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Extracellular Mechanisms of Neutrophils in Immune Cell Crosstalk

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Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
APRIL, a proliferation-inducing ligand; ARDS, acute respiratory distress syndrome; BAFF, B-cell activating factor; BCG, Bacillus Calmette-Guérin; DC, dendritic cell; EV, extracellular vesicle; G-MDSC,

ABSTRACT

Neutrophils are professional phagocytes that provide defense against invading pathogens through phagocytosis, degranulation, generation of ROS, and the formation of neutrophil extracellular traps (NETs). Although long been considered as short-lived effector cells with limited biosynthetic activity, recent studies have revealed that neutrophils actively communicate with other immune cells. Neutrophils employ various types of soluble mediators, including granules, cytokines, and chemokines, for crosstalk with immune cells. Additionally, ROS and NETs, major arsenals of neutrophils, are utilized for intercellular communication. Furthermore, extracellular vesicles play a crucial role as mediators of neutrophil crosstalk. In this review, we highlight the extracellular mechanisms of neutrophils and their roles in crosstalk with other cells.

Keywords: Neutrophils; Neutrophil extracellular trap; Extracellular vesicles; Immune cell crosstalk

INTRODUCTION

Neutrophils are one of the first responders of immune system and have long been considered as short-lived effector cells with limited biosynthetic activity (1,2). They provide defense against invading pathogens through phagocytosis, degranulation, generation of ROS, and the formation of neutrophil extracellular trap (NET) (3). In addition to these defense mechanisms, neutrophils have been shown to have additional biological functions, such as the release of soluble factors, cytokines, chemokines, growth factors, alarmins, and specialized pro-resolving mediators (4-7). They also generate extracellular vesicles (EVs) that exert either proinflammatory or anti-inflammatory responses (8,9). Recent studies have also shown that neutrophils play a role in antigen (Ag) presentation by releasing immunomodulatory molecules (4,6,7). This suggests that neutrophils actively communicate with other innate and adaptive immune cells rather just exerting their phagocytic role (7,10).

Neutrophils are known to indirectly regulate adaptive immune cells by regulating innate immune cells, such as macrophages or dendritic cells (DCs). However, recent studies

granulocytic myeloid derived suppressor cell; IRF1, interferon regulatory factor 1; MPO, myeloperoxidase; Mtb, *Mycobacterium tuberculosis*; NDEV, neutrophil-derived extracellular vesicle; NE, neutrophil elastase; NET, neutrophil extracellular trap; TAN, tumor-associated neutrophil; pDC, plasmacytoid dendritic cell.

Author Contributions

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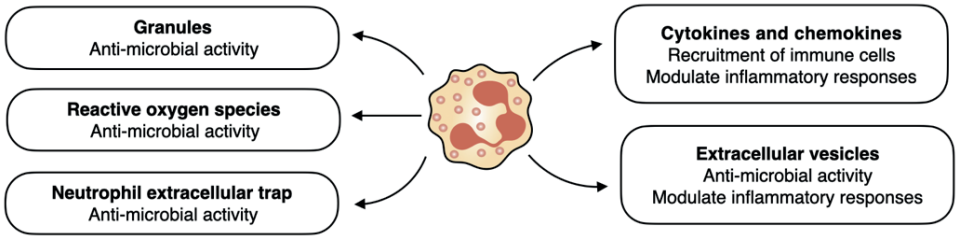

Figure 1. Overview of neutrophil interactions and immune responses. As the first responders of immune system, neutrophils employ a variety of defense mechanisms against pathogens. These mechanisms include granule release, production of ROS, formation of NETs, and secretion of cytokines, chemokines, and EVs. These arsenals not only facilitate the elimination of pathogens, but also serve as means for neutrophils to communicate with neighboring immune cells.

have shown that they can also directly interact with adaptive immune cells through Ag presentation (6). Neutrophils can populate in secondary lymphoid tissues, such as spleen and lymph nodes, and present Ags to adaptive immune cells through expression of MHC class II (6,7). They also interact with other immune cells through contact-dependent mechanisms and soluble mediators, leading to recruitment, activation, and maturation of macrophages, DCs, NK cells, B cells, and T cells (2, 9,11-16).

Neutrophils also generate EVs that mediate immune modulation and cell-to-cell communications with both immune and non-immune cells (8,9). Neutrophils thus have emerged as key components of cell crosstalk rather than merely bystander of complex immune responses (**Fig. 1**). In this review, we highlight the extracellular arsenals of neutrophils, such as soluble mediators, NETs, and EVs, and their role in crosstalk with other cells.

NEUTROPHIL-DERIVED SOLUBLE MEDIATORS

Neutrophils are equipped with various types of soluble mediators, such as granules, cytokines, and chemokines. During differentiation, neutrophils produce different types of granule proteins which are stored within intracellular pools (17). The production of these granules is stringently controlled across different stages of differentiation (1,18). Notably, neutrophils rapidly release these pre-formed granules in response to external stimuli (18). Neutrophils serve as a significant source for over 70 distinct cytokines, chemokines, and growth factors (17). Neutrophils not only store pre-formed cytokines, but also synthesize cytokines *de novo*. Mature neutrophils have mRNAs for cytokine (17), hence they *de novo* synthesize cytokines in response to external stimulation such as TLR 8 agonists (19). These soluble mediators are used by neutrophils for intercellular communication (**Fig. 2**).

Neutrophils are equipped with various types of granules, which are categorized into four groups: i) primary(azurophil) granules, containing myeloperoxidase (MPO), neutrophil elastase (NE), cathepsin G, proteinase 3, defensin, lysozyme, azurocidin, arginase, and serine proteases; ii) secondary(specific) granules, containing lysozyme, lactoferrin, nicotinamide adenine dinucleotide phosphate oxidase components, cathelicidin, collagenase, and plasminogen activator inhibitor-1; iii) tertiary granules, containing gelatinase, leukolysin, collagenase, cathepsin D, and neutrophil gelatinase-associated lipocalin; and iv) secretory vesicles, containing complement receptors, Fc receptors, chemokine receptors, adhesion molecules, cytokines, chemokines, and growth factors (1). Neutrophils release these granule proteins to extracellular milieu through exocytosis (1,17). Neutrophils eliminate pathogens

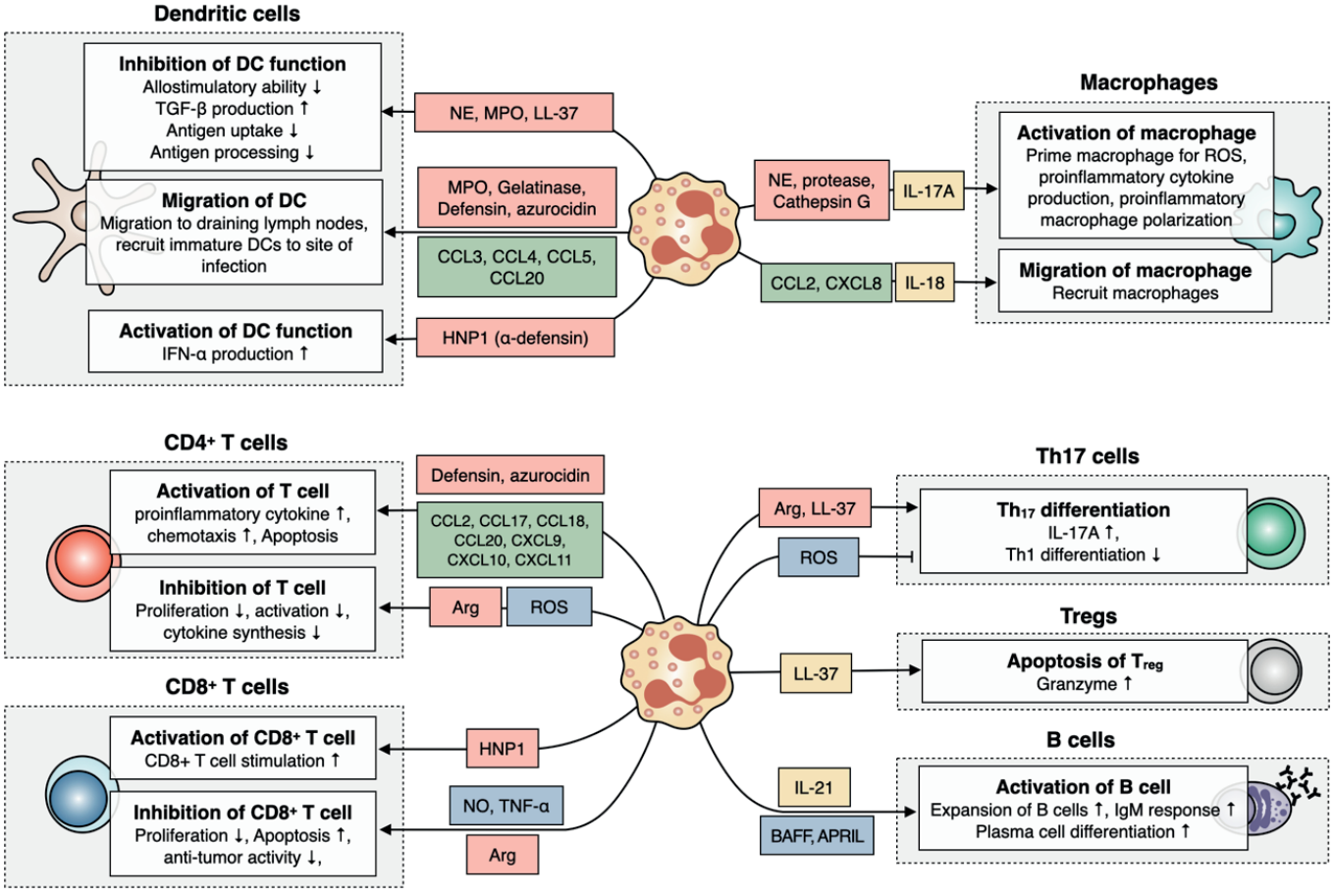

Figure 2. Intercellular crosstalk by neutrophils through soluble mediators. Neutrophils employ various soluble mediators, including granules, cytokines, chemokines, and ROS, for intercellular communication with neighboring immune cells. Neutrophils activate macrophages through IL-17A, protease, NE, and cathepsin G, and induce macrophage migration via CCL2, CXCL8, and IL-18. While neutrophils suppress DC functions through NEs, MPO, and LL-37, they enhance DC activities via HNP1. Granules and chemokines released by neutrophils stimulate DC migration. Neutrophils also communicate with adaptive immune cells through soluble mediators. Neutrophils inhibit T cell function through Arg, and ROS, and promote differentiation into Th17 cells via Arg, LL-37, and ROS. Certain granule proteins, such as defensin and azurocidin, induce proinflammatory cytokine production and apoptosis in $CD4^+$ T cells, while chemokines induce chemotaxis of $CD4^+$ T cells. LL-37 triggers apoptosis in Tregs. Arg, NO, and TNF-α inhibit functions of $CD8^+$ T cells through suppression of proliferation and induction of apoptosis, resulting in the inhibition of anti-tumor activities of $CD8^+$ T cells. HNP1 rather enhances the function of $CD8^+$ T cell. Neutrophils also communicate with B cells via BAFF, APRIL, and IL-21.
HNP1, human neutrophil peptide 1; Arg, arginase; NO, nitric oxide.

through antimicrobial activity of these granules and also utilize them for transmigration through tissue destruction. However, these granules also allow intercellular communications by neutrophils.

NE induces differentiation of macrophages into a pro-inflammatory phenotype through activation of the Srk kinase family (20) and attenuates allostimulatory ability of DCs through skewing maturation of DCs into TGF-β secreting cells (21). MPO secreted by neutrophils inhibits DC activation through its catalytic activity, suppressing adaptive functions of DCs such as migration, Ag uptake, and Ag processing (22). In contrast, MPO and gelatinase are essential for DC migration into draining lymph nodes and subsequent T cell priming in contact hypersensitivity (23). Cathepsin G derived from neutrophils induce chemotaxis of macrophages and activates them to produce pro-inflammatory cytokines, resulting in increased susceptibility to acute HIV-1 infection (24). Human neutrophil peptide 1 (α-defensin) stimulates DCs to produce IFN-α by activating and promoting the nuclear

translocation of IFN regulatory factor 1 (IRF1) (25). Indeed, defensin triggers the secretion of proinflammatory cytokines such as IFN-γ, IL-2, and IL-8 from T cells through NF-κB activation, and also induce T cell apoptosis (26). Defensin and azurocidin induce chemotaxis and regulate functions of naïve T cells and DCs (27,28). Proteases released from neutrophils prime macrophages for more effective oxidative response against microorganism and tumor cells (29). Arginase released from neutrophils suppresses the proliferation, activation, and cytokine synthesis in T cells (30,31) and promotes Th17 cell differentiation (32). Arginase generated from granulocytic myeloid derived suppressor cells (G-MDSCs) suppress proliferation of both $CD4^+$ and $CD8^+$ T cells (33). LL-37, a member of the cathelicidin family of antimicrobial peptides, inhibits DC maturation and activation triggered by TLR ligands, resulting in a reduced ability to activate T cells (34). LL-37 has a broader role beyond its effect on DCs. LL-37 suppresses the differentiation of Th1 cells while promoting IL-17A production from T cells by enhancing aryl hydrocarbon receptor and RORγt expression in a TGF-β dependent manner (35). Moreover, LL-37 induces granzyme-mediated apoptosis in Tregs and stimulated $CD8^+$ T cells (36,37).

Neutrophils are also major sources of chemokines. Activated neutrophils release CXCL1, CXCL8 (also known as IL-8), CXCL9 (monokine induced by gamma IFN), CXCL10 (IFN gamma-induced protein 10), CXCL11 (IFN-inducible T-cell alpha chemoattractant), CXCL12 (stromal cell-derived factor 1), CXCL13 (B cell-attracting chemokine 1), CCL2 (MCP-1), CCL3 (MIP-1 α), CCL4 (MIP-1β), CCL17 (MIP-3β), and CCL20 (MIP-3α). These neutrophil-derived chemokines orchestrate the recruitment of various immune cells, including monocytes, macrophages, DCs, NK cells, various T cell subsets, resulting in an amplification of immune responses (27). Neutrophils release CCL2, recruiting macrophages and enhancing the replication of HIV (38). Neutrophils synthesize chemokines *de novo* and recruit immature DCs to the site of infection via CCL3, CCL4, CCL5, and CCL20 during *Toxoplasma gondii* infection (39). Bacillus Calmette-Guérin (BCG)-activated neutrophils produce chemokines that promote T cell chemotaxis, thereby enhancing the effectiveness of BCG immunotherapy (40). Furthermore, activated neutrophils attract various T cell subsets, including Th1, Th17, naïve T cells and $CD8^+$ T cells, to inflammation sites through the release of chemokines such as CCL2, CXCL9, CXCL10, CXCL11, CCL17, CCL18, and CCL20 (27).

In addition to chemokines, neutrophils produce various cytokines and growth factors including IL-1β, IL-1ra (IL-1 receptor antagonist), IL-6, IL-12, IL-17A, IL-18, IL-21, IFN-α, TGF-β1, TNF-α, G-CSF, M-CSF, and GM-CSF (28,41,42). While many of these neutrophil-derived cytokines foster proinflammatory responses, they also mediate intercellular communication between neutrophils and other immune cells. Neutrophil derived IL-17A coordinates IFN-γ-mediated programming of M1 proinflammatory macrophages during acute pneumonic plague (43). IL-18, another cytokine produced by neutrophils, is involved in recruitment of macrophages and replication of R5HIV (38). TNF-α released from tumor-associated neutrophils (TANs) triggers apoptosis of non-activated $CD8^+$ T cells and inhibits their anti-tumor activity (44). Inflammatory cytokines derived from BCG-activated neutrophils also indirectly stimulate T cell chemotaxis and improve effectiveness of BCG immunotherapy (40).

Neutrophils also produce large amounts of ROS in response to external stimulation, causing oxidative damage against pathogens. However, neutrophils utilize ROS production as a localized signaling mechanism to communicate with neighboring immune cells (45,46). Both mature neutrophils and G-MDSCs utilize localized ROS production to suppress T cell

immune responses (46,47). Additionally, TANs inhibit the proliferation of IL-17 producing T cells through ROS production (48). Furthermore, nitric oxide released from TANs impairs the anti-tumor activity of $CD8^+$ T cells (44).

Neutrophils also communicate with nearby immune cells through expression of certain ligands. They express B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), both of which are crucial for the survival, maturation, and differentiation of B cells (42). Neutrophil-derived BAFF drives protective B cell immunity against lethal *Salmonella typhimurium* infection by fostering expansion of B cells and promoting IgM responses (49). B helper neutrophils, found in the marginal zone of secondary lymphoid tissue, secrete higher amounts of BAFF, APRIL, and IL-21, thereby activating marginal B cells (42). Moreover, APRIL produced by inflammation-recruited neutrophils contributes to establishment of plasma cell niches in mucosa-associated lymphoid tissue, ensuring sustained local Ab production (50).

NETs

NETs are complex structures composed of extracellular DNA, granule proteins, and histones. They were first identified as an arsenal of neutrophils to trap and eliminate pathogens extracellularly (51,52). Initial studies on NETs focused on their role in inflammation, but recent findings have uncovered their wider biological implications that extend beyond their antimicrobial activities (**Fig. 3**). NETs have been associated with a range of immunological diseases, including autoimmune diseases, cardiovascular diseases, pulmonary diseases, thrombosis, sepsis, and cancer (reviewed in (52,53)). Furthermore, the persistence of NETs in circulation provides a crucial source of autoantigen that incites autoantibody production,

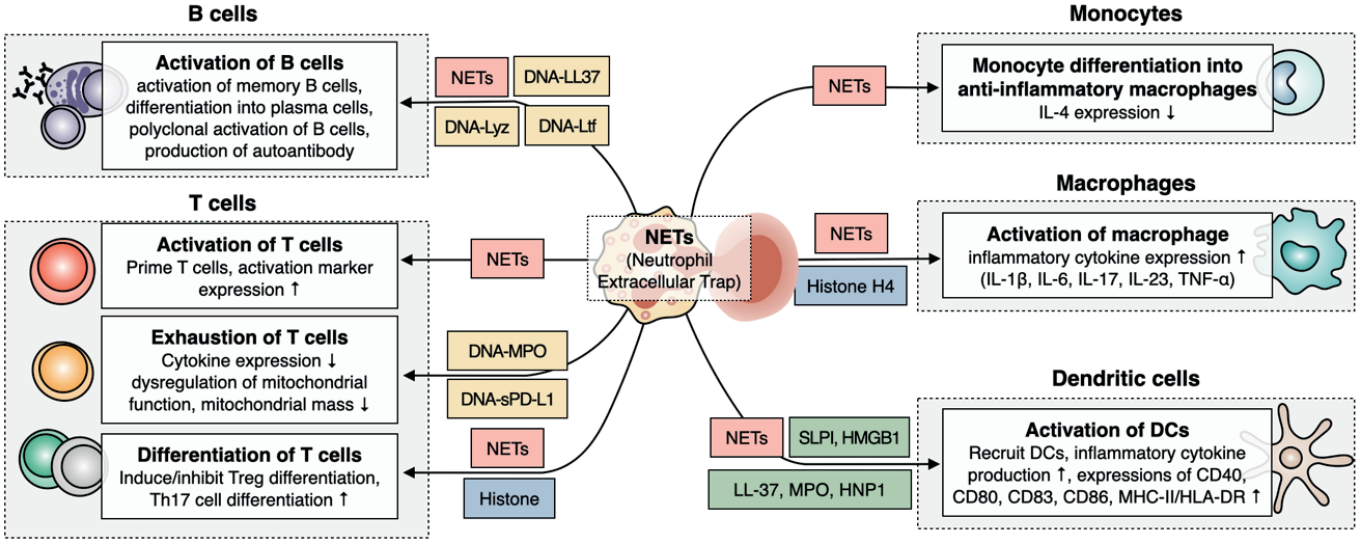

Figure 3. Intercellular crosstalk by neutrophils through NET. NETs, composed of DNA, granule proteins, and histones, regulate neighboring immune cells either directly or via tangled granule proteins and histones. They stimulate macrophages to produce inflammatory cytokines and induce monocyte differentiation into anti-inflammatory macrophages through reduced IL-4 expression. NETs and their granule proteins recruit DCs, trigger inflammatory cytokine production, and induce upregulation of activation marker expressions. Prolonged exposure to NETs cause apoptosis of macrophages and DCs through mitochondrial dysfunction. NETs and granule proteins also activate memory B cells, stimulate the differentiation of naïve B cells into plasma cells, and drive auto-antibody production in B cells. NETs exhibit ambivalent effects on T cells, leading to either activation or exhaustion. NETs either stimulate or inhibit the differentiation of Tregs, while consistently inducing Th17 cell differentiation.
SLPI, secretory leukoprotease inhibitor; HMGB1, high mobility group box 1; HNP1, human neutrophil peptide 1; HLA-DR, human leukocyte antigen-DR isotype.

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thereby exacerbating autoimmune reactions (reviewed in (5,54)). Moreover, NETs can directly stimulate various immune cells, such as B cells, T cells, and Ag-presenting cells, leading to autoimmune reactions (reviewed in (5,54)). Additionally, NETs have been shown to entrap $CD4^+$ T cells, $CD8^+$ T cells, B cells, and monocytes, contributing to either depletion or loss of immune cells during HIV/simian immunodeficiency virus infections (55).

Macrophages are one of the first responders to NETs and play a key role in their clearance. NETs trigger the activation of macrophages, facilitating transfer of antimicrobial peptides to enhance their antimicrobial functions (11). Additionally, NETs stimulate macrophages to produce inflammatory cytokines such as IL-1β, IL-6, IL-17, IL-23, and TNF-α, which exacerbate autoimmune and inflammatory diseases (56,57). In patients with Behcet's disease, elevated levels of histone H4 found in NETs have been associated with increased macrophage activation and the production of IL-8 and TNF-α (58). NETs produced by neutrophils stimulated with IL-8 via CXCR2 exacerbate the progression of atherosclerosis by activating TLR9-dependent NF-κB pathways in macrophages (59). Interestingly, NETs can reprogram the differentiation of monocytes into anti-inflammatory macrophages by downregulating the expression of IL-4 receptors (60). However, prolonged exposure of NETs can induce macrophage death through caspase-induced mitochondrial damage and activation of apoptosis induced factor-dependent pathways (61). Macrophages play a crucial role in clearing NETs from both circulation and tissues. They degrade NETs through extracellular digestion and then uptake them through micropinocytosis (62,63). Impaired NET clearance by macrophages has been closely associated with aggravation of inflammatory diseases, as observed in patients with acute respiratory distress syndrome (ARDS) (64). A failure of macrophages to effectively phagocytose NETs triggers pyroptosis of alveolar macrophages, leading to exacerbation of inflammation during ARDS (65). Either a complete failure or a frustrated phagocytosis of NETs activates innate immune sensors, such as cyclic GMP-AMP synthase-STING, leading to type I IFN production in macrophages (66).

DCs are also an important responder of NETs. NETs recruit DCs and activate them via Fc fragment of IgG through low affinity IIa receptor (FCγII, CD32), leading to production of IFN-α through TLR9 (61,67,68). Certain granule proteins on NETs, such as LL-37, α-defensin, β-defensin, high mobility group box 1, MPO, and secretory leukocyte proteinase inhibitor, activate plasmacytoid DCs (pDCs) to produce inflammatory cytokines including TNF-α, IL-6, and IFN-α during autoimmune diseases (22,67,68). Upon exposure to NETs, pDCs exhibit increased surface expressions of CD40, CD80, CD83, CD86, and MHC-II/human leukocyte antigen-DR isotype, and elevated secretion of proinflammatory cytokines, such as IL-1β, IL-6, IL-8, IL-10, IL-12, and TNF-α (69). However, NETs can hinder differentiation of DCs (60) and maturation of LPS-stimulated monocytic DCs (70). Furthermore, prolonged exposure to NETs can induce the death of DCs through mitochondrial damage (61). These studies suggest the dual roles of NETs on influencing the function of DCs.

Recent studies suggest that NETs also interact with adaptive immune cells. NETs modulate T cells through direct contact with TCR signaling (71). NETs prime $CD4^+$ T cells through direct contact with TCR, leading to a reduced activation threshold and enhanced Ag-specific responses (71). Interestingly, NET-exposed $CD4^+$ T cells also exhibit increased expressions of activation markers, CD25 and CD69 (71). A similar pattern of activation marker expression is found in NET-exposed $CD8^+$ T cells (71). MPO-DNA components in NETs, in conjunction with sPD-L1, contribute to the exhaustion and dysfunction of T cells within the tumor microenvironment (72). Moreover, NETs bearing PD-L1 have been found

to exhaust T cells during ischemia and reperfusion injury in the liver, leading to decreased cytokine expressions, dysregulation of mitochondrial function, diminished mitochondrial mass, and reduced glucose and lipid uptake (72). NET-associated histones can also drive the differentiation and cytokine production in Th17 cells via TLR2/MyD88/STAT3/RORγ-dependent pathway (14). Additionally, NETs can affect T cell differentiation. NETs induce selective differentiation of naïve T cells into Tregs through metabolic reprogramming toward mitochondrial oxidative phosphorylation through TLR4 (13). In contrast, NETs inhibit Treg differentiation in *in vitro* and decrease Treg to Th17 cell ratio during neutrophilic asthma (73). NETs directly activate memory B cells (10) and promote the progression of diffuse B cell lymphoma through TLR9-dependent pathway (74). LL-37 and DNA complex in NETs stimulate a polyclonal activation of memory B cells and BCR, leading to production of Ab against LL-37 during Systemic Lupus Erythematosus (10). Lysozymes and lactoferrin complexes in NETs also activate B cells via TLR9, prompting the production of autoantibodies (10). In patients with Bullous Pemphigoid, NETs have been found to induce the differentiation of B cells into CD19+ CD38+ plasma cells via p38 MAPK pathway, thereby augmenting autoantibody release (9).

NEUTROPHIL-DERIVED EXTRACELLULAR VESICLES (NDEVs)

EVs are membrane-derived vesicles that are released by almost all types of cells, including immune cells. They are categorized into three major groups based on their size and generation mechanism: exosomes, microvesicles, and apoptotic bodies. Neutrophils can spontaneously produce EVs, or generate them in response to certain stimuli (15,16,75). The production and function of these NDEVs varies depending on the prevailing conditions of neutrophils (75). NDEVs are composed of proteins, lipids, amino-acids, glycoconjugates, and RNAs (5,15). NDEVs exert antimicrobial activity, stimulate chemotaxis of immune cells such as macrophages and $CD8^+$ T cells (16,76), and facilitate intercellular communication through their enclosed proteins and RNAs (5) (**Fig. 4**).

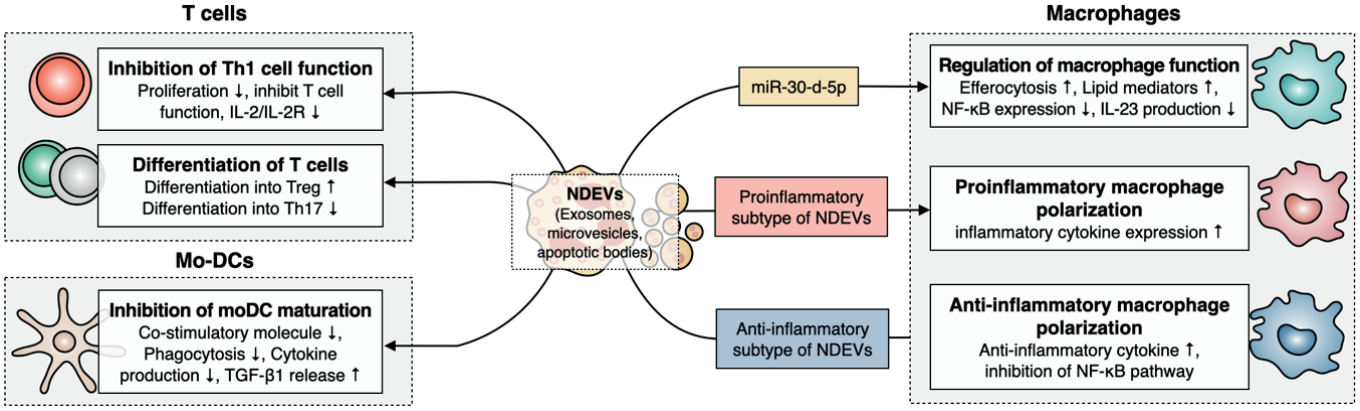

Figure 4. Intercellular crosstalk by neutrophils through NDEVs. Neutrophils produce EVs either spontaneously or in response to stimuli. The contents in NDEVs, such as proteins and RNAs, vary depending on the prevailing condition of neutrophils, resulting in different effects on neighboring immune cells. The proinflammatory subtype of NDEVs drives proinflammatory phenotype polarization of macrophages, whereas the anti-inflammatory subtype of NDEVs induces the anti-inflammatory phenotype polarization of macrophages. NDEVs also regulate macrophage functions through enclosed miRNAs. NDEVs induce the differentiation of Tregs and inhibit Th17 differentiation. They also inhibit the function of Th1 cells through downregulation of IL-2 and IL-2R, and they inhibit maturation of moDCs.
moDC, monocytic dendritic cell.

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NDEVs trigger the release of TGF-β from macrophages, thereby promoting their anti-inflammatory functions (77-79). They activate various signaling pathways, including Mer Tyrosine Kinase activation, NF-κB translocation inhibition, Ca2+ signaling induction, and TGF-β release induction, thereby regulating macrophage responses at the post-transcriptional level (77-79). Anti-inflammatory subtypes of NDEV drive macrophages toward an anti-inflammatory phenotype, resulting in the inhibition of inflammatory functions (16,80). However, NDEVs from *Mycobacterium tuberculosis* (Mtb)-infected neutrophils induce the differentiation of macrophages into proinflammatory phenotype (81,82). Similarly, NDEVs generated by activated neutrophils during sepsis can skew the polarization of macrophages toward proinflammatory phenotype and prime them for pyroptosis through the exosomal miR-30-d-5p-mediated activation of NLRP3 (83). This proinflammatory subtype of NDEVs also induces polarization of macrophages into proinflammatory phenotype through miRs (16). Macrophages phagocytose NDEVs via Tim-4 and MFG-E8, and these macrophages exhibit an increase in IL-10 secretion with reduced numbers during sepsis (84). NDEVs also enhance the efferocytosis of apoptotic neutrophils by macrophages and increase production of specific lipid mediators (85). They also inhibit the maturation of Mo-DCs, impairing the expression of costimulatory molecules, cytokine secretion, and phagocytic activity while increasing the release of TGF-β1 (70). EVs generated by PMN-MDSCs inhibit the differentiation of naïve T cells into Th1 and Th17, rather promoting differentiation into Tregs (86,87). Furthermore, NDEVs suppress the activation and proliferation of T-helper cells by down-regulating IL-2 and IL-2 receptor (88). Marcrophages and DCs phagocytose apoptotic neutrophils and clear them through efferocytosis, which provides antimicrobial molecules and stimulates the production of specialized pro-resolving mediators (85).

Apoptotic bodies from neutrophils elicit an anti-inflammatory response in macrophages through the suppression of NF-κB activation (89,90). They also enhance the production of immunosuppressive cytokine from LPS-stimulated monocytes (91) and suppress the production of anti-inflammatory cytokines in macrophages through expression of proteinase 3 (92). In contrast, apoptotic bodies of Mtb-stimulated neutrophils stimulate proinflammatory responses from macrophages (93,94). Both macrophages and DCs clear apoptotic bodies through efferocytosis (95). The efferocytosis of neutrophil apoptotic bodies dampen the production of IL-23 in macrophages (95) and inhibit DC activation by suppressing the expression of costimulatory molecule (8,96). Notably, LPS accelerate the clearance of neutrophil apoptotic bodies by monocyte-derived macrophages (97). Furthermore, apoptotic bodies from neutrophils stimulated with progesterone induce differentiation of naïve T cells into Tregs through transfer neutrophil proteins, such as forehead box protein, while inhibiting differentiation into Th17 cells (12).

CONCLUSION

Neutrophils, as pivotal components of the innate immune system, interact with a variety of immune cells through various mechanisms. They communicate with both innate and adaptive immune cells, either directly or indirectly, via soluble mediators, NETs, and EVs. The complex and dynamic nature of neutrophil communication highlights their multifaceted role within the immune system and provides insights into their contribution to both physiological function of the immune system and the pathogenesis of various diseases.

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REFERENCES

1. Borregaard N. Neutrophils, from marrow to microbes. *Immunity* 2010;33:657-670.
PUBMED | CROSSREF
2. Nathan C. Neutrophils and immunity: challenges and opportunities. *Nat Rev Immunol* 2006;6:173-182.
PUBMED | CROSSREF
3. Nauseef WM, Borregaard N. Neutrophils at work. *Nat Immunol* 2014;15:602-611.
PUBMED | CROSSREF
4. Tamassia N, Bianchetto-Aguilera F, Arruda-Silva F, Gardiman E, Gasperini S, Calzetti F, Cassatella MA. Cytokine production by human neutrophils: revisiting the "dark side of the moon". *Eur J Clin Invest* 2018;48 Suppl 2:e12952.
PUBMED | CROSSREF
5. Tsai CY, Hsieh SC, Liu CW, Lu CS, Wu CH, Liao HT, Chen MH, Li KJ, Shen CY, Kuo YM, et al. Cross-talk among polymorphonuclear neutrophils, immune, and non-immune cells via released cytokines, granule proteins, microvesicles, and neutrophil extracellular trap formation: a novel concept of biology and pathobiology for neutrophils. *Int J Mol Sci* 2021;22:3119.
PUBMED | CROSSREF
6. Lin A, Loré K. Granulocytes: new members of the antigen-presenting cell family. *Front Immunol* 2017;8:1781.
PUBMED | CROSSREF
7. Mantovani A, Cassatella MA, Costantini C, Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity. *Nat Rev Immunol* 2011;11:519-531.
PUBMED | CROSSREF
8. Hong CW. Extracellular vesicles of neutrophils. *Immune Netw* 2018;18:e43.
PUBMED | CROSSREF
9. Youn YJ, Shrestha S, Lee YB, Kim JK, Lee JH, Hur K, Mali NM, Nam SW, Kim SH, Lee S, et al. Neutrophil-derived trail is a proinflammatory subtype of neutrophil-derived extracellular vesicles. *Theranostics* 2021;11:2770-2787.
PUBMED | CROSSREF
10. Schuster S, Hurrell B, Tacchini-Cottier F. Crosstalk between neutrophils and dendritic cells: a context-dependent process. *J Leukoc Biol* 2013;94:671-675.
PUBMED | CROSSREF
11. Wilson AS, Randall KL, Pettitt JA, Ellyard JI, Blumenthal A, Enders A, Quah BJ, Bopp T, Parish CR, Brüstle A. Neutrophil extracellular traps and their histones promote Th17 cell differentiation directly via TLR2. *Nat Commun* 2022;13:528.
PUBMED | CROSSREF
12. Fang H, Shao S, Xue K, Yuan X, Qiao P, Zhang J, Cao T, Luo Y, Bai X, Li W, et al. Neutrophil extracellular traps contribute to immune dysregulation in bullous pemphigoid via inducing B-cell differentiation and antibody production. *FASEB J* 2021;35:e21746.
PUBMED | CROSSREF
13. Monteith AJ, Miller JM, Maxwell CN, Chazin WJ, Skaar EP. Neutrophil extracellular traps enhance macrophage killing of bacterial pathogens. *Sci Adv* 2021;7:eabj2101.
PUBMED | CROSSREF
14. Wang H, Zhang H, Wang Y, Brown ZJ, Xia Y, Huang Z, Shen C, Hu Z, Beane J, Ansa-Addo EA, et al. Regulatory T-cell and neutrophil extracellular trap interaction contributes to carcinogenesis in non-alcoholic steatohepatitis. *J Hepatol* 2021;75:1271-1283.
PUBMED | CROSSREF
15. Nadkarni S, Smith J, Sferruzzi-Perri AN, Ledwozyw A, Kishore M, Haas R, Mauro C, Williams DJ, Farsky SHP, Marelli-Berg FM, et al. Neutrophils induce proangiogenic T cells with a regulatory phenotype in pregnancy. *Proc Natl Acad Sci U S A* 2016;113:E8415-E8424.
PUBMED | CROSSREF

16. Gestermann N, Di Domizio J, Lande R, Demaria O, Frasca L, Feldmeyer L, Di Lucca J, Gilliet M. Netting neutrophils activate autoreactive B cells in lupus. *J Immunol* 2018;200:3364-3371.
PUBMED | CROSSREF

17. Sheshachalam A, Srivastava N, Mitchell T, Lacy P, Eitzen G. Granule protein processing and regulated secretion in neutrophils. *Front Immunol* 2014;5:448.
PUBMED | CROSSREF

18. Hong CW. Current understanding in neutrophil differentiation and heterogeneity. *Immune Netw* 2017;17:298-306.
PUBMED | CROSSREF

19. Zimmermann M, Aguilera FB, Castellucci M, Rossato M, Costa S, Lunardi C, Ostuni R, Girolomoni G, Natoli G, Bazzoni F, et al. Chromatin remodelling and autocrine TNFα are required for optimal interleukin-6 expression in activated human neutrophils. *Nat Commun* 2015;6:6061.
PUBMED | CROSSREF

20. Krotova K, Khodayari N, Oshins R, Aslanidi G, Brantly M. Neutrophil elastase activates mmps in macrophages and promotes adhesion and cytokine expression through the integrin – Srk pathway. *J Immunol* 2018;200:102.11.
CROSSREF

21. Maffia PC, Zittermann SE, Scimone ML, Tateosian N, Amiano N, Guerrieri D, Lutzky V, Rosso D, Romeo HE, Garcia VE, et al. Neutrophil elastase converts human immature dendritic cells into transforming growth factor-beta1-secreting cells and reduces allostimulatory ability. *Am J Pathol* 2007;171:928-937.
PUBMED | CROSSREF

22. Odobasic D, Kitching AR, Yang Y, O'Sullivan KM, Muljadi RC, Edgtton KL, Tan DSY, Summers SA, Morand EF, Holdsworth SR. Neutrophil myeloperoxidase regulates T-cell-driven tissue inflammation in mice by inhibiting dendritic cell function. *Blood* 2013;121:4195-4204.
PUBMED | CROSSREF

23. Strzepa A, Gurski CJ, Dittel LJ, Szczepanik M, Pritchard KA Jr, Dittel BN. Neutrophil-derived myeloperoxidase facilitates both the induction and elicitation phases of contact hypersensitivity. *Front Immunol* 2021;11:608871.
PUBMED | CROSSREF

24. Moriuchi H, Moriuchi M, Fauci AS. Cathepsin G, a neutrophil-derived serine protease, increases susceptibility of macrophages to acute human immunodeficiency virus type 1 infection. *J Virol* 2000;74:6849-6855.
PUBMED | CROSSREF

25. Wang F, Qiao L, Lv X, Trivett A, Yang R, Oppenheim JJ, Yang D, Zhang N. Alarmin human α defensin HNP1 activates plasmacytoid dendritic cells by triggering NF-κB and IRF1 signaling pathways. *Cytokine* 2016;83:53-60.
PUBMED | CROSSREF

26. Lu W, de Leeuw E. Pro-inflammatory and pro-apoptotic properties of human defensin 5. *Biochem Biophys Res Commun* 2013;436:557-562.
PUBMED | CROSSREF

27. Tecchio C, Cassatella MA. Neutrophil-derived chemokines on the road to immunity. *Semin Immunol* 2016;28:119-128.
PUBMED | CROSSREF

28. Tecchio C, Micheletti A, Cassatella MA. Neutrophil-derived cytokines: facts beyond expression. *Front Immunol* 2014;5:508.
PUBMED | CROSSREF

29. Speer CP, Pabst MJ, Hedegaard HB, Rest RF, Johnston RB Jr. Enhanced release of oxygen metabolites by monocyte-derived macrophages exposed to proteolytic enzymes: activity of neutrophil elastase and cathepsin G. *J Immunol* 1984;133:2151-2156.
PUBMED

30. Vonwirth V, Bülbül Y, Werner A, Echchannaoui H, Windschmitt J, Habermeier A, Ioannidis S, Shin N, Conradi R, Bros M, et al. Inhibition of arginase 1 liberates potent T cell immunostimulatory activity of human neutrophil granulocytes. *Front Immunol* 2021;11:617699.
PUBMED | CROSSREF

31. Munder M, Schneider H, Luckner C, Giese T, Langhans CD, Fuentes JM, Kropf P, Mueller I, Kolb A, Modolell M, et al. Suppression of T-cell functions by human granulocyte arginase. *Blood* 2006;108:1627-1634.
PUBMED | CROSSREF

32. Wu H, Zhen Y, Ma Z, Li H, Yu J, Xu ZG, Wang XY, Yi H, Yang YG. Arginase-1-dependent promotion of Th17 differentiation and disease progression by MDSCs in systemic lupus erythematosus. *Sci Transl Med* 2016;8:331ra40.
PUBMED | CROSSREF

33. Köstlin N, Hofstädter K, Ostermeir AL, Spring B, Leiber A, Haen S, Abele H, Bauer P, Pollheimer J, Hartl D, et al. Granulocytic myeloid-derived suppressor cells accumulate in human placenta and polarize toward a Th2 phenotype. *J Immunol* 2016;196:1132-1145.
PUBMED | CROSSREF

34. Kandler K, Shaykhiev R, Kleemann P, Klescz F, Lohoff M, Vogelmeier C, Bals R. The anti-microbial peptide LL-37 inhibits the activation of dendritic cells by TLR ligands. *Int Immunol* 2006;18:1729-1736.
PUBMED | CROSSREF

35. Minns D, Smith KJ, Alessandrini V, Hardisty G, Melrose L, Jackson-Jones L, MacDonald AS, Davidson DJ, Gwyer Findlay E. The neutrophil antimicrobial peptide cathelicidin promotes Th17 differentiation. *Nat Commun* 2021;12:1285.
PUBMED | CROSSREF

36. Mader JS, Ewen C, Hancock REW, Bleackley RC. The human cathelicidin, LL-37, induces granzyme-mediated apoptosis in regulatory T cells. *J Immunother* 2011;34:229-235.
PUBMED | CROSSREF

37. Mader JS, Marcet-Palacios M, Hancock REW, Bleackley RC. The human cathelicidin, LL-37, induces granzyme-mediated apoptosis in cytotoxic T lymphocytes. *Exp Cell Res* 2011;317:531-538.
PUBMED | CROSSREF

38. Yoshida T, Kobayashi M, Li XD, Pollard RB, Suzuki F. Inhibitory effect of glycyrrhizin on the neutrophil-dependent increase of R5 HIV replication in cultures of macrophages. *Immunol Cell Biol* 2009;87:554-558.
PUBMED | CROSSREF

39. Bennouna S, Bliss SK, Curiel TJ, Denkers EY. Cross-talk in the innate immune system: neutrophils instruct recruitment and activation of dendritic cells during microbial infection. *J Immunol* 2003;171:6052-6058.
PUBMED | CROSSREF

40. Suttmann H, Riemensberger J, Bentien G, Schmaltz D, Stöckle M, Jocham D, Böhle A, Brandau S. Neutrophil granulocytes are required for effective Bacillus Calmette-Guérin immunotherapy of bladder cancer and orchestrate local immune responses. *Cancer Res* 2006;66:8250-8257.
PUBMED | CROSSREF

41. Zhou SL, Zhou ZJ, Hu ZQ, Huang XW, Wang Z, Chen EB, Fan J, Cao Y, Dai Z, Zhou J. Tumor-associated neutrophils recruit macrophages and T-regulatory cells to promote progression of hepatocellular carcinoma and resistance to sorafenib. *Gastroenterology* 2016;150:1646-1658.e17.
PUBMED | CROSSREF

42. Puga I, Cols M, Barra CM, He B, Cassis L, Gentile M, Comerma L, Chorny A, Shan M, Xu W, et al. B cell-helper neutrophils stimulate the diversification and production of immunoglobulin in the marginal zone of the spleen. *Nat Immunol* 2011;13:170-180.
PUBMED | CROSSREF

43. Bi Y, Zhou J, Yang H, Wang X, Zhang X, Wang Q, Wu X, Han Y, Song Y, Tan Y, et al. IL-17A produced by neutrophils protects against pneumonic plague through orchestrating IFN-γ-activated macrophage programming. *J Immunol* 2014;192:704-713.
PUBMED | CROSSREF

44. Michaeli J, Shaul ME, Mishalian I, Hovav AH, Levy L, Zolotriov L, Granot Z, Fridlender ZG. Tumor-associated neutrophils induce apoptosis of non-activated CD8 T-cells in a TNFα and NO-dependent mechanism, promoting a tumor-supportive environment. *OncoImmunology* 2017;6:e1356965.
PUBMED | CROSSREF

45. Yang W, Tao Y, Wu Y, Zhao X, Ye W, Zhao D, Fu L, Tian C, Yang J, He F, et al. Neutrophils promote the development of reparative macrophages mediated by ROS to orchestrate liver repair. *Nat Commun* 2019;10:1076.
PUBMED | CROSSREF

46. Pillay J, Kamp VM, van Hoffen E, Visser T, Tak T, Lammers JW, Ulfman LH, Leenen LP, Pickkers P, Koenderman L. A subset of neutrophils in human systemic inflammation inhibits T cell responses through Mac-1. *J Clin Invest* 2012;122:327-336.
PUBMED | CROSSREF

47. Singel KL, Emmons TR, Khan ANH, Mayor PC, Shen S, Wong JT, Morrell K, Eng KH, Mark J, Bankert RB, et al. Mature neutrophils suppress T cell immunity in ovarian cancer microenvironment. *JCI Insight* 2019;4:e122311.
PUBMED | CROSSREF

48. Mensurado S, Rei M, Lança T, Ioannou M, Gonçalves-Sousa N, Kubo H, Malissen M, Papayannopoulos V, Serre K, Silva-Santos B. Tumor-associated neutrophils suppress pro-tumoral IL-17+ γδ T cells through induction of oxidative stress. *PLoS Biol* 2018;16:e2004990.
PUBMED | CROSSREF

49. Kuley R, Draves KE, Fuller DH, Giltiay NV, Clark EA, Giordano D. B cell activating factor (BAFF) from neutrophils and dendritic cells is required for protective B cell responses against Salmonella typhimurium infection. *PLoS One* 2021;16:e0259158.
PUBMED | CROSSREF

50. Huard B, McKee T, Bosshard C, Durual S, Matthes T, Myit S, Donze O, Frossard C, Chizzolini C, Favre C, et al. APRIL secreted by neutrophils binds to heparan sulfate proteoglycans to create plasma cell niches in human mucosa. *J Clin Invest* 2008;118:2887-2895.
PUBMED | CROSSREF

51. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, Weinrauch Y, Zychlinsky A. Neutrophil extracellular traps kill bacteria. *Science* 2004;303:1532-1535.
PUBMED | CROSSREF

52. Delgado-Rizo V, Martínez-Guzmán MA, Iñiguez-Gutierrez L, García-Orozco A, Alvarado-Navarro A, Fafutis-Morris M. Neutrophil extracellular traps and its implications in inflammation: an overview. *Front Immunol* 2017;8:81.
PUBMED | CROSSREF

53. Mutua V, Gershwin LJ. A review of neutrophil extracellular traps (NETs) in disease: potential anti-nets therapeutics. *Clin Rev Allergy Immunol* 2021;61:194-211.
PUBMED | CROSSREF

54. Costa S, Bevilacqua D, Cassatella MA, Scapini P. Recent advances on the crosstalk between neutrophils and B or T lymphocytes. *Immunology* 2019;156:23-32.
PUBMED | CROSSREF

55. Sivanandham R, Brocca-Cofano E, Krampe N, Falwell E, Venkatraman SM, Ribeiro RM, Apetrei C, Pandrea I. Neutrophil extracellular trap production contributes to pathogenesis in SIV-infected nonhuman primates. *J Clin Invest* 2018;128:5178-5183.
PUBMED | CROSSREF

56. Chen X, Li Y, Qin L, He R, Hu C. Neutrophil extracellular trapping network promotes the pathogenesis of neutrophil-associated asthma through macrophages. *Immunol Invest* 2021;50:544-561.
PUBMED | CROSSREF

57. Hu Z, Murakami T, Tamura H, Reich J, Kuwahara-Arai K, Iba T, Tabe Y, Nagaoka I. Neutrophil extracellular traps induce IL-1β production by macrophages in combination with lipopolysaccharide. *Int J Mol Med* 2017;39:549-558.
PUBMED | CROSSREF

58. Li L, Yu X, Liu J, Wang Z, Li C, Shi J, Sun L, Liu Y, Zhang F, Chen H, et al. Neutrophil extracellular traps promote aberrant macrophages activation in Behçet's disease. *Front Immunol* 2021;11:590622.
PUBMED | CROSSREF

59. An Z, Li J, Yu J, Wang X, Gao H, Zhang W, Wei Z, Zhang J, Zhang Y, Zhao J, et al. Neutrophil extracellular traps induced by IL-8 aggravate atherosclerosis via activation NF-κB signaling in macrophages. *Cell Cycle* 2019;18:2928-2938.
PUBMED | CROSSREF

60. Guimarães-Costa AB, Rochael NC, Oliveira F, Echevarria-Lima J, Saraiva EM. Neutrophil extracellular traps reprogram Il-4/GM-CSF-induced monocyte differentiation to anti-inflammatory macrophages. *Front Immunol* 2017;8:523.
PUBMED | CROSSREF

61. Donis-Maturano L, Sánchez-Torres LE, Cerbulo-Vázquez A, Chacón-Salinas R, García-Romo GS, Orozco-Uribe MC, Yam-Puc JC, González-Jiménez MA, Paredes-Vivas YL, Calderón-Amador J, et al. Prolonged exposure to neutrophil extracellular traps can induce mitochondrial damage in macrophages and dendritic cells. *Springerplus* 2015;4:161.
PUBMED | CROSSREF

62. Haider P, Kral-Pointner JB, Mayer J, Richter M, Kaun C, Brostjan C, Eilenberg W, Fischer MB, Speidl WS, Hengstenberg C, et al. Neutrophil extracellular trap degradation by differently polarized macrophage subsets. *Arterioscler Thromb Vasc Biol* 2020;40:2265-2278.
PUBMED | CROSSREF

63. Farrera C, Fadeel B. Macrophage clearance of neutrophil extracellular traps is a silent process. *J Immunol* 2013;191:2647-2656.
PUBMED | CROSSREF

64. Grégoire M, Uhel F, Lesouhaitier M, Gacouin A, Guirriec M, Mourcin F, Dumontet E, Chalin A, Samson M, Berthelot LL, et al. Impaired efferocytosis and neutrophil extracellular trap clearance by macrophages in ARDS. *Eur Respir J* 2018;52:1702590.
PUBMED | CROSSREF

65. Li H, Li Y, Song C, Hu Y, Dai M, Liu B, Pan P. Neutrophil extracellular traps augmented alveolar macrophage pyroptosis via aim2 inflammasome activation in LPS-induced ALI/ARDS. *J Inflamm Res* 2021;14:4839-4858.
PUBMED | CROSSREF

66. Apel F, Andreeva L, Knackstedt LS, Streeck R, Frese CK, Goosmann C, Hopfner KP, Zychlinsky A. The cytosolic DNA sensor cGAS recognizes neutrophil extracellular traps. *Sci Signal* 2021;14:eaax7942.
PUBMED | CROSSREF

67. Lande R, Ganguly D, Facchinetti V, Frasca L, Conrad C, Gregorio J, Meller S, Chamilos G, Sebasigari R, Riccieri V, et al. Neutrophils activate plasmacytoid dendritic cells by releasing self-DNA-peptide complexes in systemic lupus erythematosus. *Sci Transl Med* 2011;3:73ra19.
PUBMED | CROSSREF

68. Garcia-Romo GS, Caielli S, Vega B, Connolly J, Allantaz F, Xu Z, Punaro M, Baisch J, Guiducci C, Coffman RL, et al. Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. *Sci Transl Med* 2011;3:73ra20.
PUBMED | CROSSREF

69. Matsushima H, Geng S, Lu R, Okamoto T, Yao Y, Mayuzumi N, Kotol PF, Chojnacki BJ, Miyazaki T, Gallo RL, et al. Neutrophil differentiation into a unique hybrid population exhibiting dual phenotype and functionality of neutrophils and dendritic cells. *Blood* 2013;121:1677-1689.
PUBMED | CROSSREF

70. Barrientos L, Bignon A, Gueguen C, de Chaisemartin L, Gorges R, Sandré C, Mascarell L, Balabanian K, Kerdine-Römer S, Pallardy M, et al. Neutrophil extracellular traps downregulate lipopolysaccharide-induced activation of monocyte-derived dendritic cells. *J Immunol* 2014;193:5689-5698.
PUBMED | CROSSREF

71. Tillack K, Breiden P, Martin R, Sospedra M. T lymphocyte priming by neutrophil extracellular traps links innate and adaptive immune responses. *J Immunol* 2012;188:3150-3159.
PUBMED | CROSSREF

72. Kaltenmeier C, Yazdani HO, Morder K, Geller DA, Simmons RL, Tohme S. Neutrophil extracellular traps promote t cell exhaustion in the tumor microenvironment. *Front Immunol* 2021;12:785222.
PUBMED | CROSSREF

73. Ma Y, Li L, Hu Y, Han S, Yang Q, Pu W, Zhang X, Zhang J. Low-dose nanotherapy-mediated site-specific inhibition of neutrophil extracellular traps for immunoregulatory treatment of asthma. Preprint at https://www.researchsquare.com/article/rs-200054/v1 (2021).
CROSSREF

74. Nie M, Yang L, Bi X, Wang Y, Sun P, Yang H, Liu P, Li Z, Xia Y, Jiang W. Neutrophil extracellular traps induced by IL8 promote diffuse large B-cell lymphoma progression via the TLR9 signaling. *Clin Cancer Res* 2019;25:1867-1879.
PUBMED | CROSSREF

75. Kolonics F, Kajdácsi E, Farkas VJ, Veres DS, Khamari D, Kittel Á, Merchant ML, McLeish KR, Lőrincz ÁM, Ligeti E. Neutrophils produce proinflammatory or anti-inflammatory extracellular vesicles depending on the environmental conditions. *J Leukoc Biol* 2021;109:793-806.
PUBMED | CROSSREF

76. Lim K, Hyun YM, Lambert-Emo K, Capece T, Bae S, Miller R, Topham DJ, Kim M. Neutrophil trails guide influenza-specific $CD8^+$ T cells in the airways. *Science* 2015;349:aaa4352.
PUBMED | CROSSREF

77. Gasser O, Schifferli JA. Activated polymorphonuclear neutrophils disseminate anti-inflammatory microparticles by ectocytosis. *Blood* 2004;104:2543-2548.
PUBMED | CROSSREF

78. Eken C, Martin PJ, Sadallah S, Treves S, Schaller M, Schifferli JA. Ectosomes released by polymorphonuclear neutrophils induce a MerTK-dependent anti-inflammatory pathway in macrophages. *J Biol Chem* 2010;285:39914-39921.
PUBMED | CROSSREF

79. Eken C, Sadallah S, Martin PJ, Treves S, Schifferli JA. Ectosomes of polymorphonuclear neutrophils activate multiple signaling pathways in macrophages. *Immunobiology* 2013;218:382-392.
PUBMED | CROSSREF

80. Rhys HI, Dell'Accio F, Pitzalis C, Moore A, Norling LV, Perretti M. Neutrophil microvesicles from healthy control and rheumatoid arthritis patients prevent the inflammatory activation of macrophages. *EBioMedicine* 2018;29:60-69.
PUBMED | CROSSREF

81. Duarte TA, Noronha-Dutra AA, Nery JS, Ribeiro SB, Pitanga TN, Lapa E Silva JR, Arruda S, Boéchat N. Mycobacterium tuberculosis-induced neutrophil ectosomes decrease macrophage activation. *Tuberculosis (Edinb)* 2012;92:218-225.
PUBMED | CROSSREF

82. Alvarez-Jiménez VD, Leyva-Paredes K, García-Martínez M, Vázquez-Flores L, García-Paredes VG, Campillo-Navarro M, Romo-Cruz I, Rosales-García VH, Castañeda-Casimiro J, González-Pozos S, et al. Extracellular vesicles released from mycobacterium tuberculosis-infected neutrophils promote macrophage autophagy and decrease intracellular mycobacterial survival. *Front Immunol* 2018;9:272.
PUBMED | CROSSREF

83. Jiao Y, Zhang T, Zhang C, Ji H, Tong X, Xia R, Wang W, Ma Z, Shi X. Neutrophil-derived exosomes induce m1 macrophage polarization and prime macrophage pyroptosis via mir-30d-5p in sepsis. Preprint at https://www.researchsquare.com/article/rs-665364/v1 (2021).
CROSSREF

84. Johnson BL 3rd, Midura EF, Prakash PS, Rice TC, Kunz N, Kalies K, Caldwell CC. Neutrophil derived microparticles increase mortality and the counter-inflammatory response in a murine model of sepsis. *Biochim Biophys Acta BBAMol Basis Dis* 2017;1863:2554-2563.
PUBMED | CROSSREF

85. Dalli J, Serhan CN. Specific lipid mediator signatures of human phagocytes: microparticles stimulate macrophage efferocytosis and pro-resolving mediators. *Blood* 2012;120:e60-e72.
PUBMED | CROSSREF

86. Wang Y, Tian J, Tang X, Rui K, Tian X, Ma J, Ma B, Xu H, Lu L, Wang S. Exosomes released by granulocytic myeloid-derived suppressor cells attenuate DSS-induced colitis in mice. *Oncotarget* 2016;7:15356-15368.
PUBMED | CROSSREF

87. Zhu D, Tian J, Wu X, Li M, Tang X, Rui K, Guo H, Ma J, Xu H, Wang S. G-MDSC-derived exosomes attenuate collagen-induced arthritis by impairing Th1 and Th17 cell responses. *Biochim Biophys Acta Mol Basis Dis* 2019;1865:165540.
PUBMED | CROSSREF

88. Shen G, Krienke S, Schiller P, Nießen A, Neu S, Eckstein V, Schiller M, Lorenz HM, Tykocinski LO. Microvesicles released by apoptotic human neutrophils suppress proliferation and IL-2/IL-2 receptor expression of resting T helper cells. *Eur J Immunol* 2017;47:900-910.
PUBMED | CROSSREF

89. Greenlee-Wacker MC. Clearance of apoptotic neutrophils and resolution of inflammation. *Immunol Rev* 2016;273:357-370.
PUBMED | CROSSREF

90. Marwick JA, Mills R, Kay O, Michail K, Stephen J, Rossi AG, Dransfield I, Hirani N. Neutrophils induce macrophage anti-inflammatory reprogramming by suppressing NF-κB activation. *Cell Death Dis* 2018;9:665.
PUBMED | CROSSREF

91. Byrne A, Reen DJ. Lipopolysaccharide induces rapid production of IL-10 by monocytes in the presence of apoptotic neutrophils. *J Immunol* 2002;168:1968-1977.
PUBMED | CROSSREF

92. Thieblemont N, Witko-Sarsat V, Ariel A. Regulation of macrophage activation by proteins expressed on apoptotic neutrophils: subversion towards autoimmunity by proteinase 3. *Eur J Clin Invest* 2018;48 Suppl 2:e12990.
PUBMED | CROSSREF

93. Persson YAZ, Blomgran-Julinder R, Rahman S, Zheng L, Stendahl O. Mycobacterium tuberculosis-induced apoptotic neutrophils trigger a pro-inflammatory response in macrophages through release of heat shock protein 72, acting in synergy with the bacteria. *Microbes Infect* 2008;10:233-240.
PUBMED | CROSSREF

94. Andersson AM, Larsson M, Stendahl O, Blomgran R. Efferocytosis of apoptotic neutrophils enhances control of mycobacterium tuberculosis in HIV-coinfected macrophages in a myeloperoxidase-dependent manner. *J Innate Immun* 2020;12:235-247.
PUBMED | CROSSREF

95. Stark MA, Huo Y, Burcin TL, Morris MA, Olson TS, Ley K. Phagocytosis of apoptotic neutrophils regulates granulopoiesis via IL-23 and IL-17. *Immunity* 2005;22:285-294.
PUBMED | CROSSREF

96. Clayton AR, Prue RL, Harper L, Drayson MT, Savage COS. Dendritic cell uptake of human apoptotic and necrotic neutrophils inhibits CD40, CD80, and CD86 expression and reduces allogeneic T cell responses: relevance to systemic vasculitis. *Arthritis Rheum* 2003;48:2362-2374.
PUBMED | CROSSREF

97. Ren Y, Xie Y, Jiang G, Fan J, Yeung J, Li W, Tam PK, Savill J. Apoptotic cells protect mice against lipopolysaccharide-induced shock. *J Immunol* 2008;180:4978-4985.
PUBMED | CROSSREF