Of special interest in this context is the interaction of the actin cytoskeleton with pathogenic mycobacteria, which thrive in self-generated niches within macrophages [60, 73]. The interrelation between different modes of Wnt signaling and mycobacterial infection, although much studied [74, 75], needs to be better understood with respect to actin dynamics. Now that Wnt5A signaling has been shown to play a major role in the regulation of actin cytoskeletal modulation and autophagy [11, 12, 76], future experiments addressing whether this can also facilitate the adaptive immune response through antigen processing and presentation may prove fruitful.

At this juncture of our understanding of Wnt signaling and immune response by macrophages, it is important to know how the different Wnt ligands operate in the regulation of immune response by the different types of macrophages that are distributed in different tissues under the varied conditions of intracellular milieu and infection. Macrophages (microglia) present in the brain and spinal cord maintain an active immune defense scheme against pathogens that affect the central nervous system. Alveolar and airway macrophages likewise protect the respiratory tract and lungs from the toxic effect of infectious agents. Peritoneal macrophages of the peritoneum and Kupffer cells of the liver also encounter and confront infectious agents for host protection. Quite naturally, the roles played by Wnt signaling in the combat mechanism of each macrophage type in its paradigm of immune defense is expected to be different at least to some extent on account of potential variations in cellular environmental cues and modes of host-pathogen interactions.

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Conflict of interest

The authors declare that there is no conflict of interest.

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