Current Trends in Immunology
Vol. 25, 2025

Review

Highlighting neutrophil intracellular signaling: thinking inside the box

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ABSTRACT

Often neutrophils are characterized by their effector functions. There are many articles characterizing the activity of these cells under various physiological conditions. Their beneficial and detrimental activity play a role in all tissue types. This ability to adapt and react to various stimuli suggests an intracellular uniqueness that enables these cells to adapt quickly to cues and respond accordingly. In this review, we will summarize the most common intracellular pathways that are involved in neutrophil ROS production, migration, degranulation, and NETosis.

KEYWORDS: neutrophils, MyD88, JAK, metabolism, migration, degranulation, NETosis, intracellular signaling.

1. Introduction

Neutrophils are the most abundant white blood cells in the human body and play an important role in innate immunity. They are the first line of defense for the immune system as they are the fastest migrating immune cell. They have a short half-life and are always being replenished by the bone marrow. Neutrophil half-life seems to vary among organisms. For example, in a model organism like mice neutrophils have a half-life of 6-12 hours [1], while human neutrophils have a half-life between 2-3 days [2]. Interestingly, the proportion of neutrophils in circulation also varies across species. In humans, neutrophils make up approximately 40-70% of circulating white blood cells, whereas in mice, they account for around 25-40% [3]. Whether these differences in frequency and half-life suggest a difference in physiology remains to be elucidated.

The bone marrow is a well-established source of neutrophils. However, recent studies have revealed that the spleen also produces and harbors neutrophil progenitor cells [4]. This splenic neutrophil population increases under various inflammatory conditions [5]. It is yet unknown whether this population originates from a stem cell resident to the spleen or whether active repopulation events occur at given intervals to maintain this population. The presence of extramedullary neutrophil production raises a question on neutrophil progenitor displacement during development. There are fundamental species differences in neutrophil progenitor displacement. In humans, developing fetuses have very few neutrophils which are in the bone marrow and liver. In comparison, there is a very large reservoir of neutrophils in the liver of rodents during embryogenesis. Of note, regardless of the developmental source of these cells, in all adult mammalian systems, neutrophils are generated in the bone marrow and play a critical role in the inflammatory process [6].

In the bone marrow, the differentiation of neutrophils begins with the hematopoietic stem cell (HSC) population [7]. This population gives

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rise to granulocyte-monocyte progenitor (GMP) cells, a committed myeloid progenitor population. GMP cells give rise to myeloblasts which differentiate into meta-myelocytes, then into band cells, and finally into mature neutrophils with hyper-segmented nuclei. Under normal conditions, only mature neutrophils are found in circulation. Under inflammatory conditions, like sepsis, the high neutrophil demand leads to the release of band cells in circulation [8].

Like all cell types, neutrophils undergo an aging phenomenon, which happens exclusively outside the bone marrow. Due to its short half-life, neutrophil aging is characterized by changes in cell surface receptors, morphological features, and activity profile. At any given time, circulating neutrophil population consists of 'fresh' ($CD62L^{HI}/CXCR4^{LO}$) and aged neutrophil population ($CD62L^{LO}/CXCR4^{HI}$). Due to the short half-life of these cells, the field needs to consider the difference between the activity of neutrophils after being freshly released and neutrophils that have been in circulation for a while (aged). A consideration should also be made on the biological age of the animal and how that affects the neutrophil progenitor pools in the bone marrow.

Even with new functions ascribed to neutrophils every few years, there are classical effector functions that have been characterized in these cells extensively. These classical functions include the production of reactive oxygen species (ROS), release of cytokines and chemokines, the release of granules proteins (degranulation), the internalization of various external actors (phagocytosis), and production of extracellular traps (NETs) [9]. There are currently excellent reviews that have synthesized our current understanding of these processes in neutrophils [10-13]. Many of these effector functions were first described in the context of antimicrobial activity. All these effector functions have now been characterized in sterile inflammatory processes as well. Details of the specific changes observed in both types of environments can be found in various comprehensive reviews [14].

Though sophisticated and intricate, all neutrophil functions are cellular responses to various stimuli leading to a coordination of intracellular signals. The intracellular mechanism underlying these functions can at times be unclear. As such, the remainder of this article will focus on elucidating the mechanisms that underlie these effector functions, with a focus on janus kinase (JAK) signaling, myeloid differentiation primary response 88 (MyD88) signaling, and metabolism (Figure 1).

2. Migration

As an immune cell, migration is a critical function of neutrophils. Several reviews have summarized neutrophil movement and recruitment in response to various stimuli. A critical aspect of migration is cytoskeletal rearrangement and stabilization. Neutrophil cytoskeletal structure is made mostly of actin. Indeed, actin makes up the cytoplasmic, membranous, and phagosomal cytoskeleton of neutrophils [15]. Actin-related protein (ARP) 2/3 complex is critical to the rearrangement of actin filament which facilitate both neutrophil polarization and migration towards various molecular gradients. The discrete subcellular localization of this complex is critical, dictating the site of actin polymerization needed to direct migration and establish the leading edge of the neutrophil. Indeed, mutations leading to defects in ARP2/3 complex formation leads to deficiencies in neutrophil migration and transmigration [16]. Of note, although microtubule dynamics are implicated in migration of other immune cells, its role in neutrophil migration is disputed [17-19]. Although minimal, the microtubule cytoskeleton is critical to the placement of the nucleus in neutrophils [20]. Migration is initiated through the presence of chemotactic molecules or various damage- or pathogen-associated molecular patterns (DAMPs/PAMPs). It is well established that these DAMPs and PAMPs activate specific receptors on neutrophils. For example, various chemokines, cytokines, and growth factors activate receptors with janus kinase (JAK) associated intracellular proteins. Toll like receptors (TLRs) rely on the recruitment of myeloid differentiation primary response 88 (MyD88) to mediate their downstream migratory function.

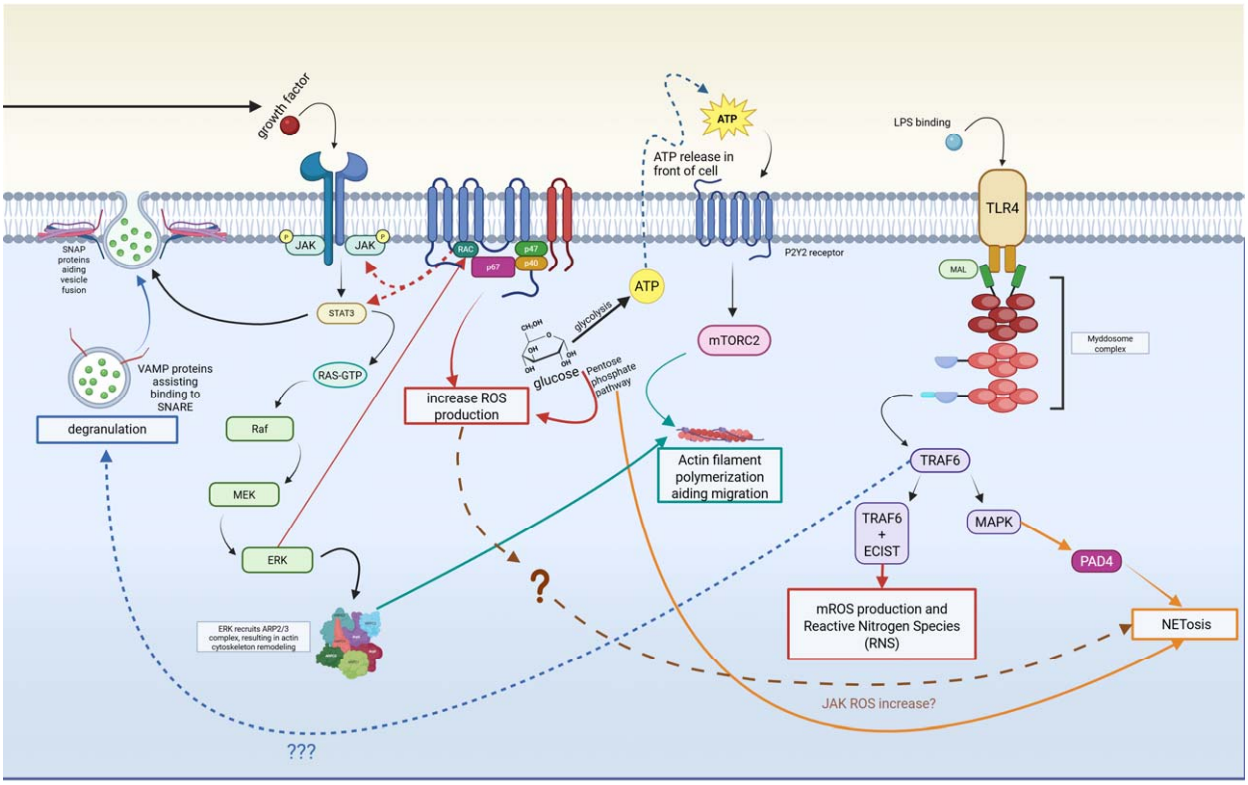

Figure 1. JAK, MyD88, and metabolism contribution to neutrophil migration (teal arrows), reactive oxygen species (ROS; red arrows), degranulation (blue arrows), and NETosis (orange arrows). Upon growth factor binding, JAK phosphorylation leads to the phosphorylation of STAT3. STAT3 in return phosphorylate the Raf/MEK/ERK pathway leading to the formation of the ARP2/3 complex. The same pathway leads to the recruitment of the Rac2 proteins leading to the stabilization of the NOX complex and generation of ROS species. Glucose metabolism can lead to migration through the production of ATP and its release at the leading edge of the cell or increase ROS production through the pentose phosphate pathway. This ROS production and ATP are critical components in the initiation of NETosis in neutrophils. The activation of the family of Toll like and IL1 receptors lead to the recruitment of MyD88 and the generation of the myddosome. The Myddosome activates TRAF6 which in turn stimulates the mitochondria to produce mitochondrial ROS (mROS) and reactive nitrogen species. TRAF6 can also activate the MAPK pathway leading to the activation of PAD4 and the initiation of NETosis.

2.1. JAK signaling in migration

JAK signaling is a ubiquitous pathway used by all immune cells. JAK proteins are non-covalently bound to the intracellular domain of various receptors, including growth factor receptors and cytokine/chemokine receptors. Both canonical and non-canonical signaling pathways have been attributed to JAK activation [21]. Canonical JAK signaling involves the activation of proteins in the signal transducer and activator of transcription (STAT) family. The phosphorylation of the STAT proteins leads to their dimerization and nuclear translocation. The non-canonical JAK pathway is mediated by the action of non-phosphorylated STAT activity within the cell.

In neutrophils the activation of JAK2 has been implicated in both mobilization and chemotaxis upon stimulation with granulocyte/granulocyte-monocyte colony stimulating factor (G/GM-CSF) [22]. This phenomenon is mediated by the phosphorylation of STAT3 [23]. In macrophages the activation of JAK2/STAT3 pathway leads to increased expression of ARP2/3 complex [24]. Furthermore, there is evidence that STAT3 activation leads to the modulation of RAS/MEK/ERK signaling pathway. ERK signaling regulates

the recruitment of ARP2/3 to the sites of actin polymerization [25]. Our lab recently demonstrated that JAK2 modulated neutrophil migration by enhancing the expression of ARPC2 and ARPC3, two essential components of the ARP2/3 complex [26]. This enhancement supports actin filament branching and cytoskeletal stability. Additionally, JAK2 signaling affects membrane composition by suppressing IGF-1 signaling and influence the release of chemoattractants, such as SDF-1α and CXCL2. These mechanisms show that not only does JAK2 regulate ARP2/3 expression but also modulate the autocrine regulation of chemotactic cues of these cells.

2.2. MyD88 in migration

Toll-like receptors (TLRs) are a widely studied family of pathogen recognition receptors that are used to detect a wide range of pathogens. Myeloid Differentiation Primary Response Protein 88 (MyD88) is an important intermediary protein in many toll-like receptors (TLRs) and interleukin-1 receptor (IL-1R)-mediated intracellular pathways. MyD88 is a cytoplasmic protein with a Toll/IL-1R (TIR) domain, an intermediate domain, and a death domain (DD) [27]. These various domains are critical for the interaction of MyD88 with its associated proteins. Ligand binding to IL-1R or TLRs lead to receptor dimerization and interactions of their TIR domains. The TIR domains interact with MyD88 and trigger its oligomerization. This facilitates the recruitment of the interleukin receptor associated kinase (IRAK) family by the MyD88 DD domain. This interaction generates a functional complex called the Myddosome (TIR-MyD88-IRAK4-IRAK1/2). This protein complex then interacts with tumor necrosis factor receptor associated factor 6 (TRAF6) through the C-terminal region of the IRAK1/2 proteins [28, 29]. TRAF6 is the effector protein of this pathway [30]. Its activity dictates the cellular changes needed to produce a specific reaction to MyD88 activation. TRAF6 interaction with the family members of the non-receptor tyrosine kinase Src facilitates its modulation of actin filament. This is mediated through its activation of phosphoinositide 3 (PI-3) kinase and Ras protein [31]. Ras protein regulates the activity of diaphanous-related formin G (ForG) [32]. Formins act in concert with ARP2/3 to facilitate cytoskeletal rearrangement and cell movement [33].

2.3. Metabolism in migration

It is well understood that metabolism is important for all cellular functions [34, 35]. For example, kinases, like JAK proteins, need ATP to perform their functions within cells. As such, understanding metabolic contribution to cellular function is critical to the full understanding of the underlying intracellular changes. Neutrophils depend on glucose for migration. Impaired neutrophil glycolysis has been shown to diminish chemotaxis [36]. Absence of mobility has been observed in neutrophils exposed to 2-deoxyglucose, which is unable to be converted to ATP [37, 38]. Although neutrophils contain large stores of glycogen, there is evidence that the glucose used by neutrophils to migrate is not dependent on intracellular glycogen levels [39]. On the other hand, neutrophils from patients with glycogen storage disorders show impaired chemotaxis [40]. These data suggest that neutrophils are dependent on both intracellular and extracellular glucose to migrate.

Glycolysis products act two-fold in neutrophil migration. The ATP produced enables the activity of critical enzymes and proteins in stabilizing the actin cytoskeleton, increasing/decreasing expression of various adhesion molecules, and influencing the extension of the leading edge of the cell. In addition, ATP can also be released extracellularly to the front of the neutrophils to act as an autocrine signal that is recognized by the neutrophil purinergic receptor P2Y2. This binding activates mammalian target of rapamycin complex 2 (mTORC2) to stimulate actin polymerization resulting in a forward protrusion [41]. A previous subproteomic analysis has shown that several metabolic enzymes play direct roles in neutrophil cytoskeleton rearrangement [42]. Indeed, enzymes involved in glycolysis (phosphoglycerate mutase), pentose phosphatase pathway (transkelotase and phosphogluconate dehydrogenase), glutamate metabolism (n-acetylglucosamine kinase), and aldehyde oxidation (aldehyde dehydrogenase) directly influence the stability of actin filaments. This suggests that the activity of metabolic enzymes may directly influence the stability of the cytoskeleton.

3. Reactive oxygen species (ROS) production

Reactive oxygen species (ROS) are a critical arsenal in neutrophil activity. Neutrophil-derived ROS is made through the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) [43]. Of note, neutrophils mainly express the NOX2 enzyme. NOX is a complex protein formed by the interaction of several subunits, including gp91-phox (phagocyte oxidase), p22-phox, p47-phox, p67-phox, p40-phox, and Rac2 (a Rho-GTPase). Under normal conditions, gp91-phox (main catalytic domain) and p22-phox form a heterodimer that is anchored to the plasma membrane [44]. NOX activation is dependent on the translocation of the other subunits, which are cytosolic, to the plasma membrane to interact with the gp91-phox and p22-phox subcomplex. This translocation is fully dependent on the activation of Rac2 protein. Furthermore, after assembly, NOX depends on phosphorylation to initiate the production of ROS species. The complexity of this process ensures various checks to regulate both the production and the release of ROS by neutrophils. It is important to note that under basic conditions, the gp91-phox p22-phox subcomplex is localized to the secondary granules. Therefore, the activation or initiation of NOX complex formation requires the fusion of secondary granules with the plasma membrane or phagosomal membrane [45].

3.1. JAK signaling in ROS production

Most JAK activation is mediated by its phosphorylation of its downstream target in the STAT family of proteins. There is evidence that JAK can influence NOX assembly in both STAT-dependent and independent pathways. Our lab recently showed that JAK2 inhibition significantly reduced NOX1 expression [26]. It is unclear if this modulation is STAT-dependent or independent. The STAT-dependent pathway in neutrophils is mediated through the activity of STAT3. STAT3 activation regulates the phosphorylation of the RAS/MEK/ERK pathway. ERK1/2 is critical to the phosphorylation and activation of p47-phox [46]. This phosphorylation leads to a conformational change that exposes its Src-homology (SH) domain and facilitates its interaction with p22-phox [45]. This interaction leads to the production of phosphoinositides at the membrane which stabilizes the NOX complex leading to a prolonged generation of ROS species [47]. In addition, it has been shown that G-protein couple receptor (GPCR) activation of Rac can create a positive feedback on NOX activity by modulating JAK2 and STAT3 activity [48]. Indeed, GPCR activation of Rac leads to activation of NOX and the production of ROS species. The presence of ROS can also mediate the phosphorylation of JAK2 leading to the phosphorylation of STAT3, which in turn modulates the activation of Rac. The STAT-independent modulation of Rac activity is mediated by JAK phosphorylation of the Ras protein. This pathway is often activated by growth hormone interaction with JAK-associated extracellular receptors. In this pathway, Ras activation leads to the phosphorylation and activation of both MAPK and ERK1/2 [49], which activate Rac and facilitate the formation of the NOX complex. Indeed, aberrant Ras activation has been linked to excessive production of ROS species in myeloid leukemia [50].

3.2. MyD88 in ROS production

As mentioned above, the Myddosome formation leads to the activation of TRAF6, its main effector protein within the cell. TRAF6 modulation of ROS production is a mitochondrion-mediated process. Neutrophils contain only a few mitochondria. It is still unclear whether the mitochondria play a significant role in ROS production in neutrophils. It has however been shown that under certain hypoxic conditions, neutrophils can release mitochondria ROS (mROS) species [51]. This is mediated by the interaction between hypoxia-inducible factor1-alpha (HIF1-alpha) and glycolysis. Whether TRAF6 activation plays a role in this process is yet unknown. However, there is ample evidence that TLR activation in neutrophils and other immune cells leads to the production and release of ROS species [52]. In macrophages, TLR activation of TRAF6 can interact and form a complex with evolutionarily conserved signaling intermediate in toll pathways (ECSIT) [53]. This complex facilitates the translocation and fusion of mitochondria with the phagosome. Here, this NOX-independent ROS production is mediated by

the activity of the mitochondria electron transport chain. Although not covered here, the activation of MyD88 leads to an increase in cell production of reactive nitrogen species (RNS). The underlying mechanism of the MyD88-mediated RNS production is well characterized in a recent review by Li and colleagues [54].

3.3. Metabolism in ROS production

Neutrophil ROS production occurs mainly through the pentose phosphate pathway (PPP). Indeed, neutrophils exposed to antimycin A, an inhibitor of the mitochondrial complex III, had no effect on ROS production [54]. In neutrophils, glucose can be shuffled into the PPP to generate more NADPH, which is critical for the production of reactive oxygen species (ROS) [55]. A recent seminal report showed that neutrophil activation leads to the shuffling of glucose into the cyclic PPP. The cyclic PPP allows neutrophils to produce 6 NADPH molecules from one glucose molecule [55]. Neutrophils contain a large reserve of glycogen which can be used to generate glucose as needed. The neutrophils of patients with glycogen storage disorders show impaired ROS production and decreased concentration of NADPH and NOX activity [56]. Indeed, patients with glycogen storage disorder suffer from neutropenia (low circulating neutrophil levels) [57].

4. NETosis

NETosis refers to the mechanism underlying the release of neutrophil extracellular traps (NETs). NETs are made of modified chromatin speckled with the content of neutrophil granules, including myeloperoxidase and elastase [13]. NETosis requires an increased production of ROS, intracellular degranulation, and chromatin modification. Due to its reliance on ROS production, NETosis is modulated by all the intracellular signaling cascades required for ROS production. Both NOX-dependent and independent mechanisms have been described in NETosis. The NOX-dependent NETosis is influenced by all the molecular mechanisms critical to the NOX-dependent generation of ROS species [13]. The NOX-independent pathway relies on mitochondria-degenerated ROS species. This pathway is dependent on increases in intracellular calcium and the activation of additional proteins like c-Jun N-terminal kinase, Focal adhesion kinase 2, and the inhibitor of nuclear factor-κB kinase (I κB) [58]. Of note, there are two forms of NETosis that have been documented, lytic and vital. Vital NETosis occurs fast within one hour of stimulation [59]. During this process, the cell can release either nuclear or mitochondria DNA [60]. The lytic form of NETosis is often classified as a method of neutrophil programmed cell death, similar to apoptosis. There is not yet a consensus on whether this form of NET production requires novel transcription in the cell. NETosis is also dependent on chromatin de-condensation, which is mediated by histone citrullination by peptidylarginine deiminase 4 (PAD4). There has been evidence of PAD4-independent NETosis [61]. However, its molecular mechanism has not yet been described.

The initiation of NETosis is mediated by the intracellular release of several primary granule proteins, including myeloperoxidase, elastase, cathepsin G, and azurocidin [62]. The interaction of myeloperoxidase with the intracellular ROS leads to the production of hypochlorite anion and the activation of intracellular serine proteases, including elastase. The activity of these proteases leads to the breakdown of the cytoskeleton and the nuclear membrane. At the same time, intracellular ROS leads to the activation of PAD4. PAD4 is then translocated to the nucleus, where it citrullinates histones 3 and 4. PAD4 also mediates the activation of gastermin D, leading to the formation of pores on remaining granules and the neutrophil plasma membrane, and the release of the decondensed nuclear content [13]. The consensus in the field is that ROS, PAD4, and gastermin D are critical factors in this process.

4.1. JAK signaling in NETosis

As stated above, JAK signaling plays a crucial role in the formation of the NOX complex. Currently, our lab showed that JAK2 does not directly regulate NETosis, as inhibition of JAK2 had no effect on NET production or PAD4 levels [26]. However, JAK2 inhibition did influence proteins involved in NETosis-related pathways, including an increase in neutrophil elastase and

a reduction in NOX1 levels [26]. These results imply that while JAK2 may not be a primary driver of NET formation, it contributes to the regulation of upstream effector mechanisms essential for ROS-dependent NETosis in models of myeloproliferative neoplastic disorders, which are underscored by an overactivation of JAK2. In these diseases, a greater level of NETs has been documented [63]. It has been shown that neutrophils in these disorders are primed to produce NETs, which could be a result of JAK2 effect on ROS production.

4.2. MyD88 signaling in NETosis

TRAF6 is known to interact with and lead to the activation of mitogen activated protein kinases (MAPK), which then signals to PAD4. Elastase plays a central role in NETosis. MyD88 activation, through interleukin 8, leads to an increase in neutrophil elastase through the activity of TRAF6 [64].

4.3. Metabolism in NETosis

It has been shown that the process of NETosis is highly dependent on glycolysis [65]. While oligomycin (ATP synthase inhibitor) exposure diminished NET formation by neutrophils, 2-deoxyglucose (glycolysis inhibitor) prevented the process entirely [66]. Additionally, the removal of glucose from culture media prevented NET formation while the removal of glutamine did not, further showing that glycolysis-derived ATP is necessary for NETosis. The use of glucose to produce ROS also makes glucose metabolism a central player in this process. Interestingly, in COVID-19 patients, an increase in NETosis has been correlated to an increased glycolysis in neutrophils as well as increased expression of the glucose transporter GLUT1 and lactate dehydrogenase [67]. The neutrophils of these patients exhibited increased glycogen stores and inhibition of glycogenolysis resulted in loss of NETosis.

5. Degranulation

Neutrophil degranulation is the process of the release of granular content into the extracellular space. Neutrophils' cytoplasm contains primary, secondary, tertiary granules, and secretory vesicles. All granules are made and packaged during the maturation process of neutrophils, except for secretory vesicles. Due to the high threshold of activity required for their release, degranulation often refers to the release of primary and secondary granule content. Tertiary granules and secretory vesicles are released regularly by neutrophils due to the role their content play in neutrophil mobility and migration [68].

Like exocytosis in general, degranulation in neutrophils depends on actin and microtubule cytoskeletal rearrangement, granule docking at the plasma membrane through protein interactions, and fusion of granule membrane with the cell plasma membrane. This process has been well described [see reviews 69, 70]. In brief, the actin/microtubule cytoskeletal rearrangement for this process is dependent on the activation/ recruitment of the Rac2 protein (which is a subunit of the NOX complex), increase in intracellular calcium, and the hydrolyzation of triphosphate species (ATP/GTP). The actin rearrangement leads to the localization of granules to the plasma membrane. Granule docking is mediated by the interaction of granule membrane proteins with the plasma membrane. For example, the expression of the vesicle-associated proteins (VAMP) on each granule facilitates this interaction. The VAMP proteins interact with syntaxin and synaptosomal-associated protein (SNAP) on the plasma membrane of the cell. Finally, there is evidence that polyphosphoinositide proteins (i.e. PIP2, PIP3, etc) and kinases (i.e. PI3K), and non-receptor protein phosphatase MEG2 are critical for the fusion of granule membrane with the plasma membrane.

5.1. JAK and myD88 signaling in degranulation

Our lab has recently shown that JAK2 modulates neutrophil degranulation through the regulation of calcium signaling, SNARE complex activity, and actin cytoskeletal remodeling [26]. This regulation plays a critical role in the release of each granule type and secretory vesicles. There is also direct evidence that JAK signaling plays a role in the degranulation of mast [71] and NK cells [72]. JAK activation leads to increased NAPDH and NOX activation in neutrophils.

Rac protein, a critical component of the NOX complex, can be directly affected by JAK activation. Similar to JAK, MyD88 activation has a direct effect on mast cell degranulation [73]. However, there is little evidence of its involvement in neutrophil degranulation.

5.2. Metabolism in degranulation

Degranulation is a metabolically demanding process for neutrophils [74]. This process relies heavily on the hydrolyzation of triphosphate species. Therefore, glycolysis plays a critical role in this process. Indeed, the addition of 2-deoxyglucose to neutrophil cultures inhibits degranulation [75]. There is evidence that ATP production through the mitochondria, though minimal in neutrophils, also contribute to degranulation [76]. The production of mitochondrial ROS, though not classical metabolism, plays a role in neutrophil degranulation [77]. The activity of the mTORC2 pathway in actin remodeling suggests that it may play a role in neutrophil degranulation [41].

6. Conclusions

Neutrophil activity is critical to the inflammatory process. Neutrophils play a role in both the initiation of inflammation and its resolution. Various maladaptive conditions, like psoriasis, have been linked to aberrant neutrophil function. We propose that understanding the intracellular signaling cascades that lead to these functions is critical to our understanding of how various stimuli elicit specific functions from these cells. We hope that the content of this review highlights the gaps remaining in the relationships between JAK signaling, MyD88 signaling, metabolism, and various functional outcome of neutrophils.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts to disclose.

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