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Review

Immunoreceptors on neutrophils

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ABSTRACT

Neutrophils play a critical role in the host defense against infection, and they are able to perform a variety of effector mechanisms for this purpose. However, there are also a number of pathological conditions, including autoimmunity and cancer, in which the activities of neutrophils can be harmful to the host. Thus the activities of neutrophils need to be tightly controlled. As in the case of other immune cells, many of the neutrophil effector functions are regulated by a series of immunoreceptors on the plasma membrane. Here, we review what is currently known about the functions of the various individual immunoreceptors and their signaling in neutrophils. While these immunoreceptors allow for the recognition of a diverse range of extracellular ligands, such as cell surface structures (like proteins, glycans and lipids) and extracellular matrix components, they commonly signal via conserved ITAM or ITIM motifs and their associated downstream pathways that depend on the phosphorylation of tyrosine residues in proteins and/or inositol lipids. This allows for a balanced homeostatic regulation of neutrophil effector functions. Given the number of available immunoreceptors and their fundamental importance for neutrophil behavior, it is perhaps not surprising that pathogens have evolved means to evade immune responses through some of these pathways. Inversely, some of these receptors evolved to specifically recognize these pathogens. Finally, some interactions mediated by immunoreceptors in neutrophils have been identified as promising targets for therapeutic intervention.

1. The dynamic and versatile nature of the neutrophil: opportunities for regulation

Neutrophils (also called polymorphonuclear leukocytes: PMNs) are the most abundant type of white blood cell in the human body. Their primary task is to protect the body from harmful microbial infections, particularly those exerted by bacterial and fungal pathogens [1,2]. The importance of neutrophils in host defense is well illustrated by the enhanced susceptibility to such opportunistic infections often observed in patients with acquired or inherited defects in neutrophil formation or function [3–5]. To fulfill their obligations, PMNs can perform a variety of effector functions, such as migration to an infectious site, phagocytosis of pathogens, the intracellular killing in phagosomes with the help of reactive oxygen species (ROS) generated via the phagocyte NADPH oxidase, and with anti-microbial components from the granules [6]. While much of the intracellular production of these mediators ensures that microbial killing occurs in a contained fashion, with minimal collateral damage to the surrounding healthy tissue, there is definitely also extracellular production and this inevitably gives rise to some level of inflammation. In fact, some neutrophil activities are directed into the extracellular milieu. For

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; ANCAs, anti-neutrophil autoantibodies; Btk, Bruton's tyrosine kinase; DAG, diacyl-glycerol; DAP12, DNAX activation protein of 12 kDa; ERK, extracellular signal-regulated kinase; fMLP, *N*-Formylmethionine-leucyl-phenylalanine; GBS, group B *Streptococci*; GEF, guanine nucleotide exchange factor; GPCR, G protein-coupled receptor; GPI, glycophosphatidylinositol; Grb2, growth factor receptor-bound protein 2; IgSF, Immunoglobulin superfamily; IP_3, inositol triphosphate; IRAK, interleukin-1 receptor-associated kinase; ITAM, immunoreceptor tyrosine-based activating motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; IVIg, intravenous immunoglobulins; MAPK, mitogen-activated protein kinase; MLCK, myosin light-chain kinase; MPO, myeloperoxidase; MRP8, myeloid-related protein 8; NADPH, nicotinamide adenine dinucleotide phosphate; NETs, neutrophil extracellular traps; ORF, open reading frame; PE, phosphatidylethanolamine; PH domain, pleckstrin homology domain; $PI(3,4)P_2$, phosphatidylinositol (3,4)-bisphosphate; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PIP_2, phosphatidylinositol (4,5)-bisphosphate; PIP_3, phosphatidylinositol (3,4,5)-trisphosphate; PKC, protein kinase C; PLC, phospholipase C; PMN, polymorphonuclear leukocytes; PS, phosphatidylserine; PTPN6, tyrosine-protein phosphatase non-receptor type 6; RA, rheumatoid arthritis; ROS, reactive oxygen species; SH2, Src homology 2; SHIP, SH2-domain containing inositol phosphatase; SHP, SH2-domain containing phosphatase; SLE, systemic lupus erythematosus; SLP-76, SH2 domain containing leukocyte protein of 76 kDa; SNP, single-nucleotide polymorphism; SOCS, suppressor of cytokine signaling proteins; Syk, spleen tyrosine kinase.

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instance, neutrophils are apparently also capable of releasing their DNA content and to form so-called neutrophil extracellular traps (NETs) with presumed anti-microbial activity *in vivo* [7]. In addition, neutrophils communicate with other immune cells through the secretion of cytokines and chemokines [1,8]. However, inadequate neutrophil recruitment and functioning can contribute to serious disease. For example, the chronic inflammatory response in autoimmune diseases, such as *e.g.* autoimmune rheumatoid arthritis (RA), leads to the recruitment of neutrophils that subsequently contribute substantially to tissue damage, ultimately resulting in irreversible processes like cartilage destruction [9]. In cancer, neutrophils, often designated as tumor-associated neutrophils (TANs), can confer either pro- or anti-tumor effects, depending on the conditions. Whereas neutrophils involved in associated inflammatory processes may actually support tumor progression, *e.g.* by releasing tissue-degrading proteins from granules, cytokine production and even ROS production [10–12], the presence of therapeutic antibodies directed against the tumor, may change the situation radically and turn the cancer cells into targets for neutrophil-mediated antibody-dependent cellular cytotoxicity (ADCC) [13,14]. It thus seems clear that, while maintaining the capacity to mobilize these highly efficient mechanisms when required, it is also very important to tightly control the effector functions of neutrophils to avoid undesirable collateral damage. One of the most striking examples of lack of inherent neutrophil control is that observed in neutrophil-specific deficiency of the tyrosine phosphatase SHP-1 in mice, which, even in the absence of any deliberate pathogenic challenge, causes an obvious cutaneous inflammatory phenotype [15]. SHP-1 and other inhibitory signaling molecules act downstream of a variety of immune inhibitory receptors that counterbalance the activities of activating immunoreceptors. The interplay between these activating and inhibitory receptors is a major determinant of the behavior of the neutrophil.

In this review, we consider the different immunoreceptors that are expressed on neutrophils. For this purpose we define an immunoreceptor as a transmembrane structure containing extracellular immunoglobulin (Ig)-like domains and intracellular signaling via conserved immunoreceptor tyrosine-based activation motifs (ITAMs) or immunoreceptor tyrosine-based inhibitory motifs (ITIMs). We will describe in detail the immunoreceptors known to be expressed on either human or murine neutrophils. We will also explain whether and how these receptors modulate the functions of neutrophils and discuss their roles in different pathological conditions.

2. Immunoreceptors

Several classes of cell surface receptors on neutrophils are involved in cellular activation and intracellular signal transduction. These include G protein-coupled receptors (GPCRs), cytokine and chemokine receptors, adhesion receptors (*e.g.* integrins or selectins) and pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) or C-type lectin receptors (CLRs) [16–18]. Additionally, modulation of immune responses by neutrophils is regulated through activating and inhibitory immunoreceptors, that we defined in Section 1 as structures containing Ig-like binding domains that mediate signaling via intracellular ITAM or ITIM motifs.

Historically, receptors containing ITAM motifs became acknowledged first [19], and somewhat later FcγRIIb was described as the first inhibitory immunoreceptor containing ITIM motifs [20]. In the late 1990s a theory arose, proposing the existence of structurally closely related paired receptors that trigger opposing cellular responses in immune cells, to help shaping a fragile balance between host responses to pathogens and tolerance [21]. A whole repertoire of paired receptors has since been described for innate immune cells, of which many are also expressed on neutrophils [22]. The net response of these immunological "yin and yang" forces is determined by the strength of the ligand binding as the extracellular part of both siblings is very similar, if not identical [23]. Analysis of genes encoding for paired receptor families showed that these have evolved rapidly [24], suggesting a strong evolutionary pressure coming most likely from exposure of the host to various pathogens. The ability of pathogens to develop evasion strategies can include for instance the hijacking of the inhibitory receptor, thereby inhibiting immune responses. As a consequence of this never-ending battle between host and pathogen, the immune system created a counterbalancing mechanism of activating receptors that overcome the inhibitory signal. Until now, a number of bacterial and viral pathogens have been identified to interact with immunoreceptors expressed on leukocytes [25], including neutrophils, as will be discussed in more detail below.

A number of activating and inhibitory receptors use conserved signaling motifs situated in the cytoplasmic tail; these are the ITAMs or ITIMs. The ITAM is defined by the consensus sequence $Y_{XX}L_{X6-8}Y_{XX}L/I$ and the inhibitory motif by $I/V/L/S_XY_{XX}L/V/I$ (where X represents any amino acid). However, some activating receptors lack intrinsic signaling motifs and instead associate with ITAM-containing signaling modules such as DNAX activation protein of 12 kDa (DAP12) or the Ig-FcR γ-chain (FcRγ) [27,28]. The ITAM domain is situated in the cytoplasmic domain of these transmembrane adaptor molecules and facilitates downstream signaling upon receptor assembly [26,28–31]. The structural arrangement of the transmembrane domain of the immunoreceptor determines the association with either DAP12 or FcRγ: a transmembrane basic arginine in the receptor pairs with FcRγ, while a lysine in the receptor interacts with DAP12 [32]. The importance of DAP12 and FcRγ signaling modules has been shown in double knockout mice, leading to neutrophils that were strongly impaired in their respiratory burst and degranulation activated through integrin signaling [33]; the mice were furthermore defective in osteoclast development [34]. In humans, loss-of-function mutations or deletions in the genes encoding for DAP12 or one of its recruiting receptors TREM-2, results in Nasu-Hakola disease, which presents with recurrent bone fractures and early-onset dementia [35,36]. Although TREM-2 and DAP12 are essential for osteoclastogenesis and bone-remodeling in these patients [35,36], they do not suffer from apparent immunodeficiencies, possibly due to functional redundancy of FcRγ and DAP12 [33]. In addition to ITAM and ITIM domains, some immunoreceptors contain other signaling motifs as well, which include docking sites for *e.g.* PI3K ($Y_{XX}M$, found for instance in DAP10), Grb2 (Y_XN_X), Fyn or SOCS. While these motifs are vital for functional signaling in immune cells, these will not be discussed in detail here, where we will focus on signaling via the ITAM and ITIM motifs of the various receptors in neutrophils.

2.1. Signaling via immunoreceptor ITAM and ITIM motifs

Upon receptor ligation and aggregation, ITAM phosphorylation of the tyrosine (Y) residues by Src-family kinases, of which mainly Hck, Lyn, Fgr and to a lesser extent also Src are expressed by neutrophils, recruits and activates spleen tyrosine kinase (Syk). Src-family kinases are bound to the inner face of the plasma membrane by their N-terminal acetylation sites, and provide, after initiating phosphorylation of the ITAM adapters, docking sites for the pivotal kinase Syk [37]. Syk binds the dual phosphorylated tyrosines within the ITAM with its SH2 domains and subsequently initiates an activating signaling cascade by recruiting and phosphorylating additional signal molecules (Fig. 1). Both Src-family kinases and Syk have been described to be indispensable for typical ITAM signaling. Src-family kinases are involved in many

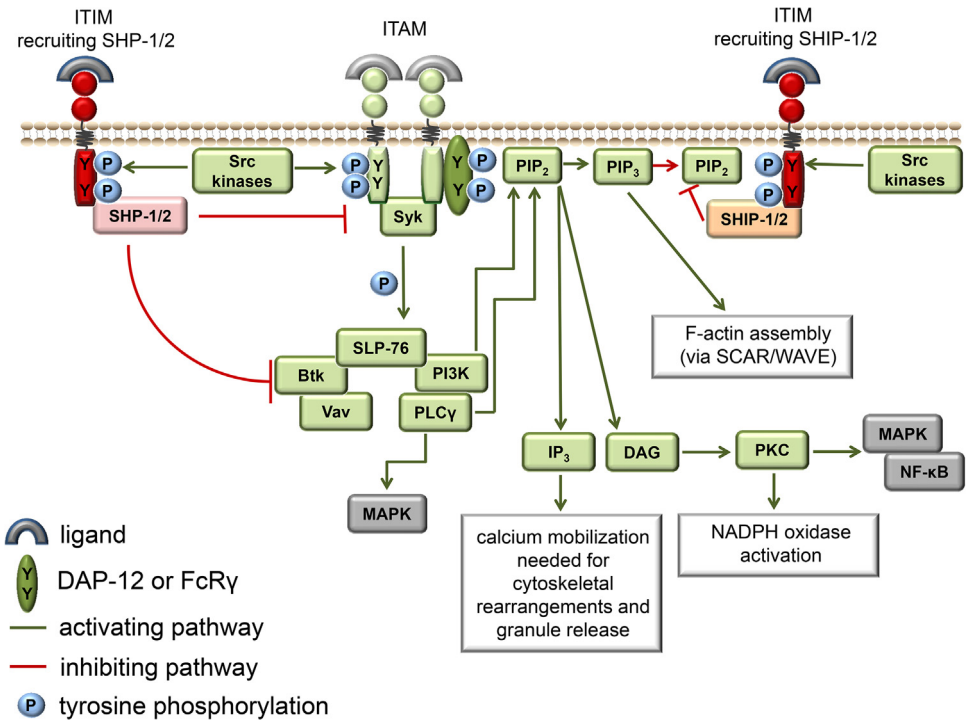

Fig. 1. Signaling via immunoreceptor ITAM and ITIM motifs in neutrophils. Neutrophils express a large variety of immunoreceptors, specified in more detail in Table 1 and in the text, which signal through either ITAM or ITIM motifs. The available, often multimeric, ligands that are recognized by these immunoreceptors induce receptor cross-linking, that triggers Src-family kinase-mediated phosphorylation of the tyrosine (Y) residues in the ITAM or ITIM motifs. In immunoreceptors without intrinsic ITAM motifs, such activation occurs alternatively through associated ITAM-containing adaptor molecules such as DAP-12 or the FcRγ-chain. ITAM phosphorylation results in both instances in the recruitment and activation of the pivotal tyrosine kinase Syk [33]. Syk mediates the subsequent phosphorylation of the SLP-76 protein complex consisting of SLP-76, Btk, Vav, PI3K, and PLCγ and this leads to activation of downstream MAP kinases. Additionally, PI3K and PLCγ are responsible for production of phosphatidylinositol metabolites from membrane phospholipids. While different types of PI3K in neutrophils [54] convert PIP_2 into PIP_3, PLCγ hydrolyses PIP_2 into IP_3 and DAG. PIP_3 accumulation at the plasma membrane leads to the recruitment of PH domain-containing proteins of the appropriate specificity, and as such is directly involved in *e.g.* F-actin assembly through the SCAR/WAVE complex. This then leads to cytoskeletal rearrangements needed for motility and phagocytosis of neutrophils. IP_3 triggers calcium mobilization, further supporting proper cytoskeletal changes and enabling *e.g.* chemotaxis or intracellular granule release. Another product of PIP_2 hydrolysis, DAG, activates PKC isoforms that comprise a family of serine and threonine kinases involved in *e.g.* regulation of the NADPH oxidase system and bacterial killing [51]. Furthermore, PKC isoenzymes are involved in activation of MAP kinases and NF-κB, which may trigger downstream events, including transcriptional regulation of genes. Signaling through activating immunoreceptors is counterbalanced by signals emerging from ITIM-containing inhibitory immunoreceptors. Upon ligand binding to these receptors, Src-family kinases phosphorylate the ITIMs that in turn may recruit two major classes of phosphatases present in neutrophils, *i.e.* the tyrosine phosphatases SHP-1 and SHP-2 [61] and the inositol phosphatases SHIP-1 and SHIP-2 [45]. SHP-1, and to a lesser extent also SHP-2, controls phosphorylation events on several points. First, SHP-1 can dephosphorylate Syk, but also the various components of the SLP-76 complex. SHIP-1 and -2 are involved in phosphatidylinositol metabolism through converting PIP_3 into PIP_2. The net outcome of ITAM and ITIM signaling, which is regulated in a strictly spatiotemporal fashion at the neutrophil plasma membrane, determines the strength and nature of the downstream process affected.

different pathways, but knocking out individual members of this family did not yield striking phenotypes, indicating functional redundancy of these kinases. Mice however lacking two or more Src-family kinases presented with different phenotypes, ranging from mild immunodeficiencies to embryonic lethality, depending on the Src-family kinases missing [38]. Moreover, Syk-deficiency in neutrophils leads to aberrant responses. Mice with Syk-deficient neutrophils showed impaired integrin-mediated effector functions [39] as well as defective immunoreceptor activation [40]. Similar to ITAMs, ITIMs in inhibitory receptors are phosphorylated by Src-family kinases as well. Notably, Lyn was found to be the first Src-family kinase that can, at least in neutrophils, activate both ITAM- and ITIM-mediated signaling [41,42]. Whereas protein kinases such as Syk mediate activating pathways, protein phosphatases counterbalance these actions and play a central role in the inhibitory pathways. ITIM phosphorylation recruits SH2 domain-containing phosphatase (SHP)-1 or -2 or SH2 domain-containing inositol phosphatase (SHIP)-1 or -2 that dephosphorylate substrates of the activating signaling pathways. These phosphatases are functionally distinct: SHIP dephosphorylates inositol phosphates whereas SHP dephosphorylates tyrosine-phosphorylated proteins, including the ITAM. The majority of ITIMs recruits either SHP or SHIP [28,30,31,43–45]. Noteworthy, FcγRIIb (not expressed on neutrophils) can bind both SHP and SHIP: a leucine at ITIM position Y+2 has been shown to determine SHIP binding, whereas an isoleucine at Y−2 facilitates SHP binding. This enables FcγRIIb to inhibit two distinct signaling pathways simultaneously [46]. Furthermore, ITIMs also seem to have different affinities for either SHP-1 or SHP-2, which may contribute to the differential inhibitory capacity; SHP-1 is truly inhibitory, but SHP-2, at least in non-hematopoietic cells, most commonly mediates positive signaling in the context of cytokine or growth factor receptor signaling [31]. Actually, thus far the role of SHP-2 in various individual leukocyte populations, including neutrophils, has not been investigated in detail.

2.1.1. *Signaling downstream of ITAMs*

Upon phosphorylation of the ITAMs by Src-family kinases, Syk binding and concomitant activation results in the recruitment, phosphorylation and activation of SLP-76, PLCγ, Btk, Vav and PI3K, and all of these are also known to be present and active in neutrophils [16,26,28]. The physiological relevance of Syk signaling in neutrophils is well exemplified by a study of Van Ziffle and Lowell [47], who described impaired leukocyte activation and reduced host defense against *Staphylococcus aureus* in neutrophil-specific Syk-deficient mice.

After activation by Syk, the adaptor protein SLP-76 assembles with above mentioned proteins such as PLCγ, the guanine exchange factor Vav, Btk, and the p85 subunit of PI3K to form a complex [48,49]. Signaling mediated by the SLP-76 complex branches into two principally distinct, but nevertheless cooperating, pathways (Fig. 1). PLCγ in the SLP-76 complex can activate MAP kinases (MAPK), but the more prominent pathway involves the metabolism of phosphatidylinositol products located at the plasma membrane to facilitate changes at the neutrophil membrane. In particular, PLCγ hydrolyzes PI(4,5)P_2 (PIP_2) to produce IP_3 and DAG, which initiate calcium mobilization from the ER and PKC activation, respectively [26]. Ca^{2+} in its turn is important for the regulation of a variety of processes in both neutrophils and other cells, including those that involve cytoskeletal rearrangements, amongst others via calmodulins and the myosin light-chain kinase (MLCK). This is pivotal for migration, but also for instance for the fusion of the different neutrophil cytoplasmic granules to the phagosome or the plasma membrane. Signaling downstream of PKC, of which isoenzymes PKCα, -β and -δ can be found in neutrophils [50], can be important in activation of the NADPH oxidase in neutrophils, and PKCδ, for instance, has recently been implicated in an apparently novel anti-microbial killing mechanism that is both independent of the oxidase and granules [51]. Interestingly, PKC has also been shown to recruit and activate SHP-1 upon FcγR signaling, indicating a potential PKC-SHP-1-mediated negative feedback loop of FcγR [52]. Another important function of PKC is activation of MAPK and NF-κB for the induction of various responses, including those that involve changes in gene expression. However, with a few exceptions (such as IL-8 production and a few other mediators) the NF-κB pathway was found to be not very prominent in neutrophils, as most LPS-induced responses were shown to be independent of IRAK4-mediated NF-κB activation, at least in human neutrophils [53].

In parallel with PLCγ, PI3K in the SLP-76 complex phosphorylates PIP_2, generating PI(3,4,5)P_3 (PIP_3) [54]. PIP_3 at the inner leaflet of the plasma membrane, or at the organelles derived from it, such as the phagosome, then binds Pleckstrin Homology (PH)-domain-containing proteins such as Btk, Akt and Rho GEFs (including Vav) and also PLCγ, to mediate changes at the neutrophil membrane needed for *e.g.* chemotaxis or phagocytosis [28,55]. For instance, Vav-activated GTPases activate, amongst other pathways, the SCAR/WAVE complex that is needed for the F-actin assembly that directs the cytoskeletal rearrangements necessary for various neutrophil functions [56]. Of interest, PIP_3 also recruits and binds subunits $p40^{phox}$ and $p47^{phox}$, for the assembly of the NADPH oxidase system and the subsequent respiratory burst [57,58].

2.1.2. Signaling downstream of ITIMs

The exact inhibitory signaling pathways that act via SHP-1 or -2 and SHIP-1 or -2 are less well defined, but in general these enzymes dephosphorylate substrates, *i.e.* either phosphoproteins or phospholipids outlined above, many of which are created by the activating signaling pathways initiated via ITAM signaling. Inhibitory receptors basically become activated in a similar way as activating receptors, *i.e.* by aggregation or co-aggregation with other (activating) receptors, which causes phosphorylation of the ITIM tyrosines by Src-family kinases. This allows phosphatases to be recruited and to counteract activating pathways, thereby balancing or fine-tuning the downstream responses that determine the activities of the neutrophil [31]. SHP-1 and -2 are structurally similar tyrosine phosphatases both containing two in tandem arranged N-terminal SH2 domains and a tyrosine phosphatase domain. The consensus ITIM sequence contains only one tyrosine (described in Section 2), suggesting that more ITIMs are needed for consecutive SHP-1 or -2 binding. Indeed, ITIM motifs in inhibitory receptors tend to occur in pairs of two or more. The arrangement of the two SH2 domains in SHP-1 and -2 matches therefore, in many cases, the spacing of two tyrosines in the ITIM domains of inhibitory immunoreceptors. By comparison, one ITAM contains two tyrosines for cooperative binding of the two SH2 domains of Syk. Upon binding to tyrosine-phosphorylated ITIMs, the auto-inhibitory SH2 domains of SHP-1 or -2 are released, and the catalytic site is exposed and thereby effectively activated [59–61]. While SHP-2 is ubiquitously expressed, SHP-1 is confined to hematopoietic cells and certain epithelial cells [60,62]. Although both phosphatases may compete, at least for most ITIMs, SHP-1 seems in many cases to play the most dominant role of the two in hematopoietic cells, including neutrophils. The importance of SHP-1 in neutrophils was elegantly demonstrated by Abram and Lowell [15], using conditional SHP-$1^{-/-}$ neutrophils (in SHP-$1^{fl/fl}$ × MRP8-CRE mice). The resultant mice suffered specifically from cutaneous inflammation due to uninhibited integrin signaling, thereby explaining part of the phenotype observed in the natural mutations of SHP-1 in mice *i.e.* the *motheaten* or *viable motheaten* mutations. Furthermore, the study showed that SHP-1 deletion in neutrophils could not recapitulate the autoimmune and (spontaneous) pneumonitis aspects of the *motheaten* phenotype. Instead, it appeared that SHP-1 in DCs was responsible for the autoimmunity observed in *motheaten* mice [15]. As in mice, neutrophilic dermatoses are also seen in humans carrying spontaneous mutations in the PTPN6 gene, encoding for SHP-1, most probably due to neutrophilia [63]. SHP-1 has been shown to dephosphorylate many binding partners, amongst others SLP-76, Vav, PI3K, Sfk and PIPKIγ, proteins also found to be interacting with Syk [62]. PIPKIs are involved in the production of PIP_2 (through phosphorylation of phosphatidylinositol), which is the substrate for PI3K, responsible for the generation of PIP_3 [54]. PIP_3 provides an important docking site for many proteins with the appropriate PH domains, thereby stabilizing their interaction with the plasma or phagosomal membrane [28,64]. As indicated, PIP_3 is the substrate for the inositol 5′phosphatases SHIP-1 and -2, which by hydrolyzing PIP_3 to P(3,4)P_2 counteract many of the activities triggered by PI3K (Fig. 1) [55,64]. The inhibitory regulation of PIPKI and PI3K by SHP-1 acts as a double break on PIP_3 generation [65,66]. However, not only PIP_3, but also some of the other inositol lipids have clear-cut functions. For instance, PIP_2 induces conformational changes in talin, a cytoskeletal protein involved in linking integrins to the actin cytoskeleton, which is, given the pivotal role of integrins, particularly the CD11b/CD18 integrin in neutrophils, an important event in these cells. This conformational change results in increased affinity of talin for integrins and, subsequently, in adhesion [67]. This explains in fact the hyper-adhesive phenotype of SHP-$1^{-/-}$ neutrophils [15]: without SHP-1-mediated regulation of PIPKI activity, PIP_2 levels remain enhanced and maintain talin binding to integrins [65]. Although SHIP-2 is ubiquitously expressed, it appears to play only a minor role in hematopoietic cells, in contrast to the hematopoietic-specific SHIP-1 [55]. SHIP-1 is essential for cell migration and adhesion, as neutrophils from SHIP-$1^{-/-}$ mice were, like SHP-$1^{-/-}$ neutrophils, hyper-adhesive [68].

2.1.3. Non-classical ITIM and ITAM signaling

The dogma that activating signals are transmitted by ITAMs and inhibitory signals via ITIMs has become somewhat diffuse in recent years. Activating and inhibitory signals are not strictly regulated via either ITAM or ITIMs, and ITIM-containing receptors seem to be able to signal in the absence of activating receptor co-aggregation [69]. ITAM-associated FcαRI is a clear example of both positive and negative signaling. Whereas many receptors are paired, *i.e.* having both an activating and inhibitory counterpart, FcαRI is the only IgA receptor expressed on myeloid cells. It does not contain an intrinsic ITAM domain but associates with the well-known ITAM-containing FcRγ chain [70]. Pasquier et al. [71] found that FcαRI triggering with

IgA complexes caused strong ITAM phosphorylation and Syk and ERK recruitment. In contrast, FcαRI monomeric targeting resulted in weak phosphorylation of ITAM and surprisingly in SHP-1 recruitment, resulting in turn in dephosphorylation of Syk and ERK. With multimeric crosslinking of FcαRI, ERK was strongly recruited and aborted SHP-1 recruitment, whereas low levels of triggering and phosphorylation recruited predominantly SHP-1. A few years later, the inhibitory potential of mouse FcγRIII was shown in response to IVIg ligation. Binding of IVIg to low-affinity FcγRIII possibly initiates a similar SHP-1 and ERK feedback loop, in which SHP-1 prevails and prevents downstream activating signaling [72,73]. Intriguingly, inhibitory signaling may also occur via the other adaptor, DAP12, which seems to be able to support both activating and inhibitory signaling. The mechanism seems to be similar to FcαRI signaling; high-avidity ligands trigger activation, while low-avidity ligands result in inhibitory signaling [74]. Furthermore, in analogy to the above-mentioned examples, SHIP-1 recruitment to the DAP12-associated TREM-2 receptor in macrophages and osteoclasts has been reported, where SHIP-1 actually inhibited PI3K recruitment by binding to the ITAM. It was hypothesized that through Syk phosphorylation via DAP12 ITAMs, SHIP-1 was recruited and down-modulated at least part of the activating signals [75]. Conversely, inhibitory receptors may not only transmit inhibitory signals. As described in Section 2.1, ITIMs may have affinity for either SHP-1 or SHP-2, and the latter often mediates positive effects on downstream signaling, at least in a variety of non-hematopoietic cells, but perhaps also in myeloid cells. For example, platelet endothelial cell adhesion molecule (PECAM)-1 that is also expressed on neutrophils, contains two ITIM domains that have affinity for both SHP-1 and SHP-2, as well as for SHIP. It was shown that SHP-2 recruitment to PECAM-1 facilitated rather than inhibited cell migration [76], and that blocking homotypic interactions of PECAM-1 on neutrophils consequently inhibited leukocyte recruitment [77]. Finally, the original idea that an inhibitory receptor would function primarily when co-aggregated with its activating counterpart may not be true for every receptor or in every condition. Murine inhibitory receptor PIR-B (paired Ig-like receptor B, the proposed analogue of the human Ig-like transcript receptors, ILTs) was found to inhibit neutrophils and DCs in the apparent absence of an activating counterpart. Here the Src-family kinases Hck and Fgr (phosphorylating the tyrosine residues in the ITIM) maintained PIR-B in a constitutively phosphorylated state, supplying the cell continuously with inhibitory signals. In fact, $Hck^{-/-}$ and $Fgr^{-/-}$ mutant mice displayed a higher Ca^{2+} flux after stimulation of chemokines, as well as enhanced ERK activation and F-actin polymerization. Furthermore, upon chemokine stimulation in wild type neutrophils, the phosphorylation levels of PIR-B declined [78].

3. Immunoreceptors expressed on neutrophils

After focusing on the various activating and inhibitory pathways in general terms and also on the general aspects of the activating and inhibitory pathways in neutrophils, we will now turn to the individual immunoreceptors on neutrophils. Human and mouse neutrophils are known to contain a wide variety of ITAM- and ITIM-associated immunoreceptors, that are summarized in Table 1. Given the different ligand specificities, and the fact that these ligands may interact with the immunoreceptor either in *cis*, in *trans*, or both, this provides the host with a range of opportunities to control the behavior of neutrophils. The vast majority of the immunoreceptors on neutrophils are members of the Immunoglobulin superfamily (IgSF), characterized by the presence of extracellular Ig-like domains, which are generally either of the V- or C-set types [79]. In the following sections, the different (families of) immunoreceptors expressed on neutrophils will be examined more closely. Hereafter, the roles of these receptors in different disease settings (cancer, host defense and infection, inflammation and autoimmunity) will be discussed in more detail.

3.1. Fc receptors

Undoubtedly the best characterized family of immunoreceptors on neutrophils, in both humans and mice, is that of the Fc receptors. FcγR are receptors for the Fc portions of (aggregated) IgG, and therefore play a prominent role in the uptake of IgG-opsonized pathogens and perhaps host particles as well, and in the initiation of ADCC [80,81]. Clearly, the phagocytosis of IgG-opsonized bacteria, yeasts and fungi is very important in the host defense against these microbes; this notion is supported by the findings in individuals with common variable immunodeficiencies (CVID), who have inheritable defects in immunoglobulin production and an increased susceptibility to infections [82]. A prominent role of neutrophils in ADCC against cancer cells has also been demonstrated, both *in vivo* in mice [13] as well as *in vitro* with human PMNs [14].

Human neutrophils express three types of Fcγ receptors: high-affinity FcγRI (CD64), which is only expressed by activated neutrophils, and the medium-affinity FcγRIIa (CD32a) and FcγRIIIb (CD16b), which are constitutively expressed. FcγRI and FcγRIIa are typical activating receptors. FcγRI associates with the FcRγ chain upon receptor ligation, while FcγRIIa contains an intrinsic ITAM motif [83,84]. In ~20% of the Caucasian population, a SNP in exon 3 of *FCGR2C* generates an ORF, resulting in additional FcγRIIc expression. FcγRIIc is essentially a hybrid molecule originating from an unequal crossing over event, involving the extracellular region of the FcγRIIb inhibitory receptor (not expressed on neutrophils) and the cytoplasmic part of FcγRIIa [85,86]. Due to its intracellular ITAM motif, FcγRIIc is an activating receptor. FcγRIIIb lacks signaling motifs and is linked to the membrane by a GPI moiety. Its function remains unclear [83]. In addition, neutrophils express FcαR (CD89), the receptor for IgA, which associates with FcRγ. Notably, mice do not express this receptor [70,87], although they do have IgA. Murine neutrophils have ITIM-containing FcγRIIb and ITAM-containing FcγRIII (the ortholog of human FcγRIIA), but in addition have FcγRIV, which also contains a cytoplasmic ITAM. Mouse FcγRIV was proposed to be the functional ortholog of human FcγRIIIa or FcγRI and seems to recognize IgG2 primarily [83].

3.2. CD300 receptors

CD300 receptors are encoded by seven distinct genes in humans and by nine in mice, and are expressed by cells of the innate immune system [88,89]. CD300 molecules have similar extracellular IgV-like domains, and recognize lipids such as ceramide, phosphatidylserine (PS) and phosphatidylethanolamine (PE), which are often expressed on dead cells [88]. Nomenclature for the human CD300 proteins is alphabetically, whereas the mouse proteins are designated with different names (CLM, LMIR, MAIR or DIgR). Human neutrophils express CD300a, CD300b, CD300c and CD300f [88–90]. CD300a and CD300c are known to be paired receptors [88,91]. Human CD300a and CD300f, and mouse CLM-1 and CLM-8, mediate inhibitory signals and are recruited from the intracellular granules of the neutrophils during LPS or GM-CSF stimulation. Of note, CD300f is mainly stored in granules, as expression is low on resting neutrophils [88,92–94]. Interestingly, co-ligation of CD300a with FcγRIIa on human neutrophils inhibits FcγRIIa-mediated ROS production, while this does not occur when co-ligating CD300a with TLR4, indicating a selective role for CD300a [92]. ITIM phosphorylation of human CD300a can recruit both SHP and SHIP phosphatases [91], although this has not been directly confirmed

Table 1
Immunoreceptors expressed on human and mouse neutrophils. Neutrophils express a variety of receptors with either ITAM (green), ITIM (red) or divergent (grey) signaling potentials. By definition, the immunoreceptors on neutrophils included here are members of the immunoglobulin superfamily that signal via either intrinsic ITAMs or ITIMs encoded in the cytoplasmic tail, or via ITAM-containing adaptors (*i.e.* FcRγ or DAP12). Family members with GPI-linkages or divergent signaling modules are indicated here as well. Receptor families and their individual members are listed here, together with their alternative names, gene designations, cytoplasmic signaling motifs, and signaling molecules.

Human					Mouse						
Receptor	Alternative names	Gene	Cytoplasmic motif or adaptor	Signaling	Receptor	Alternative names	Gene	Cytoplasmic motif or adaptor	Signaling	Additional information	References
Fcγ receptors (ligand: Fc domain of Immunoglobulin G)											
FcγRI	CD64	FCGR1A	FcRγ	Syk	FcγRIIb	CD32, Ly-17, Fcgr2b	Fcgr2	ITIM	SHIP	hFcγRI: inducible upon activation.	80, 83, 84, 86
FcγRIIa/c	CD32a/c	FCGR2A/C	ITAM	Syk	FcγRIII	CD16, FcRIII	Fcgr3	ITAM	Syk		
FcγRIIIb	CD16b	FCGR3B	GPI-linked		FcγRIV	Fcgr4, Fcgr3a	Fcgr4	ITAM	Syk		
Fcα receptors (ligand: Fc domain of Immunoglobulin A)											
FcαR	CD89	FCAR	FcRγ	Syk, SHP-1	-					Can mediate inhibitory signaling via SHP-1.	70, 71, 87
CD300 (ligand: lipids)											
CD300a	CMRF-35H, IRC1, IRC2, IRp60	CD300A	3 ITIMs	SHP-1	CLM-8	CLM-8, LMIR-1, MAIR-I	Cd300a	2 ITIMs	SHP-1	May associate with SHP-2 and SHIP as well. Contains additional Grb2 and PI3K binding sites. hCD300f is expressed on low levels on resting neutrophils.	88, 89, 91-94, 97, 98
CD300f	CD300lf, IgSF13, IREM-1	CD300LF	2 ITIMs	SHP-1, SHP-2	CLM-7	LMIR-5, CD300b, mIREM3	Cd300lb	DAP12	Syk		
CD300b	CD300lb, IREM-3	CD300LB	DAP12	Grb2, Syk	CLM-1	DlgR2, LMIR-3, MAIR-V	Cd300lf	2 ITIMs	SHP-1, SHP-2, PI3K, Grb2		
CD300c	CMRF-35A	CD300C	DAP12, FcRγ	Syk	CLM-5	MAIR-IV, LMIR-4	Cd300ld	FcRγ	Syk		
Siglecs (ligand: sialic acids in various linkages)											
Siglec-3	CD33, gp67	CD33	2 ITIMs	SHP-1, SHP-2	Siglec-3	-	Cd33	ITIM-like	SHP-1, SHP-2		99, 100, 102, 104
Siglec-5	CD170, CD33L2, OBBP2	SIGLEC5	2 ITIMs	SHP-1, SHP-2	Siglec-E	Siglec12, Siglec5, Siglec1	Siglec12	ITIM	SHP-1, SHP-2		
Siglec-9	CD329	SIGLEC9	2 ITIMs	SHP-1, SHP-2							
Siglec-14	-	SIGLEC14	DAP12	Syk							
CEACAM (ligand: CEACAM molecules, Opa)											
CEACAM-1	CD66a, BGP	CEACAM1	2 ITIMs	SHP-1	CEACAM-1	Bgp-1, CD66a, MHV-R	Ceacam-1	2 ITIMs	SHP-1		105, 109, 115, 117, 175
CEACAM-3	CD66d, CGM1	CEACAM3	ITAM-like	Syk							
CEACAM-4	CGM7	CEACAM4	ITAM-like	PI3K, Nck							
CEACAM-6	CD66c, NCA	CEACAM6	GPI-linked								
CEACAM-8	CD66b, CD67, CGM6	CEACAM8	GPI-linked								
SIRP (ligand: SIRPα: CD47; SIRPβ: unknown)											
SIRPα	BIT, CD172A, PTPNS1, SHPS1	SIRPA	2 ITIMs	SHP-1, SHP-2	SIRPα	Bit, Myd1, Ptpns1, Shps1	Sirpa	ITIM	SHP-1, SHP-2		120, 121
SIRPβ1	CD172B	SIRPB1	DAP12	Syk							
SIRPβ2	PTPN1L, PTPNS1L3	SIRPB2	DAP12	Syk							
ILT & PIR (ligand: HLA class I molecules)											
ILT-1	LIR-7, CD85H	LILRA2	ITAM-FcRγ	Syk	PIR-A	-	Pira	FcRγ	Syk		78, 132-134, 136, 137
ILT-4	LIR-2, CD85D, MIR-10	LILRB2	4 ITIMs	SHP-1, SHP-2, SHIP	PIR-B	LIR-3	Lilrb3	3 ITIMs	SHP-1, SHP-2		
ILT-5	LIR-3, CD85A	LILRB3	4 ITIMs	SHP-1, SHP-2, SHIP							
ILT-3	LIR-5, CD85K	LILRB4	2 ITIMs	SHP-1, SHP-2, SHIP							
PILR (sialylated proteins, CD99)											
PILRα	FDF03	PILRA	2 ITIMs	SHP-1, SHP-2	PILRα	FDF03	Pilra	2 ITIMs	SHP-1, SHP-2	Binds SHP-2 with greater affinity.	139, 140, 143
PILRβ	FDFACT	PILRB	DAP12	Syk	PILRβ	Fdfact	Pilrb	DAP12	Syk		
TREM (ligand: unknown)											
TREM-1	CD354	TREM1	DAP12	Syk	TREM-1	CD354	Trem1	DAP12	Syk		145, 150, 151, 154
TLT-2	-	TREML2	?		TLT-2	-	Treml2	?			
CD200R (human ligand: CD200 (OX2); mouse ligand: unknown)											
CD200R	CRTR2, MOX2R, OX2R	CD200R1	NPXY motif	Dok-1, Dok-2, SHIP	CD200R	Mox2	Cd200	NPXY motif	Dok-1, Dok-2, SHIP	Contains no ITIM; but is still inhibitory. Recruits Dok-1 and -2 that in turn recruit SHIP.	31, 156, 158, 59
SIRL (ligand: unknown)											
SIRL-1	-	VSTM1	2 ITIMs	SHP-1, SHP-2	?						162, 163
LAIR-1 (ligand: collagens)											
LAIR-1	CD305	LAIR1	2 ITIMs	SHP-1, SHP-2, Csk	mLAIR-1	CD305	Lair1	2 ITIMs	SHP-2	Inducible upon activation. hLAIR-1: SHP-1 predominantly mediates inhibitory signaling.	165, 168-170

for neutrophils. By means of SHP-1-, SHP-2- and SHIP-deficient B and NK cell lines, it was shown that SHP-1 plays a predominant role in inhibiting for example BCR-mediated Ca^{2+} mobilization and transcriptional activity upon co-ligating BCR and CD300a with mAbs [95]. Notably, inhibitory CD300f has activating potential as well, in both mice and human. This may be caused by the cytoplasmic tail containing additional PI3K- and Grb2-binding motifs. This was in fact demonstrated in murine mast cells, where CD300f recruits FcRγ and augments cytokine responses upon TLR4 stimulation, but intriguingly suppresses responses via other TLRs [93,96]. However, whether this is relevant for neutrophils has not been established. Activating CD300 receptors are CD300b and CD300c. These both have short cytoplasmic tails and assemble with either FcRγ (CD300c) or DAP12 (CD300b). Additionally, CD300b is able to recruit DAP10 and Grb2 [88,89,93]. Murine DAP12-associated CLM-7 (analog of human CD300b) is also expressed on neutrophils; these cells have been shown to additionally shed a soluble form of this receptor [97]. Mouse neutrophils also express CLM-5 that associates with the FcRγ chain [88]. CLM-1 was found to inhibit CLM-5 signaling: triggering CLM-5 with mAbs results in LPS-mediated cytokine production, while co-ligation of CLM-5 and CLM-1 abrogates this production, presumably to exert negative feedback control over neutrophil activation. Finally, formation of homo- and heterodimers in the CD300 family may add to the complexity of signaling through these molecules, although the actual functional relevance has not been studied yet [88,98].

3.3. Siglec receptors

Sialic acid binding Ig-like lectins (Siglecs) comprise a family of sialic acid-recognizing activating and inhibitory receptors, many of which are expressed on myeloid cells. Sialic acids are negatively charged sugars expressed and/or secreted by host cells and also by a number of pathogens. Siglecs can therefore to a certain extent distinguish self from non-self and to regulate the activities of immune cells accordingly [99–101]. All Siglecs contain a membrane distal V-set Ig-like domain that binds sialic acids in combination with a variable number of C-set Ig-like extracellular domains [99,100]. Siglecs may mediate *trans* interactions with cellular ligands, but also *cis* interactions with cellular as well as glycoprotein ligands. These interactions mediate various processes, ranging from hematopoiesis and blood cell proliferation and differentiation to the induction of apoptosis or the inhibition of cellular activation [99,100,102]. Human neutrophils express ITIM-encoding Siglec-3, Siglec-5, and Siglec-9 and the DAP12-associating Siglec-14 [99,102]. Siglec-5 and Siglec-14 are typical paired receptors, differing only in the cytoplasmic domain (ITIM and DAP12, respectively). Mouse neutrophils express the ITIM-containing Siglec-3

and Siglec-E, the latter representing the ortholog of human Siglec-9 [99,103,104].

3.4. CEACAM receptors

Carcinoembryonic antigen (CEA)-related cell adhesion molecules (CEACAMs) recognize host molecules as well as pathogens (especially bacterial opacity-associated (Opa) proteins) and regulate cell–cell interaction processes. CEACAMs mediate both homophilic and heterophilic interactions, also with other CEACAM family members, rendering their biology complicated to understand in detail. The extracellular regions of CEACAMs contain up to six Ig-like domains [105,106]. CEACAMs are not only expressed on epithelial cells, but also on hematopoietic cells. Human neutrophils express CEACAM-1, -3, -4, -6 and -8 [107]. CEACAM genes exhibit abundant sequence variety in vertebrates: mice express 22 CEACAM-related genes, of which only CEACAM-1 is identified as a true ortholog of human CEACAM-1. Notably, this CEACAM is expressed on neutrophils. Moreover, most murine CEACAMs are secreted: only CEACAM-1 and CEACAM-2 are transmembrane bound [108,109]. Whether murine neutrophils express other CEACAM receptors, and what the physiological role of these receptors is, has not been thoroughly investigated.

Activation of CEACAMs via mAbs activates CD11/CD18 integrins and stimulates human neutrophil adhesion [110]. CEACAM-1 (CD66a) is the only inhibitory CEACAM expressed on neutrophils and is thought to dampen neutrophil responses during bacterial infection. Using mouse CEACAM-1$^{-/-}$ neutrophils it was shown that LPS-stimulation led to hyper-production of IL-1β by these cells, which was resolved upon *in vivo* reconstitution [111]. LPS-TLR4 interaction induced the phosphorylation of Syk, which in turn phosphorylated CEACAM-1, causing SHP-1 recruitment. This negative feedback loop suggests a protective role of at least murine CEACAM-1 during infection [111]. Whether human CEACAM-1 has similar functions remains to be established. Human CEACAM-3 (CD66d) is exclusively expressed by neutrophils and possesses a unique and somewhat atypical ITAM-like sequence ($Y_{XX}L_{X7}Y_{XX}M$) that nevertheless appears to function as an ITAM [112]. The $Y_{XX}M$ motif suggests a PI3K-binding site, although it was shown that the PI3K p55 subunit bound to the phosphorylated tyrosine at position 230 of the cytoplasmic domain of CEACAM-3, and not to the ITAM-like motif [113]. Moreover, CEACAM-3 appears the most prominent receptor that mediates opsonin-independent uptake of several human pathogenic bacteria [114]. Interestingly, whereas bacterial killing and respiratory burst were affected after PI3K inhibition, uptake via CEACAM-3 was not [113], which is surprising given the fact that *e.g.* FcR-mediated phagocytosis is clearly PI3K-dependent. Overall, this suggests that the atypical CEACAM-3 ITAM-like motif does not behave exactly as classical ITAMs. The structure of CEACAM-4 is closely related to CEACAM-3, although its function remains elusive. By means of a chimeric CEACAM-3/CEACAM-4 receptor, it was found that CEACAM-4 would be able to function as a phagocytic receptor, although its precise ligand, if any, remains unknown [115]. CEACAM-6 (CD66c) and -8 (CD66b; often used as a marker for neutrophil specific granules) contain a GPI anchor that nevertheless transmits activating signals [110]. CEACAM-6, for instance, was found to mediate neutrophil-mediated ADCC towards B cell lymphoblasts *in vitro* [116]. CEACAM-6 can bind to other CEACAM-6 molecules, but binds also to CEACAM-1, -8 and CEA. Instead, CEACAM-8 showed only binding to CEACAM-6 [110,117]. However, CEACAM-8 Fc fragments were able to bind CEACAM-1 when expressed on epithelial cells [118]. Singer et al. investigated the function of CEACAM-8 [118] and found that this was secreted by neutrophils in response to TLR9-dependent bacterial DNA recognition. CEACAM-8 Fc fragment binding to CEACAM-1 on epithelial cells was accompanied with reduced TLR2-dependent inflammation. This inhibitory feedback mechanism may also apply for neutrophils themselves, as these also express CEACAM-1. Clearly, the CEACAM family holds considerable potential for multiple regulatory interactions, that we are only beginning to understand.

3.5. SIRP receptors

The prototypic receptor of this family, signal regulatory protein α (SIRPα), is a myeloid inhibitory receptor containing three Ig-like domains and a cytoplasmic region containing two ITIMs [119]. SIRPβ1 and SIRPγ have similar extracellular domains, but lack a cytoplasmic tail with ITIMs. SIRPβ1 instead can associate with DAP12. Only SIRPα and perhaps also SIRPβ1 are expressed on human neutrophils. The principal ligand for SIRPα is CD47, an ubiquitously expressed glycosylated protein [120,121]. CD47 functions as a "don't eat me signal" by binding to inhibitory SIRPα and thereby inhibits certain effector functions of neutrophils and macrophages, including host cell phagocytosis. As such SIRPα negatively regulates erythrocyte and platelet clearance by macrophages in mice [122]. Of interest, tumor cells often over-express CD47 and thereby avoid antibody-dependent destruction by human neutrophils and macrophages [14,123,124]. Therapeutic interference with CD47-SIRPα may therefore be used for potentiating antibody therapy against cancer. SIRPα is subject to considerable polymorphic variation, and the NOD mouse has a variant that binds strongly to human CD47, thereby explaining the superiority of this mouse strain over other strains in the engraftment of human cells and tissues [125–127]. In neutrophils SIRPα is expressed on the surface as well as in granules that can be mobilized upon activation by *e.g.* fMLP [128]. Although the roles of SIRPα in the regulation of host cell phagocytosis and tumor cell killing are clearly established, there is also some evidence for regulation of other human and murine neutrophil functions, including transendothelial migration [128,129] and phagocyte NADPH oxidase activity [130]. Whereas putative ligands for SIRPβ have not been identified, cross-linking of the receptor triggers DAP12 association, Syk recruitment, and phagocytosis in mouse macrophages [131].

3.6. ILT and PIR receptors

Immunoglobulin-like transcript (ILT) receptors, also known as leukocyte immunoglobulin-like receptors (LILR or LIR), are transmembrane proteins with two to four Ig-like domains. MHC-I molecules have been identified as ligands for at least some of the ILT receptors, as has been confirmed for ILT-2 and ILT-4. The precise function of these receptors has not been clarified yet, although it has been proposed that they may be important for the maintenance of immunological tolerance [132–134]. The murine analogs of the LILR receptors are thought to be the paired Ig-like receptors (PIR)-A and -B [135,136]. Human neutrophils express ILT-1, ILT-3, ILT-4 and ILT-5, whereas mouse neutrophils express PIR-A and PIR-B. ILT-1 is the only activating receptor; it assembles with the FcRγ chain upon receptor ligation, whereas ILT-3, -4 and -5 contain intrinsic ITIM domains [132,137]. PIR-A and PIR-B have six Ig-like domains; PIR-A is thought to associate with FcRγ, whereas PIR-B has a typical ITIM motif [138].

3.7. PILR receptors

Human and mouse paired immunoglobulin-like receptor (PILR)α and -β are paired receptors with inhibitory and activating potential, respectively. Both human and mouse neutrophils express PILRα and -β [139]. PILRα contains a single extracellular V-set Ig-like domain and two ITIM motifs, whereas truncated PILRβ transmits its activating signals via DAP12. Human and mouse

PILRα share 40% homology, where the ligand interaction regions remain conserved [139–142]. Both SHP-1 and SHP-2 are recruited to phosphorylated ITIMs of PILRα, although SHP-2 shows greater affinity [139]. PILRα interacts *in cis* with sialylated glycoprotein host ligands, such as CD99, an abundantly O-glycosylated transmembrane protein, and also collectin-12 and neural proliferation factor-1 (NPDC-1) [142,143]. Interestingly, PILRα shares approximately 22% sequence homology with Siglec-1, which includes a conserved arginine that Siglecs and PILRα need to bind to sialylated ligands [142]. PILR receptors are thought to play a role in the regulation of immune responses through CD99 binding, which is widely expressed on immune cells and also on endothelial cells [141,144].

3.8. TREM receptors

Triggering receptors expressed by myeloid cells (TREM)-1, -2 and -3 are activating receptors expressed both in human and mice. Additionally, human and mice also express TREM-like transcripts (TLT)-1 and -2 [145,146], but only TREM-1 and TLT-2 are expressed on neutrophils [147,148]. Putative ligands for TREM and TLT have remained elusive, although both host molecules and bacterial ligands have been proposed [145,149]. TREM-1 has a single extracellular Ig-like domain and associates with DAP12 [145,150,151]. Upon LPS stimulation TREM-1 is up-regulated and regulates cytokine secretion and neutrophil degranulation in human and mice [147,149]. Furthermore, TREM-1 was found to increase inflammation and induce septic shock as inhibition of TREM-1 protected mice against these symptoms [152]. Only little is known about the TLTs. While TLT-1 is known to associate with SHP-1 after intrinsic ITIM phosphorylation [153], TLT-2 on neutrophils appears to act as an activating receptor, although intrinsic motifs or associated molecules are as yet unknown. TLT-2 resides in the primary (azurophilic) granules and is up-regulated through degranulation after stimulation with inflammatory mediators [148,154]. TLT-2 is then able to mediate neutrophil activation and chemotaxis after agonists (fMLP) binding to GPCRs on neutrophils [155].

3.9. CD200R

The CD200 receptor (CD200R) does not contain ITAM or ITIM domains, and therefore does not exactly fit the immunoreceptor definition (Section 1). However we will briefly describe it, as CD200R is expressed on myeloid cells, including both human and mouse neutrophils [156,157]. The CD200 receptor (interacts with cell surface glycoprotein CD200 (OX2) and is involved in many immunomodulatory processes. CD200R contains, like CD200, two extracellular Ig-like domains and presumably evolved from gene duplication. CD200R has a cytoplasmic NP_XY motif that associates with Dok1 and Dok2 proteins, which subsequently recruit inhibitory SHIP. The ligand CD200, also a member of the IgSF, is widely expressed and therefore CD200R-CD200 interactions are involved in many immune-regulatory processes [156,158]. For instance, CD200R was found to attenuate inflammation in neurodegenerative and cardiovascular disorders, and also in allergy [159]. Pathogens and cancer cells may have evolved means that result in immune evasion: CD200 is up-regulated in leukemias and large DNA viruses including herpes- and poxviruses, seem to bind CD200 [159–161].

3.10. SIRL-1

A recently identified myeloid inhibitory receptor on human monocytes and neutrophils is signal inhibitory receptor on leukocytes (SIRL)-1. SIRL-1 contains one extracellular V-set Ig-like domain and two cytoplasmic ITIM motifs that recruit SHP-1 and SHP-2. No homolog of SIRL-1 in mice has been identified. SIRL-1 is homologous to LAIR-1, that is expressed on activated neutrophils in particular (see Section 3.11), although its expression pattern resembles SIRPα more closely [162]. SIRL-1 inhibits amongst other processes FcεRI-mediated degranulation and TNF-α production [162], and was shown to dampen FcγR-mediated ROS production but not phagocytosis in neutrophils [163]. Moreover, *in vitro* SIRL-1 was found to inhibit NET formation in neutrophils obtained from systemic lupus erythematosus (SLE) patients or in healthy control neutrophils stimulated with plasma from SLE patients [164].

3.11. LAIR-1

LAIR (leukocyte-associated immunoglobulin-like receptor)-1 receptor and also the related soluble LAIR-2 molecule both act as receptors for collagens [165]. LAIR-1 possibly dampens immune cell activation in tissues after extravasation as collagens are not exposed to flowing blood; at least not while the vasculature is intact [166]. LAIR-1 is expressed on activated neutrophils and contains an Ig-like extracellular domain and two intracellular ITIM domains, that recruit both SHP-1 and SHP-2 [167–169]. LAIR-1 has been relatively conserved: mouse LAIR-1 shares 40% sequence identity with human LAIR-1 (the least sequence identity was found in the C-terminal ITIM domain), although mice do not seem to express soluble LAIR-2. Furthermore, mLAIR-1 recruits SHP-2 only. This can be explained by the modified C-terminal ITIM sequence; SHP-1 needs two phosphorylated ITIMs to be able to bind [170], whereas apparently only one functional ITIM is sufficient to mediate SHP-2 recruitment. LAIR-1 is a potent inhibitory receptor, and has been shown to inhibit cytotoxicity, degranulation or calcium mobilization in different immune cells. This has not been directly shown for neutrophils yet [165,167], although an inhibitory role for neutrophils may be anticipated as well.

4. Immunoreceptor function in disease

Neutrophils are dynamic and versatile cells with a primary role in the host defense against bacteria, but have also been shown to be important in other inflammatory diseases, including autoimmunity, and accumulating evidence suggest that they also play a role in cancer. As above described, neutrophils are equipped with an impressive variety of immunoreceptors that have the capacities to control and fine-tune the many effector functions of these cells through largely defined canonical activating and inhibitory signaling pathways. Why neutrophils have so many of such activating and inhibitory receptors is probably related to the differences in ligand specificity between these receptors. This offers the appropriate capacity for control under a variety of conditions, which likely include their residence in tissues or not, the proximity of signals from antibodies, host cells and others, or the absence of these. To really understand the various functions of the individual immunoreceptor in neutrophils, we need to know, in both homeostatic and the relevant pathologic conditions, exactly where and when they are functional. We are currently only beginning to scratch the surface here. Studies with conditional, neutrophil-specific, gene targeted mice, for instance, may provide clues about an overall involvement of a given immunoreceptor. The following part is intended to provide an overview of what is known about the roles of the different immunoreceptors on neutrophils in different disease settings.

4.1. Infection

There is convincing evidence that at least some of the activating immunoreceptors on neutrophils contribute to the recognition of pathogens, thereby promoting activation of some or all of the

various neutrophil effector functions, and which ultimately lead to the elimination of the infection. Conversely, because inhibitory receptors attenuate immune cell activation, it is not surprising that pathogens also acquired ways to manipulate neutrophil inhibitory receptor pathways to evade immunity. Bacteria have actually demonstrated to interfere with immunoreceptor signaling in a generic fashion by expressing for instance ITIM-bearing virulence factors or the tyrosine phosphatases in these signaling pathways [171]. They may also express ligands for some of the inhibitory receptors to promote inhibitory receptor triggering. On the other hand, the host may have activating receptors against such pathogens that may directly activate immune cells, including neutrophils.

An example of bacterial immune evasion through inhibitory immunoreceptors is Group B *Streptococci* (GBS) and their interaction with the inhibitory Siglec-9. Siglec-9 (and its mouse ortholog Siglec-E) mediates inhibition of neutrophil phagocytosis, NET formation and respiratory burst when aggregated by sialylated N-acetyllactosamine. GBS expresses precisely these glycans to promote their own survival [172]. Additionally, GBS use their surface anchored β-protein to bind to inhibitory Siglec-5, to impair macrophage phagocytosis and neutrophil activation and killing [173]. To counteract this immune suppressive mechanism of GBS, Siglec-14, the activating counterpart of Siglec-5 that probably arose from Siglec-5 by duplication (and divergence), initiates an activating pathway upon β-protein-mediated GBS binding. Interestingly, individuals with a polymorphism resulting in Siglec-14 deficiency were found to be more susceptible for persistent GBS infection [104]. CEACAMs play important roles in host defense against certain bacteria such as *Neisseria*, *Salmonella* and *Escherichia coli* [107]. Opa adhesion proteins expressed by *Neisseria meningitidis* and *Neisseria gonorrhoeae* bind to CEACAM-1, -3, -5, -6: only CEACAM-5 is not expressed on neutrophils [106]. Only uptake of *N. gonorrhoeae* via CEACAM-3 results in neutrophil activation, pro-inflammatory cytokine production and subsequently, in intracellular granule release and respiratory burst, contributing to the killing of the bacteria [174,175]. Neutrophil activation through CEACAM-3 involves Src-mediated phosphorylation of the ITAM-like motif, followed by Vav association and Rac activation [176]; inhibition of Src-family kinases abolishes bacterial uptake [177]. Interestingly, ITIM-containing CEACAM-1 and GPI-anchored CEACAM-6 on neutrophils also phagocytose *N. gonorrhoeae* upon binding, but this does not have an impact on neutrophil activation [175]. CEACAM-1 on $CD4^+$ T cells however, was found to suppress T cell activation and proliferation [178]. It therefore seems possible that the cooperation of CEACAM-1 and -6 with CEACAM-3 acts mainly to control excessive neutrophil activation, maybe to protect the host against collateral tissue damage. In line with this notion, the murine coronavirus mouse hepatitis virus (MHV) was found to bind CEACAM-1 to mediate its own uptake; CEACAM-$1^{-/-}$ mice were found to be completely resistant to MHV infection. This apparent inhibition of neutrophil activation after CEACAM-1-mediated uptake may even be beneficial for MHV [179]. Besides CEACAM-1 exploitation, viruses have acquired many immune evasive properties to establish infection, for instance by binding CD300 receptors that bind PS or PE on apoptotic cells. Viruses can encapsulate themselves in a lipid bilayer envelope incorporating PS or PE, thereby facilitating their entry into immune cells as apoptotic bodies in disguise [180]. Additionally, several herpes viruses express CD200 orthologs that specifically bind the inhibitory CD200R. This interaction proved to be similar to host CD200-CD200R interactions [161] and resulted in down-regulation of human macrophage and basophil activity [181,182]. However, whether this down-regulation actually contributes to the virus' survival is not known yet. Moreover, CD200R was shown to dampen neutrophil-mediated inflammation during Influenza A infection in mice. Deficiency of CD200R (normally highly expressed on neutrophils) strongly promotes neutrophil influx into the lungs and neutrophil-associated pathology, but it does not affect clearance of the virus, implicating primarily a host-protective role for CD200R [183].

Another example of how immunoreceptors can influence immune responses are the HLA-class I-recognizing ILT receptors, that seem to be involved in immune regulation during HIV-1 infection. An association between HLA alleles and HIV-1 disease progression had already been established for a long time, but it has now become apparent that the allele-specific interaction between HLA class I molecules and ILT receptors contributes to HIV-1 disease outcome, and at least in part explains the HLA association of progression of HIV [184]. For instance, ITIM-containing ILT-4 (*LILRB2*) displays high-affinity binding to a specific subset of HLA-B*35 alleles, known as B*35-Px. The same allele is associated with rapid HIV-1 disease progression and attenuated DC function. This suggests that an inhibitory mechanism through specific ILT-4 interaction attenuates effective immune response upon infection [185]. However, as ILT-4 is also expressed on monocytes, macrophages and DCs, it remains to be established whether neutrophils have any involvement in this process.

4.2. Inflammation

The innate immune system is crucial for the first line of defense against pathogens. Binding of PAMPs to PRRs triggers inflammatory responses that are needed to combat pathogens. However, this response needs to be controlled to prevent collateral tissue damage and excessive immune responses. Inhibitory receptors play pivotal roles in this control. For example, inhibitory PILRα was found to protect against damage inflicted by murine neutrophils during LPS-inflicted inflammation. PILR$\alpha^{-/-}$ mice were more susceptible to endotoxin-induced shock than wild type mice, likely caused by the PILR$\alpha^{-/-}$ neutrophils, which, besides high MPO activity, also showed increased chemotaxis and adhesion capacity [186]. Similarly, in a PILR$\alpha^{-/-}$ mouse model of inflammatory arthritis, more inflammatory cytokines were produced, and conversely, mAbs targeting PILRα in wild type mice reduced inflammatory arthritis. However, as macrophages and DCs also express PILRα, a specific contribution of neutrophils cannot be endorsed [187]. A similar protective role was found for CD300a. Co-ligation of CD300a and FcγRIIa negatively regulates the FcγRIIa-mediated ROS production by human neutrophils, but ROS production is not inhibited when CD300a is co-ligated with TLR-4, suggesting a specific protective role of CD300a in inflammation but not in infection [92]. Siglec-E, described in Section 4.1 as an inhibitory receptor that is activated upon the binding of sialic acids expressed by GBS, was shown to serve a neutrophil-specific protective role during pulmonary inflammation. Siglec-E-deficient mice presented with high neutrophil influx to the lungs that was, intriguingly, abrogated upon CD11b integrin blockade, suggesting that Siglec-E suppresses CD11b "outside-in" signaling and thereby limits neutrophil adhesive properties [188]. Collectively, insights in inhibitory receptors will create opportunities for intervention and the development of therapeutics. This is the case for instance in Crohn's disease where SIRPα targeting with a CD47-Fc protein suppresses inflammatory cytokine production in SIRPα-expressing cells [189].

But how are neutrophils still able to combat pathogens with all these inhibitory signals? It seems that when inhibitory receptors are activated simultaneously with PRRs, the inhibitory signal is easily overruled by the activating signals, as illustrated *e.g.* above with the co-ligation of CD300a with TLR-4, and/or alternatively, that the inhibitory receptor expression decreases by *e.g.* down-regulation. The latter was shown for instance with SIRL-1, which negatively regulates the respiratory burst of human phagocytes.

Yet, upon simultaneous PRR triggering, SIRL-1 expression is quickly down-regulated, which enabled FcR-mediated activation of the NADPH oxidase, and killing of the pathogens [163]. Another example is SIRPα, which becomes quickly down-regulated on mouse macrophages upon LPS exposure, to permit effector responses [190]. Londino et al. essentially confirmed this by showing that SIRPα is proteolytically cleaved from monocytes and human lung epithelial cells upon LPS and TNF-α stimulation, and that this results in enhanced NF-κB pathway activation [191]. A similar practice was found in mouse and human neutrophils, in which, conversely, the intracellular ITIM domains were cleaved from SIRPα [192], suggesting a mechanism by which neutrophils can shape their inflammatory responses.

4.3. Autoimmunity

Autoimmune diseases are characterized by detrimental and harmful immune activation directed against auto-antigens and immunity towards host tissues. Abnormal signaling through activating or inhibitory receptors may certainly contribute to autoimmune development and maintenance. There is at present (indirect) genetic evidence in humans to support this. For instance, SNPs in CD300 genes have been linked to psoriasis susceptibility [193]. Furthermore, there is direct evidence to demonstrate a link between immunoreceptors and the susceptibility to autoimmunity in mice. As indicated above, the (genetic) targeting of CD47-SIRPα interactions in Crohn's disease [189], as well as a variety of other T cell-mediated inflammatory diseases, such as experimental colitis [194], experimental autoimmune encephalomyelitis [195], and collagen- or *S. aureus*-induced arthritis [196–198], has proven to be beneficial. In the past several years, the role of neutrophils in autoimmune diseases has been more and more acknowledged [9]. For example, the chronic inflammatory response in autoimmune diseases, such as *e.g.* RA, leads to the recruitment of neutrophils that subsequently contribute substantially to tissue damage, ultimately resulting in irreversible processes like cartilage destruction [199]. Moreover, anti-neutrophil autoantibodies (ANCAs) produced, for instance, in SLE may target neutrophils for autoimmunity by binding neutrophil surface antigens, causing the activation of the neutrophil and subsequently trigger neutrophil effector mechanisms, which contributes to the pathology of the disease [200,201]. However, in spite of the important role of neutrophils in autoimmunity, the role of immunoreceptors on neutrophils influencing or steering autoimmunity have not been extensively investigated. This is unfortunate, as these immunoreceptors might be promising therapeutic targets as was seen when, for instance, the FcγR was targeted in antibody-mediated autoimmune diseases such as RA. The role of FcγR signaling in neutrophils during RA was shown in both complete Syk knockout mice [202] and in neutrophil -specific $Syk^{-/-}$ mice [40], illustrating how neutrophil-dependent recognition of immune complexes contributes to the development of inflammatory autoimmunity. Interestingly, inhibitory receptors can also be protective during autoimmune diseases. For instance, inhibitory receptor SIRL-1 was suggested to play a protective role in SLE by preventing NET release by human neutrophils. Ligation of SILR-1 on neutrophils with anti-SIRL-1 antibodies suppressed spontaneous NET release as well as ANCA-induced NET release, providing evidence for SILR-1 being a potential therapeutic target [164].

4.4. Cancer

Apart from macrophages, also neutrophils may positively or negatively affect tumor progression. It was shown for instance that IL-17 production by γδT cells results in neutrophil accumulation. These neutrophils were subsequently able to suppress metastasis-limiting cytotoxic T lymphocytes, in at least a mouse context [11]. Currently, there is no direct evidence regarding the involvement of neutrophil immunoreceptors on tumor progression, but it seems quite likely that at least in some cases this contributes to some extent. Cancers have evolved different ways to escape immunosurveillance: one of these is the up-regulation of ligands for inhibitory receptors on immune cells. Many of these receptors are also expressed on neutrophils and may therefore inhibit neutrophil anti-tumorigenic activities. Some of these ligands may include MHC-I molecules [203,204], and also the surface glycosylation of cancer cells is known to be substantially altered by cell transformation [205,206].

A game changer for neutrophils may be the presence of tumor cell opsonizing antibodies, which is particularly relevant during monoclonal antibody therapy with, well-established antibody therapeutics such as trastuzumab, cetuximab and rituximab. Antibody-opsonization enables neutrophils to bind cancer cells, via their Fc receptors and to subsequently destroy them. Thus Fcγ, but also Fcα receptors on neutrophils can mediate the recognition and activation of the effector mechanisms by neutrophils [207]. Not only NK cells and macrophages play roles in antibody-dependent tumor cell killing, but also neutrophils, as has now been demonstrated in various studies [208–210]. There is also good evidence that neutrophils contribute to antibody-dependent destruction of cancer cells *in vivo* in mice [13,211]. Not the high-affinity FcγRI nor the highly expressed FcγRIIIb (with up to ~200,000 molecules/cell), but rather FcγRIIa appears to be the dominant FcγR to trigger neutrophil ADCC. This is also consistent with studies in which breast cancer patients with the higher-affinity FcγRIIa H131 polymorphic variant were shown to respond better to antibody therapy with the anti-Her2 antibody trastuzumab than patients with the lower-affinity R131 variant [212,213].

Still, when cancer cells express potent ligands to inhibit immune cell effector function, antibody therapy will be suboptimal at best. Therefore, more insights into these mechanisms may help develop new strategies to target both solid and leukemic tumor cells. Clearly, the challenge will be to identify the most relevant inhibitory receptors and not cause unacceptable levels of autoimmune disease. CD47-SIRPα interactions are a promising target in this context. As stated in Section 3.5, CD47 is often over-expressed on tumor cells to serve as a "don't eat me" or "don't kill me" signal. The therapeutic potential of targeting CD47-SIRPα interactions has specifically been shown in both human and mice by abrogating CD47-SIRPα signaling in antibody-dependent killing of tumor cells [123,214], and this may involve stimulation of both macrophage phagocytosis and/or neutrophil ADCC. This concept is now also being explored for clinical application [215]. Likewise, the targeting of CD200-CD200R interactions is also being evaluated in clinical trials. CD200, the ligand for inhibitory CD200R, was found to be a prognostic factor for multiple myeloma [216] and was increased in more than 50% of the patients with acute myeloid leukemia. This increased expression, moreover, correlates with a lower probability for complete remission [160,217]. That CD200R signaling is involved in tumor progression was demonstrated *in vivo*, because $CD200^{-/-}$ mice had a later onset and less chemically-induced skin papillomas compared to wild type mice. However, intriguingly, CD200R signaling controlled tumor outgrowth irrespective of CD200 expression on the tumor cells, rather suggesting an indirect role of CD200 in tumor tolerance. Indeed, $CD200^{-/-}$ mice presented with a transient skin condition: signs of a break of immune tolerance. Overall, this suggests that CD200-CD200R interactions have effects that may not be directly mediated by the tumor cells [218].

Besides CD47 or CD200 overexpression, cancer cells express a variety of molecules that can potentially inhibit immune cell effector functions. Abnormal glycosylation and excessive amounts

of sialic acids on tumor cells interact with inhibitory Siglecs to suppress anti-tumor immune activity. This has been previously shown for human NK cells [219] and DCs [220] and might also modulate neutrophil responses in *e.g.* antibody-dependent killing mechanisms. Indeed, blocking Siglec-9 on neutrophils enhances antibody-independent anti-tumor activity *in vitro* [221]. However, in spite of an initial protective role, in Siglec-E (*i.e.* the murine equivalent of Siglec-9) deficient mice, tumors grow faster once these are established, which was attributed to the polarization of pro-tumorigenic macrophages, overall suggesting a complex dual role for Siglec-E [221].

Similar to some viruses (described in Section 4.1), tumor cells may express high levels of phosphatidylserines or related phospholipids as well, which as a result, may inhibit NK cell-mediated killing through CD300a [222]. This has not been investigated for neutrophils. Another example is collagen, which often is abundant in solid tumors as a result of secretion of collagen by stromal cells in the extracellular matrix, as well as the expression of transmembrane collagen on the tumor cell membrane. It is therefore proposed that in this way tumor cells may avoid immunosurveillance by LAIR-1-expressing immune cells. However, it seems unlikely that this would apply for neutrophils, as these cells express LAIR-1 only upon cellular activation.

5. Conclusions

Taken together, it is clear from the above that neutrophil functions are modulated by the activating and inhibitory signaling pathways that are known to act downstream of ITAM- and ITIM-containing receptors. Moreover, the diverse range of immunoreceptors on neutrophils that allow detection and integration of a variety of different extracellular ligands regulate activating and inhibitory signaling. While there is scattered but nevertheless accumulating information with respect to the individual functions of some of these inhibitory receptor pathways in neutrophils *in vitro*, we have hardly started to understand their roles and their possible interplay with other signaling receptors in an *in vivo* context. The analysis of mice with neutrophil-specific deficiency or mutation in crucial genes may certainly provide useful information about this. Interestingly, targeting of some of these immunoreceptor pathways instrumental in neutrophils and also in other immune cells has already showed to be promising in a number of disease conditions, and further studies should demonstrate whether this will be of benefit to the treatment of human disease.

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