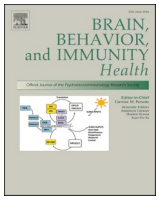
Brain, Behavior, & Immunity - Health 33 (2023) 100688

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx



A potential therapeutic target: The role of neutrophils in the central nervous system

Isabel Salken [a], Jose Javier Provencio [b], Aminata P. Coulibaly [c,*]

[a] College of Arts and Science, University of Virginia, USA
[b] Department of Neurology, University of Virginia, USA
[c] Department of Neuroscience, West Virginia University, USA

A B S T R A C T

Neutrophils play a critical role in immune defense as the first recruited and most abundant leukocytes in the innate immune system. As such, regulation of neutrophil effector functions have strong implications on immunity. These cells display a wide heterogeneity of function, including both inflammatory and immunomodulatory roles. Neutrophils commonly infiltrate the central nervous system (CNS) in response to varied pathological conditions. There is still little understanding of the role these cells play in the CNS in such conditions. In the present review, we will summarize what is known of neutrophil's role in cancer and Alzheimer's disease (AD), with a focus on highlighting the gaps in our understanding.

1. Introduction

Neutrophils, or polymorphonuclear cells, are cells of the innate immune system and the first recruited under infectious conditions. These cells are the most abundant leukocyte and display a multitude of functions that are implicated in an array of pathological processes. Although studies about neutrophils have been conducted since their discovery in the late nineteenth century by Paul Ehrlich (Amulic et al., 2012), the role they play in neuropathology is still incompletely understood. Their importance in bacterial meningitis is established, and there has been an increased interest in the effect of neutrophil physiology in other brain diseases. It is becoming increasingly important for neuroscientists, neurologists, and neurosurgeons to have a better understanding of neutrophil function. This review will explore our current understanding of the role of neutrophils, in general, in nervous system pathology with a focus on central nervous system (CNS) cancers and Alzheimer's disease (AD).

2. Basics of neutrophil biology

2.1. Neutrophils are made primarily in the bone marrow

Neutrophils are primarily produced in the bone marrow through a process known as granulopoesis. Recent evidence suggests the spleen as a secondary source of neutrophil production (Deniset et al., 2017). Whether this contributes to the number of circulating neutrophils remains to be determined. In granulopoiesis, bone marrow hematopoiesis leads to the generation of myeloblasts which mature into neutrophils. This maturation process has six stages (Amulic et al., 2012; Yang et al., 2019) (Fig. 1a). The specific factors involved in this process have been reviewed by Friedman et al., (2007) (Friedman, 2007). Under healthy conditions, the mature neutrophil is released into the blood. Under pathological conditions, both mature and band cell neutrophils, an immature phenotype, are released from the bone marrow (Eash et al., 2009).

The number of neutrophils released from the bone marrow is tightly regulated, as neutropenia (too few circulating neutrophils) and neutrophilia (too many circulating neutrophils) are associated with immunodeficiency and aberrant tissue damage, respectively. Retention and release of neutrophils in the bone marrow greatly depends on the interaction between neutrophil surface receptor C-X-C motif chemokine receptor 4 (CXCR4) and its ligand C-X-C motif chemokine ligand 12/stromal-derived factor 1 (CXCL12/SDF1) (De Filippo and Rankin, 2018). Indeed, the loss of functional CXCR4 on neutrophils leads to increased neutrophil release from the bone marrow (Eash et al., 2009). Neutrophil modulatory factors like granulocyte-colony stimulating factor (G-CSF) work primarily by affecting the expression of CXCR4 on mature neutrophils (Eash et al., 2009). Once in circulation, neutrophils typically transit for several hours (Amulic et al., 2012). During this period, they undergo a variety of changes that contribute to the heterogeneity of functions (Yang et al., 2019). As neutrophils age they upregulate their expression of CXCR4, which helps them return to the

* Corresponding author.
E-mail address: aminata.coulibaly2@hsc.wvu.edu (A.P. Coulibaly).

https://doi.org/10.1016/j.bbih.2023.100688
Received 8 December 2022; Received in revised form 14 September 2023; Accepted 16 September 2023
Available online 17 September 2023

bone marrow and lung for degradation (Adrover et al., 2016).

3. Defining roles of neutrophils following activation

As immune effector cells, neutrophils respond in an inflammatory environment in one of four ways: phagocytosis, degranulation, NETosis, and/or cytokine release (Fig. 1a) (Rosales, 2018). However, prior to these responses, neutrophils need to undergo a priming event. Indeed, unprimed neutrophils have extremely limited responses to inflammatory stimuli (Vogt et al., 2018). It has been proposed that priming is a critical factor in the enhanced neutrophil activity leading to tissue damage observed in sterile injury (Linas et al., 1992; Worthen et al., 1987). Neutrophil priming occurs in response to a variety of inflammatory molecules, including chemokines, cytokines, and alarmins (Linas et al., 1992). It has been proposed that the priming agent skews the response of neutrophils upon activation. For example, priming with tumor necrosis factor-alpha (TNFα) or lipopolysaccharide (LPS) leads to the activation of the mitogen activating protein kinase, p38, which skews the neutrophil response towards respiratory burst and degranulation (Ward et al., 2000). It is likely that priming is both stimulus and context specific, and more than one priming response is possible. It remains to be determined whether priming occurs in the vicinity of the inflammatory site or through a concentration gradient established as a result of the diffusion of cytokines and chemokines from the inflammation site. Regardless, it is evident that neutrophil activation begins prior to the infiltration of these cells.

Neutrophil activation leads to transcriptional and translational changes within the neutrophil that further influence the expression of surface molecules and receptors. Although there are multiple hypotheses regarding this process, one plausible hypothesis suggests that neutrophils are activated through the leukocyte adhesion cascade. This cascade begins with the interaction of adhesive molecules on activated endothelial cells and with glycoproteins on neutrophils (Ley et al., 2007). This initial interaction triggers β2 integrins on the neutrophil to bind to ligands on endothelial cells, such as intercellular adhesion molecule-1 (ICAM-1) and ICAM-2, allowing them to extravasate into tissues (Gorina et al., 2014). Like many immune cells, the signal transducer and activator of transcription (STAT)-3 signaling cascade is critical to the activation of neutrophils.

3.1. Metabolism

Like all cells, metabolism plays a vital role in neutrophil function. Though all metabolic pathways (including Krebs cycle, pentose phosphate pathway, and fatty acid oxidation) have been described in neutrophils (Sanders et al., 1995; McKenzie and Schreiber, 1998; Moulding et al., 1999; Richards and Endres, 2014), the most studied pathway in these cells is that of glycolysis, due to earlier studies demonstrating that neutrophils isolated from leukemia patients and in glucose rich solution consume glucose preferentially (Levene and Meyer, 1912). More definitively, a recent report shows that inhibition of mitochondria function has little to no effect on ATP production in mature neutrophils, while blocking glycolysis completely depletes ATP concentrations (Maianski et al., 2004). Mitochondria function, in neutrophils, play a significant role in the production of reactive oxygen species (ROS) (Herring et al., 2022). Neutrophils undergo a metabolic shift, from glycolysis to mitochondria mediated pentose phosphate pathway, to enhance oxidative burst upon stimulation (Britt et al., 2022). More research is needed to fully understand the role of other metabolic pathways, such as oxidative phosphorylation, in the activation of effector function of these cells (Injarabian et al., 2020).

In neutrophils, the shuffling of glucose within the cytoplasm is shown to be the main route of ATP formation. A mutation in glucose-6-phosphatase impairing glucose shuffling leads to defects in chemotaxis, respiratory burst, phagocytosis, and calcium flux (Jun et al., 2010). Recent evidence also shows that neutrophils have the highest level of glycogen granules in their cytoplasm of all circulating white blood cells (Sadiku et al., 2021). Whether the preferential use of glycolysis is due to its speed of energy production or other intracellular constraints remains to be determined. Of note, cellular preference is not due to a low number of mitochondria within the cell (Maianski et al., 2004). The glycolytic preference also enables these cells to survive under hypoxic conditions (Walmsley et al., 2005). The tolerance to hypoxia is thought to be an adaptation of these cells to the low level of oxygen in the sinusoidal regions of the bone marrow, where they marginate (Zhang and Sadek, 2014). This, in part, may explain the increased survival of neutrophils in inflammatory tissue microenvironments, as local oxygen levels decrease during inflammation (Injarabian et al., 2020).

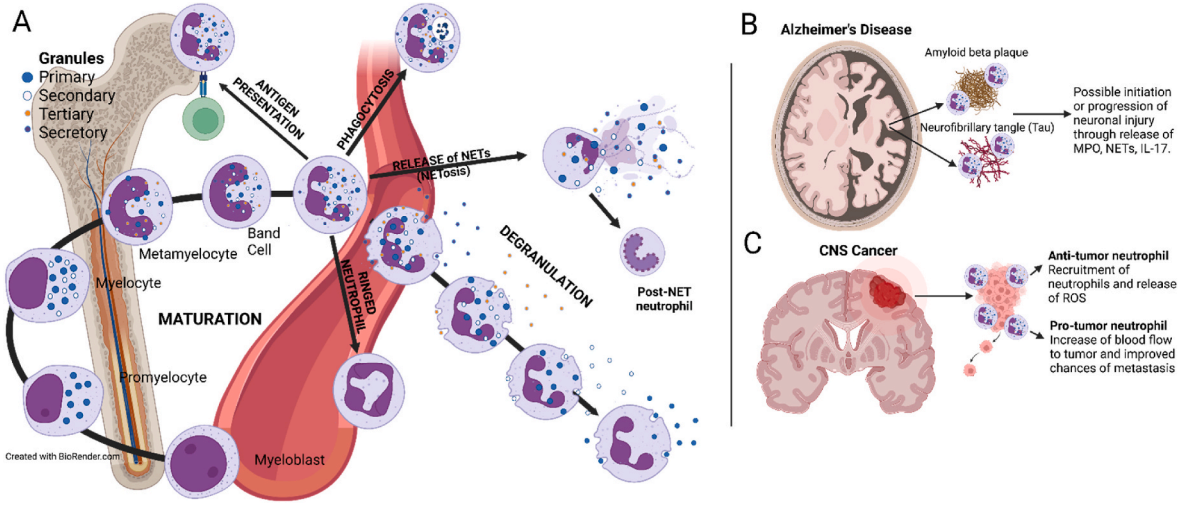


Fig. 1. Neutrophil effector function in Alzheimer's Disease and Cancer (A) Diagram depicts the formation of neutrophil from the bone marrow until release into circulation. Upon, activation, neutrophils have been shown to become antigen representing, phagocytose, release NETs, and degranulate. (B) Neutrophils have been shown to interact with deposits associated with Alzheimer's Disease, i.e. Aβ plaques. Though whether neutrophils contribute to the generation of these plaques are unknown, it is thought that its release of effectors molecules like MPO and IL-17 exacerbates disease progression. (C) In CNS cancers, neutrophils at the site of the cancer can either become pro- or anti-tumorigenic. Pro-tumor neutrophils result in increased metastasis and increased blood flow through the development of more blood vessels in tumors and anti-tumor neutrophils result in the recruitment of more neutrophils which kill tumor cells through the release of ROS.

3.2. Phagocytosis

Phagocytosis is used by neutrophils to clear pathogens and/or debris. Phagocytosis occurs through receptor mediated endocytosis. As such, this process relies on membrane receptors expressed on the surface of the cell. It has been shown that fragment crystalizable (Fc) γ receptors on neutrophils (i.e., FcγRI, FcγRII, and FcγRIII) bind IgG and other complement coated particles to internalize various pathogens (Lee et al., 2003). The regulation of these receptors is critical for neutrophil response (Sanders et al., 1995; McKenzie and Schreiber, 1998; Moulding et al., 1999). Their activation leads to endosome formation followed by lysosomal fusion and degradation of the phagocytosed element (Richards and Endres, 2014). Of note, lysosomal fusion with granules and secretory vesicles is critical to neutrophils' ability to degrade phagocytosed pathogens (Lee et al., 2003; Tapper et al., 2002).

3.3. Neutrophil extracellular traps (NET) generation (NETosis)

Neutrophils extracellular traps (NETs) are made of chromatin and proteins released by neutrophils to immobilize pathogens (Brinkmann et al., 2004; Papayannopoulos, 2018; Barnes et al., 2020). Although not fully understood, this process is thought to be highly regulated. NETosis seems to be triggered through receptor activation and cell-cell contact (Kaplan, 2013; Yipp and Kubes, 2013; Rodrigues et al., 2020). Two forms of NETosis have been described in the literature, suicidal and vital (Yipp and Kubes, 2013). "Suicidal" NETosis leads to neutrophil death, while the "vital" form results in the formation of band-like cells or cytoplast (Yipp and Kubes, 2013). NETs are disassembled by endogenous enzymes such as DNases (Kaplan, 2013). Although vital to host defense (Papayannopoulos, 2018), unrestricted NET production can be detrimental (Barnes et al., 2020). NETs have been implicated in a host of diseases (Barnes et al., 2020; Saffarzadeh et al., 2012; Veras et al., 2020; Schönrich et al., 2020; Middleton et al., 2020), including neurodegenerative disorders like AD (Pietronigro et al., 2017).

3.4. Degranulation

Neutrophils contain four major types of granules, primary or azurophilic, secondary or specific, tertiary or gelatinase, and secretory vesicles. Each granule type differs in density, content, function, signals required for secretion, and markers (Bedouhene et al., 2017). These granules have varying potency for killing bacteria, with the highest potency in primary granule proteins and lowest in secretory vesicles. The formation and packaging of these granules follow specific timing in the maturation of the cell. This timing-related formation has become known as the "targeting-by-timing" hypothesis, referencing the fact that synthesis of the various granule subsets occurs at different stages during granulopoiesis, as opposed to heterogeneity being caused by a difference in sorting mechanism (Borregaard, 2010; Le Cabec et al., 1996). The release of granules follows the exact reverse order of their formation (i.e. secretory vesicles first and primary granule last; Fig. 1a). Recent evidence has shown that the quantity of granule release also was higher for secretory vesicles (~100%) than for primary granules (~7%) (Rørvig et al., 2009). This could be a factor in the strength of the content of each granule subset or a built-in fail safe to limit the potential damage of an activated neutrophil. In fact, unregulated degranulation leading to the release of toxic contents is thought to be a common cause of autoimmune and inflammatory diseases (Delano and Ward, 2016; Schrijver et al., 2017).

Degranulation, the release of neutrophil granule content to the extracellular space through exocytosis, is highly regulated (Sheshachalam et al., 2014). Although tertiary and secretory granules are released regularly, due to their function in neutrophil motility and transmigration (Rawat et al., 2021), degranulation often refers to the release of secondary and primary granule content. As with exocytosis, in general, degranulation depends on the activity of small Ras associated binding proteins (Rab) GTPases, specifically Rab27/Munc13-4 pathway (Ramadass and Catz, 2016). Degranulation is dependent on adhesion, receptor activation, and calcium influx (Futosi et al., 2013). For example, in ascending order, each granule subset requires an increasing amount of calcium to initiate interaction with the plasma membrane (Sengeløv et al., 1995).

3.5. Cytokine release

A hallmark of the role of neutrophils in inflammatory and immune responses is their production and release of various cytokines. Cytokines work to direct biological processes, including inflammation and immunity as well as hematopoiesis and wound healing (Tecchio et al., 2014). Neutrophil-derived cytokines recruit a variety of specific cells, including other neutrophils, monocytes, T-helper cells, and others (Hughes and Nibbs, 2018). For example, our laboratory demonstrated that in subarachnoid hemorrhage, the release of interleukin (IL)-17 by neutrophils leads to the recruitment of more neutrophils to the CNS (Coulibaly et al., 2020). Particularly relevant to this review, several neutrophil-derived cytokines and chemokines have been implicated in CNS pathologies. For example, Interleukin 6 (IL-6) and Interleukin 33 (IL-33), two cytokines that act on the CNS, have been shown to directly regulate neutrophil trafficking (Erta et al., 2012; Verri et al., 2010).

Of note, the flexibility of these cells has led to the discovery of many other functions, such as the release of extracellular vesicles to entrain innate immunity (Allen et al., 2022) and antigen presentation to adaptive immune cells to modulate antibody production (Vono et al., 2017). Due to the novel nature of these functions, their possible implication in CNS pathology is truly unknown. As such, we did not include those functions in the list of functions attributed to neutrophils. However, those functions and many of the ones being described in these cells will have to be explored in their interactions with CNS in both health and disease.

4. Neutrophils in CNS disease

The modulatory effect of innate immune cell infiltration in the CNS has been under investigation for many decades. However, our understanding of the role neutrophils play in CNS pathology remains limited. Studies have often regarded these cells as infiltrating and damaging to CNS function in a multitude of pathologies. Recent reviews on neutrophil contributions in CNS pathology have focused on a specific disease or pathway. In this review, we aim to highlight the contribution of neutrophil biology to the pathology of brain tumors and AD. Using a neutrophil centric view, this review hopes to elucidate neutrophil functions that may be potential therapeutic targets for these diseases.

4.1. There is evidence that neutrophils interact with CNS cells

In trying to understand the mechanistic and cellular effects of neutrophil interaction with brain-derived cells, several investigators have exposed neuronal cultures to isolated neutrophils to determine both neuronal survival and activity. Interestingly, a co-culture model of murine cells showed that neutrophils are not inherently toxic to cortical neurons. However, interaction with the endothelium or stimulation by IL-1 leads to the release of neurotoxic factors by neutrophils (Allen et al., 2012). Conversely, neutrophil exposure leads to neuronal hyperactivity and cell death in dorsal root ganglion neurons (Shaw et al., 2008), hippocampal neurons and astrocytes (Dinkel et al., 2004). Of note, the papers cited used different isolation techniques. One paper used neutrophils isolated from the bone marrow (Allen et al., 2012), i.e., more a naïve and less primed cell profile, and the others, showing detrimental effect, used neutrophils isolated from the blood (Shaw et al., 2008; Dinkel et al., 2004). This would suggest that the activation state of neutrophils, and possibly maturation profile, may have a direct link to how they affect and interact with brain cells.

There is emerging evidence that neutrophils can release neurotrophic factors and neuromodulators under certain conditions (reviewed in (Coulibaly, 2022)). For example, neutrophils release ciliary neurotrophic factor (CNTF) in response to optic nerve injury (Sas et al., 2020), a nerve growth factor implicated in neuronal survival after injury (Gu et al., 2016). Neutrophils have also been shown to release glutamate (del Arroyo et al., 2019). Glutamate is a critical neurotransmitter for neuronal function (Collingridge et al., 2013). In addition, neutrophils are a demonstrated source of catecholamines, which directly modulate neuronal activity (Kanashiro et al., 2020; Cosentino et al., 1999). The release of catecholamine by neutrophils correlates greatly with it activation level (Flierl et al., 2007). It remains to be determined whether these neuromodulatory molecules are packaged in neutrophil granules, or produced and released in response to stimulation from neurons.

There is evidence of neutrophils contributing to the pathology of a host of CNS maladies, including injury (i.e.; stroke and more), infection, tumors and neurodegenerative conditions (i.e., multiple sclerosis). For the sake of expediency, this review will focus on CNS tumors and dementia. We have chosen to focus on these two diseases because of the lack of systematic reviews on neutrophils in CNS cancers, and the lack of a neutrophil centric review on the role of neutrophils in AD.

4.2. Neutrophils are both toxic to neoplastic cells and detrimental to the host in brain tumors

Tumors in the CNS can be divided into two categories, those that arise from brain cells (i.e., gliomas) and those derived from peripheral tumor metastases (i.e., melanoma and breast cancer). Gliomas, tumors deriving from glial cells in the brain are characterized into 3 categories, astrocytoma, ependymomas, and oligodendrogliomas (Schneider et al., 2010). In terms of peripheral tumors, those derived from lung, breast, kidney, colon and skin have been shown to metastasize to the brain (Barnholtz-Sloan et al., 2004).

Studies have demonstrated that the presence of neutrophils in gliomas can be detrimental for patient survival. For example, clinical studies show that an elevated neutrophil count in glioma patients correlates with increased disease severity and poor outcome (Schernberg et al., 2018). It is thought that neutrophils are recruited to the tumor environment by interleukin (IL)-8, macrophage migration inhibitory factor (MIF), and C-X-C motif chemokine ligand (CXCL) 8 (Hor et al., 2003). Once recruited, neutrophils release factors that promote glioma growth through the increase of oxidative stress and the release of NETs (Manda-Handzlik and Demkow, 2019). This process was reviewed in McFarlane et al., (2023). In the periphery, it has been demonstrated that neutrophils aid in cancer cell acquisition of metastasis (Kalafati et al., 2020). It is established that gliomas do not metastasize outside the brain. It would be interesting to determine whether neutrophil function is altered in the glioma environment to dampen this neutrophil function, or if the blood brain barrier impedes this process.

In general, neutrophils can promote metastasis in three ways: 1) suppressing the function of natural killer cells, 2) enhancing extravasation of tumor cells, and 3) interacting with circulating tumor cells (Long et al., 2021). These pathways facilitate tumor cell cycle progression and seeding. Though the mechanism through which this interaction occurs remains unclear, patients and mouse models of breast cancer demonstrated that the association of circulating tumor cells with neutrophils is mediated by the adhesion molecule vascular cell adhesion molecule (VCAM) 1 (Long et al., 2021; Szczerba et al., 2019).

Peripheral tumors metastasize to the brain through the detachment of primary tumor cells from parent tumor sites, where they then migrate and pass through the blood brain barrier (BBB). The mechanism through which peripheral cancer cells de-differentiate and migrate to the brain is referred to as epithelial-to-mesenchymal transition (EMT), and the mechanism through which they re-differentiate and colonize the brain is known as mesenchymal to epithelial transition (MET) (Cooper et al., 2018). The transcriptional process behind these mechanisms has been reviewed in detail in Cooper et al., 2018. It is thought that NETs may play a role in tumor progression and dissemination from primary sites and help promote transmigration to secondary sites. Some studies have suggested that stressors like surgery or carcinogen exposure promote NETs production in cancer patients (Lin et al., 2021). In addition, mouse models show tobacco smoke induced lung inflammation leads to increased NET production by neutrophils. These NETs are required to awaken dormant cancer cells and induce metastasis (Albrengues et al., 2019).

Tumor cells and neutrophils appear to work mutualistically. Extracellular RNAs from cancer cells help regulate neutrophil metabolism by inducing NET production (Li et al., 2019). In addition, tumor microenvironments induce metabolic adaptation for neutrophils. Specifically, Rice et al., 2018 showed that glucose-restricted tumor microenvironments induce metabolically adapted, oxidative neutrophils, or those capable of reactive oxygen species (ROS) production, which have increased roles in maintaining local immune suppression and therefore may impact cancer cell survival during metastasis (Rice et al., 2018). Indeed, neutrophils with their high glycolytic potential, contribute to the production of lactate which is converted to lactic acid in the tumor microenvironment. This promotes tumor survival and progression. This environmental acidification also aids in dampening immune activity in the vicinity of the tumor cell.

As in the periphery, neutrophil function can be hijacked to help brain tumors thrive and infiltrate tissue. The hypothesis is that the BBB is intact in gliomas, whether that is true for infiltrating peripheral tumors is unknown. Nonetheless, it is still unclear when neutrophils first infiltrate brain tumors, specifically gliomas. As for peripherally derived tumors, because neutrophils aid in their extravasation into the brain, we postulate that they are present in the tumor microenvironment at onset. Peripherally, there is ample evidence that neutrophils modulate the tumor microenvironment through the release of cytokines and chemokines (Oberg et al., 2019; Gabrusiewicz et al., 2016). For example, neutrophils were shown to release IL-8 and TNF-α to recruit more circulating neutrophils to the tumor environment. These tumor-associated neutrophils (TANs) have been shown to either be anti- or pro-tumorigenic.

Pro-tumor activity includes the release of factors that directly increase the survival of tumor cells (Masucci et al., 2019). For example, pro-tumor TANs secrete vascular endothelial growth factor (VEGF) which leads to the growth of more blood vessels into the tumor, providing more nutrients and oxygen to tumor cells. It has been shown that lactic acid, produced by inflammatory neutrophils, activates VEGF to stimulate angiogenesis (Giatromanolaki et al., 2006; Jiang, 2017). In addition, there is evidence that increased infiltration of pro-tumor TANs leads to more detrimental outcomes, i.e., higher grade gliomas (Quail and Joyce, 2017; Khan et al., 2020), the release of toxic factors that damage healthy tissue, and create more space for the tumor to expand (Wang et al., 2018).

On the other hand, anti-tumor TANs directly kill tumor cells by participating in cellular networks that mediate antitumor resistance (Bodac and Meylan, 2021; Jaillon et al., 2020). For example, tumor-entrained neutrophils were shown to be highly cytotoxic in the lungs where they inhibited metastatic seeding by generating toxic molecules including peroxide, as well as cytokines like C–C motif chemokine ligand (CCL) 2 to recruit more neutrophils (Andzinski et al., 2016; Granot et al., 2011; López-Lago et al., 2013). This in effect builds an antimetastatic barrier. Anti-tumor TANs release IL-12, which enhances antitumor effect and has been implicated in pre-clinical immunotherapies for glioblastoma (Lin et al., 2021; Agliardi et al., 2021). Other possible antitumoral properties of neutrophils include the direct killing of tumor cells by ROS (Long et al., 2021). Nonetheless, because of their antitumorigenic roles, neutrophils represent a potential therapeutic target. For example, blocking of the transforming growth factor (TGF) β pathway causes an increase in antitumoral neutrophils, and thus may represent a potential therapeutic target (Long et al., 2021). Clinical

trials using immunotherapies targeting neutrophil-associated pathways and chemotherapies have already begun and are reviewed in depth by Lin et al., 2021).

The polarization of neutrophils towards pro- or anti-tumor function is actively being studied. It is thought that the first neutrophils recruited to the tumor are anti-tumorigenic. However, exposure to cytokines produced by the microenvironment (G-CSF, TGF-β, etc.) in addition to the hypoxic environment causes a transcriptional shift within the cell, causing it to change phenotype (McFarlane et al., 2021). For example, TGFβ promotes the pro-tumor phenotype, a pathway involved in peripheral tumor metastasis, suggesting a possible link between neutrophils and peripheral tumors metastasizing to the brain (Lin et al., 2021). Of note, neutrophils have been shown to release extracellular vesicles to modulate inflammatory responses (Allen et al., 2012; Kolonics et al., 2021). As such, it is possible that the shift from anti-to pro-tumorigenic phenotype may occur earlier. Indeed, in glioma patients, the presence of inflammatory neutrophils in circulation is highly correlated with poor prognosis. Therefore, it is possible that TANs release extracellular vesicles that work to change neutrophil phenotypes before they encounter the tumor environment (Liu et al., 2022). We believe that more investigation needs to be done to elucidate the role of neutrophils in brain tumors, since this may also contribute to relapse of disease once treatment has begun. Recent studies have demonstrated that this switch in phenotype leads to a heterogenous neutrophil population within the tumor microenvironment. As of now, there is still debate regarding the nomenclature associated with these different neutrophil subsets.

4.3. Neutrophil activity worsens cognitive outcomes in AD

Dementia is characterized by increased memory and cognitive impairment. AD represents 60–70% of all dementia cases. AD can be further classified as early onset (familial) or late onset (sporadic). The late onset endotype makes up 95% of all AD cases (De Strooper, 2010). AD is defined by the accumulation of amyloid beta (Aβ) plaques and Tau neurofibrillary tangles in the brain. These accumulations may lead to cellular toxicity and progressive loss of brain matter (De Strooper, 2010). Until recently, most AD research was focused on the removal of Aβ plaques. However, many clinical trials have shown that the removal of these elements has very little clinical benefit.

A recent theory postulates that Aβ itself is an immune molecule (Vojtechova et al., 2022; Weaver, 2020), suggesting that AD pathology is linked directly to immune function. A recent study shows that the neutrophil enzyme myeloperoxidase (MPO) co-localizes to Aβ plaques in brains of AD patients (Green et al., 2004; Gellhaar et al., 2017). Preclinical studies have shown that the loss of MPO in neutrophils leads to better cognitive performance and less inflammatory profiles in mouse models of AD((Volkman et al., 2019)). In addition, neutrophils release NETs and IL-17 as well as express lymphocyte-function-associated antigen 1 (LFA-1) in areas with Aβ plaques (Abramov and Duchen, 2005; Zenaro et al., 2015). Blocking LFA 1 decreases neutrophil recruitment and improves memory in AD mice (Zenaro et al., 2015). Neutrophils are known sources of oxidative stress, disruptors of the BBB, and contributors of vascular dysfunction, all of which contribute to memory impairment in patients with AD((Malm et al., 2010)).

There is evidence that aging leads to an increased inflammatory phenotype in neutrophils (Gullotta et al., 2023). This inflammatory phenotype seems exacerbated in AD (Gullotta et al., 2023). Indeed, resting neutrophils from AD patients produce more reactive oxygen species when compared to those of healthy controls (Vitte et al., 2004). Recent evidence shows that inflammation contributes to both the etiology and pathology of AD. For example, neuroinflammation is observed in the brain prior to cognitive decline in a mouse model of AD(111). Neutrophils are found crawling in the microvasculature of the brain in AD models. This slow movement of cells is thought to facilitate a hypoxic like environment in the brain. Temporary removal of neutrophils, using anti-Ly6G antibody treatments leads to better cognitive outcome in several mouse models of AD (Cruz Hernández et al., 2019). Smyth et al., 2022 found that the vascular localization of neutrophils in human and mouse models of AD was a result of enhanced neutrophil adhesion to small vessels (Smyth et al., 2022).

Interestingly, in patients early in the progression of AD, circulating neutrophils are highly inflammatory and hyperactive, suggesting a systemic inflammatory state. However, this phenotype switches to a less inflammatory state later in the disease progression (Dong et al., 2018). These data suggest that neutrophils may play diverse roles in the etiology of AD (Stock et al., 2018). Though the focus of most investigation has been centered in mouse models, there is strong evidence that the dysregulation of neutrophils in AD spans across human AD cohorts (Smyth et al., 2022).

5. Novel or unexamined pathways for treatment

The evidence described above suggests neutrophils play a role in brain pathophysiology. Our understanding of how these cells function within the CNS is limited. Understanding the role of the effector functions described above (i.e., phagocytosis, cytokine release, degranulation) in different conditions is critical to our pursuit for better therapies (Fig. 1).

It is well established that neutrophils live longer and are more active in hypoxic environments. As such, it may be possible to exploit this trait to modulate their activity in neurodegeneration. NETs are being investigated as biomarkers of inflammation and neutrophil activity in many diseases (Kaplan, 2013). Therapies focused on removal of NETs may hold promise in improving disease outcome. However, it has been shown that after the release of their DNA content, “neutrophil cytoplasts,” are still active. Little is known about the role of these partially competent cells and their effect on disease state. That immature neutrophils release neurotrophic factors, and neurotransmitters suggest they may also play a role in brain disease, however, our understanding of their potential, outside the bone marrow, is still limited. Given their potential for cytotoxicity against cancer cells through direct contact and generation of ROS, neutrophils present a potential therapeutic target.

A current example of the therapeutic potential of neutrophils was described by Chang et al., 2022). Here, the authors show that the antigen presenting function of neutrophils can be exploited to better target tumors using immunotherapies. The authors genetically engineered human pluripotent stem cells with synthetic chimeric antigen receptors (CAR), resulting in CAR neutrophils with superior and specific cytotoxicity against tumors cells both in vitro and in vivo glioblastoma models (Chang et al., 2022). CARs have been used in T and natural killer cells to boost anti-tumor effects (Feins et al., 2019). CAR-neutrophil engineering may represent a novel strategy for immunotherapies going forward.

There is evidence that neutrophils and their molecules (granule proteins and cytokines) can have direct effects on brain cells. An interesting avenue of investigation may be the specific role of neutrophil granule proteins in AD. For example, MPO’s ability to affect neuronal activity and astrocyte survival makes it a promising molecule to investigate CNS conditions where neutrophils infiltrate the brain. There are current therapeutic agents that inhibit MPO function (Roth Flach et al., 2019; Chen et al., 2022). Neutrophils may be adapted for use in the brain to dampen the effect of MPO and neutrophils. Depletion of neutrophils has been suggested as a therapy to benefit AD patients (Zenaro et al., 2015). However, the high risk of infection in older patients (those more affected by AD) dampens enthusiasm for this as a treatment target. However, targeting specific molecular pathways of neutrophil effector functions presents a potentially less risky strategy. For example, it is reasonable to believe that IL-17, with its role in recruiting neutrophils into the CNS, may be a good therapeutic target. Modulation of NETs has the potential to positively affect disease outcomes. Treatments aimed at pathological contributors of AD, including the neutrophils associated with Aβ plaques, may hold promise as treatments (Aries and

Hensley-McBain, 2023).

6. Conclusions

Neutrophils play a vital role in inflammation as the first cell to be recruited under pathologic conditions. It is clear neutrophils are present in and recruited to the CNS as a part of the inflammatory response. Interactions with neutrophil activity hold promise for effective treatments in AD and CNS cancers. However, much remains unknown about the exact mechanisms through which neutrophils specifically impact CNS function under these conditions.

Declaration of competing interest

The authors have no conflict to disclose.

Data availability

No data was used for the research described in the article.

References

Abramov, A.Y., Duchen, M.R., 2005. The role of an astrocytic NADPH oxidase in the neurotoxicity of amyloid beta peptides. Philos Trans R Soc B Biol Sci 360 (1464), 2309–2314.

Adrover, J.M., Nicolás-Ávila, J.A., Hidalgo, A., 2016. Aging: a temporal dimension for neutrophils [Internet] Trends Immunol. 37 (5), 334–345. https://doi.org/10.1016/j.it.2016.03.005.

Agliardi, G., Liuzzi, A.R., Hotblack, A., De Feo, D., Núñez, N., Stowe, C.L., et al., 2021. Intratumoral IL-12 delivery empowers CAR-T cell immunotherapy in a pre-clinical model of glioblastoma [Internet] Nat. Commun. 12 (1), 1–11. https://doi.org/10.1038/s41467-020-20599-x.

Albrengues, J., Shields, M., Ng, D., Park, C.G., Ambrico, A., Poindexter, M., et al., 2019. HHS Public Access, vol. 361, 6409.

Allen, C., Thornton, P., Denes, A., McColl, B.W., Pierozynski, A., Monestier, M., et al., 2012. Neutrophil cerebrovascular transmigration triggers rapid neurotoxicity through release of proteases associated with decondensed DNA. J. Immunol. 189 (1), 381–392.

Allen, E.R., Whitefoot-Keliin, K.M., Palmatier, E.M., Mahon, A.R., Greenlee-Wacker, M. C., 2022. Extracellular vesicles from A23187-treated neutrophils cause cGAS-STING-dependent IL-6 production by macrophages [Internet] Front. Immunol. 13. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2022.949451/full.

Amulic, B., Cazalet, C., Hayes, G.L., Metzler, K.D., Zychlinsky, A., 2012. Neutrophil function: from mechanisms to disease. Annu. Rev. Immunol. 30, 459–489.

Andzinski, L., Kasnitz, N., Stahnke, S., Wu, C.F., Gereke, M., Von Köckritz-Blickwede, M., et al., 2016. Type i IFNs induce anti-tumor polarization of tumor associated neutrophils in mice and human. Int. J. Cancer 138 (8), 1982–1993.

Aries, M.L., Hensley-McBain, T., 2023. Neutrophils as a potential therapeutic target in Alzheimer's disease. Front. Immunol. 14 (March), 1–8.

Barnes, B.J., Adrover, J.M., Baxter-Stoltzfus, A., Borczuk, A., Cools-Lartigue, J., Crawford, J.M., et al., 2020. Targeting potential drivers of COVID-19: neutrophil extracellular traps. J. Exp. Med. 217 (6), 1–7.

Barnholtz-Sloan, J.S., Sloan, A.E., Davis, F.G., Vigneau, F.D., Lai, P., Sawaya, R.E., 2004. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J. Clin. Oncol. 22 (14), 2865–2872.

Bedouhene, S., Moulti-Mati, F., Dang, P.M.-C., El-Benna, J., 2017. Oleuropein and hydroxytyrosol inhibit the N-formyl-methionyl-leucyl-phenylalanine-induced neutrophil degranulation and chemotaxis via AKT, p38, and ERK1/2 MAP-Kinase inhibition [Internet] Inflammopharmacology 25 (6), 673–680. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28711992.

Bodac, A., Meylan, E., 2021. Neutrophil metabolism in the cancer context [Internet] Semin. Immunol. 57 (December), 101583. https://doi.org/10.1016/j.smim.2021.101583.

Borregaard, N., 2010. Neutrophils, from marrow to microbes [Internet] Immunity 33 (5), 657–670. https://doi.org/10.1016/j.immuni.2010.11.011.

Brinkmann, V., Reichard, U., Goosmann, C., Fauler, B., Uhlemann, Y., Weiss, D.S., et al., 2004. Neutrophil extracellular traps kill bacteria. Science 303 (5663), 1532–1535.

Britt, E.C., Lika, J., Giese, M.A., Schoen, T.J., Seim, G.L., Huang, Z., et al., 2022. Switching to the cyclic pentose phosphate pathway powers the oxidative burst in activated neutrophils. Nat. Metab. 4 (3), 389–403.

Chang, Y., Syahirah, R., Wang, X., Jin, G., Torregrosa-Allen, S., Elzey, B.D., et al., 2022. Engineering chimeric antigen receptor neutrophils from human pluripotent stem cells for targeted cancer immunotherapy. Cell Rep. 40 (3).

Chen, W., Tumanov, S., Kong, S.M.Y., Cheng, D., Michaëlsson, E., Bongers, A., et al., 2022. Therapeutic inhibition of MPO stabilizes pre-existing high risk atherosclerotic plaque [Internet] Redox Biol. 58, 102532. Available from: http://www.ncbi.nlm.nih.gov/pubmed/36375379.

Collingridge, G.L., Volianskis, A., Bannister, N., France, G., Hanna, L., Mercier, M., et al., 2013. The NMDA receptor as a target for cognitive enhancement [Internet] Neuropharmacology 64, 13–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22796429.

Cooper, J.B., Ronecker, J.S., Tobias, M.E., Mohan, A.L., Hillard, V., Murali, R., et al., 2018. Molecular sequence of events and signaling pathways in cerebral metastases. Anticancer Res. 38 (4), 1859–1877.

Cosentino, M., Marino, F., Bombefli, R., Ferrari, Marco, Lecchini, Sergio, 1999. Gianmario Frigo Department of Internal Medicine and Therapeutics , Section of Clinical Pharmacology, vol. 64. University of Insubria and University of Pavia , Varese , Italy Evidence is presented that human neutrophifs contain ca.

Coulibaly, A.P., 2022. Neutrophil modulation of behavior and cognition in health and disease: the unexplored role of an innate immune cell [Internet] Immunol. Rev. 311 (1), 177–186. Available from: http://www.ncbi.nlm.nih.gov/pubmed/35924463.

Coulibaly, A.P., Gartman, W.T., Swank, V., Gomes, J.A., Ruozhuo, L., DeBacker, J., et al., 2020. RAR-related orphan receptor gamma T (RoRγt)-Related cytokines play a role in neutrophil infiltration of the central nervous system after subarachnoid hemorrhage [Internet] Neurocritical Care 33 (1), 140–151. https://doi.org/10.1007/s12028-019-00871-9.

Cruz Hernández, J.C., Bracko, O., Kersbergen, C.J., Muse, V., Haft-Javaherian, M., Berg, M., et al., 2019. Neutrophil adhesion in brain capillaries reduces cortical blood flow and impairs memory function in Alzheimer's disease mouse models. Nat. Neurosci. 22 (3), 413–420.

De Filippo, K., Rankin, S.M., 2018. CXCR4, the master regulator of neutrophil trafficking in homeostasis and disease [Internet] Eur. J. Clin. Invest. 48 (Suppl. 2), e12949. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29734477.

De Strooper, B., 2010. Proteases and proteolysis in Alzheimer disease: a multifactorial view on the disease process [Internet] Physiol. Rev. 90 (2), 465–494. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20393191.

del Arroyo, A.G., Hadjihambi, A., Sanchez, J., Turovsky, E., Kasymov, V., Cain, D., et al., 2019. NMDA receptor modulation of glutamate release in activated neutrophils [Internet] EBioMedicine 47, 457–469. https://doi.org/10.1016/j.ebiom.2019.08.004.

Delano, M.J., Ward, P.A., 2016. The immune system's role in sepsis progression, resolution, and long-term outcome. Immunol. Rev. 274, 330–353.

Deniset, J.F., Surewaard, B.G., Lee, W.-Y., Kubes, P., 2017. Splenic Ly6Ghigh mature and Ly6Gint immature neutrophils contribute to eradication of S. pneumoniae. J. Exp. Med. 214 (5), 1333–1350.

Dinkel, K., Dhabhar, F.S., Sapolsky, R.M., 2004. Neurotoxic effects of polymorphonuclear granulocytes on hippocampal primary cultures. Proc. Natl. Acad. Sci. U. S. A. 101 (1), 331–336.

Dong, Y., Lagarde, J., Xicota, L., Corne, H., Chantran, Y., Chaigneau, T., et al., 2018. Neutrophil hyperactivation correlates with Alzheimer's disease progression [Internet] Ann. Neurol. 83 (2), 387–405. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29369398.

Eash, K.J., Means, J.M., White, D.W., Link, D.C., 2009. CXCR4 is a key regulator of neutrophil release from the bone marrow under basal and stress granulopoiesis conditions. Blood 113 (19), 4711–4719.

Erta, M., Quintana, A., Hidalgo, J., 2012. Interleukin-6, a major cytokine in the central nervous system. Int. J. Biol. Sci. 8 (9), 1254–1266.

Feins, S., Kong, W., Williams, E.F., Milone, M.C., Fraietta, J.A., 2019. An introduction to chimeric antigen receptor (CAR) T-cell immunotherapy for human cancer. Am. J. Hematol. 94 (S1), S3–S9.

Flierl, M.A., Rittirsch, D., Nadeau, B.A., Chen, A.J., Sarma, J.V., Zetoune, F.S., et al., 2007. Phagocyte-derived catecholamines enhance acute inflammatory injury. Nature 449 (7163), 721–725.

Friedman, A.D., 2007. Transcriptional control of granulocyte and monocyte development [Internet] Oncogene 26 (47), 6816–6828. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17934488.

Futosi, K., Fodor, S., Mócsai, A., 2013. Neutrophil cell surface receptors and their intracellular signal transduction pathways [Internet] Int. Immunopharm. 17 (3), 638–650. https://doi.org/10.1016/j.intimp.2013.06.034.

Gabrusiewicz, K., Rodriguez, B., Wei, J., Hashimoto, Y., Healy, L.M., Maiti, S.N., et al., 2016. Glioblastoma-infiltrated innate immune cells resemble M0 macrophage phenotype. JCI Insight 1 (2).

Gellhaar, S., Sunnemark, D., Eriksson, H., Olson, L., Galter, D., 2017. Myeloperoxidase-immunoreactive cells are significantly increased in brain areas affected by neurodegeneration in Parkinson's and Alzheimer's disease [Internet] Cell Tissue Res. 369 (3), 445–454. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28466093.

Giatromanolaki, A., Sivridis, E., Gatter, K.C., Turley, H., Harris, A.L., Koukourakis, M.I., 2006. Lactate dehydrogenase 5 (LDH-5) expression in endometrial cancer relates to the activated VEGF/VEGFR2(KDR) pathway and prognosis [Internet] Gynecol. Oncol. 103 (3), 912–918. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0090825806004392.

Gorina, R., Lyck, R., Vestweber, D., Engelhardt, B., 2014. β2 integrin–mediated crawling on endothelial ICAM-1 and ICAM-2 is a prerequisite for transcellular neutrophil diapedesis across the inflamed blood–brain barrier. J. Immunol. 192 (1), 324–337.

Granot, Z., Henke, E., Comen, E.A., King, T.A., Norton, L., Benezra, R., 2011. Tumor entrained neutrophils inhibit seeding in the premetastatic lung [Internet] Cancer Cell 20 (3), 300–314. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1535610811003096.

Green, P.S., Mendez, A.J., Jacob, J.S., Crowley, J.R., Growdon, W., Hyman, B.T., et al., 2004. Neuronal expression of myeloperoxidase is increased in Alzheimer's disease. J. Neurochem. 90 (3), 724–733.

Gu, Y.L., Gao, G.Q., Ma, N., Ye, L.L., Zhang, L.W., Gao, X., et al., 2016. CNTF protects neurons from hypoxic injury through the activation of STAT3pTyr705 [Internet] Int. J. Mol. Med. 38 (6), 1915–1921. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27748830.

Gullotta, G.S., De Feo, D., Friebel, E., Semerano, A., Scotti, G.M., Bergamaschi, A., et al., 2023. Age-induced alterations of granulopoiesis generate atypical neutrophils that aggravate stroke pathology [Internet] Nat. Immunol. 24, 925–940. Available from: https://www.nature.com/articles/s41590-023-01505-1.

Herring, S.E., Mao, S., Bhalla, M., Tchalla, E.Y.I., Kramer, J.M., Bou Ghanem, E.N., 2022. Mitochondrial ROS production by neutrophils is required for host antimicrobial function against Streptococcus pneumoniae and is controlled by A2B adenosine receptor signaling. PLoS Pathog. 18 (11), 1–29.

Hor, W.-S., Huang, W.-L., Lin, Y.-S., Yang, B.-C., 2003. Cross-talk between tumor cells and neutrophils through the Fas (APO-1, CD95)/FasL system: human glioma cells enhance cell viability and stimulate cytokine production in neutrophils [Internet] J. Leukoc. Biol. 73 (3), 363–368. Available from: https://academic.oup.com/jleukbio/article/73/3/363/6979356.

Hughes, C.E., Nibbs, R.J.B., 2018. A guide to chemokines and their receptors. FEBS J. 285 (16), 2944–2971.

Injarabian, L., Devin, A., Ransac, S., Marteyn, B.S., 2020. Neutrophil metabolic shift during their lifecycle: impact on their survival and activation. Int. J. Mol. Sci. 21 (1), 1–23.

Jaillon, S., Ponzetta, A., Di Mitri, D., Santoni, A., Bonecchi, R., Mantovani, A., 2020. Neutrophil diversity and plasticity in tumour progression and therapy [Internet] Nat. Rev. Cancer 20 (9), 485–503. https://doi.org/10.1038/s41568-020-0281-y.

Jiang, B., 2017. Aerobic glycolysis and high level of lactate in cancer metabolism and microenvironment [Internet] Genes Dis 4 (1), 25–27. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30258905.

Jun, H.S., Lee, Y.M., Cheung, Y.Y., McDermott, D.H., Murphy, P.M., De Ravin, S.S., et al., 2010. Lack of glucose recycling between endoplasmic reticulum and cytoplasm underlies cellular dysfunction in glucose-6-phosphatase-β-deficient neutrophils in a congenital neutropenia syndrome. Blood 116 (15), 2783–2792.

Kalafati, L., Mitroulis, I., Verginis, P., Chavakis, T., Kourtzelis, I., 2020. Neutrophils as orchestrators in tumor development and metastasis formation [Internet] Front. Oncol. 10. Available from: https://www.frontiersin.org/articles/10.3389/fonc.2020.581457/full.

Kanashiro, A., Hiroki, C.H., da Fonseca, D.M., Birbrair, A., Ferreira, R.G., Bassi, G.S., et al., 2020. The role of neutrophils in neuro-immune modulation. Pharmacol. Res. 151 (September 2019).

Kaplan, J.M., 2013. Neutrophil Extracelullar Traps (NETs):Double-Edged Swords of Innate Immunity 1, vol. 189, pp. 2689–2695, 6.

Khan, S., Mittal, S., McGee, K., Alfaro-Munoz, K.D., Majd, N., Balasubramaniyan, V., et al., 2020. Role of neutrophils and myeloid-derived suppressor cells in glioma progression and treatment resistance. Int. J. Mol. Sci. 21 (6), 6–9.

Kolonics, F., Kajdácsi, E., Farkas, V.J., Veres, D.S., Khamari, D., Kittel, Á., et al., 2021. Neutrophils produce proinflammatory or anti-inflammatory extracellular vesicles depending on the environmental conditions [Internet] J. Leukoc. Biol. 109 (4), 793–806. Available from: https://academic.oup.com/jleukbio/article/109/4/793/7032809.

Le Cabec, V., Cowland, J.B., Calafat, J., Borregaard, N., 1996. Targeting of proteins to granule subsets is determined by timing and not by sorting: the specific granule protein NGAL is localized to azurophil granules when expressed in HL-60 cells. Proc. Natl. Acad. Sci. U. S. A. 93 (13), 6454–6457.

Lee, W.L., Harrison, R.E., Grinstein, S., 2003. Phagocytosis by neutrophils. Microb. Infect. 5 (14), 1299–1306.

Levene, P.A., Meyer, G.M., 1912. The action of leucocytes on glucose [Internet] J. Biol. Chem. 11 (4), 361–370. https://doi.org/10.1016/S0021-9258(18)88742-7.

Ley, K., Laudanna, C., Cybulsky, M.I., Nourshargh, S., 2007. Getting to the site of inflammation: the leukocyte adhesion cascade updated. Nat. Rev. Immunol. 7 (9), 678–689.

Li, Y., Wang, W., Yang, F., Xu, Y., Feng, C., Zhao, Y., 2019. The regulatory roles of neutrophils in adaptive immunity [Internet] Cell Commun. Signal. 17 (1), 147. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31727175.

Lin, Y.J., Wei, K.C., Chen, P.Y., Lim, M., Hwang, T.L., 2021. Roles of neutrophils in glioma and brain metastases. Front. Immunol. 12 (August), 1–19.

Linas, S.L., Whittenburg, D., Parsons, P.E., Repine, J.E., 1992. Mild renal ischemia activates primed neutrophils to cause acute renal failure [Internet] Kidney Int. 42 (3), 610–616. https://doi.org/10.1038/ki.1992.325.

Liu, B., Jin, Y., Yang, J., Han, Y., Shan, H., Qiu, M., et al., 2022. Extracellular vesicles from lung tissue drive bone marrow neutrophil recruitment in inflammation [Internet] J. Extracell. Vesicles 11 (5). Available from: https://onlinelibrary.wiley.com/doi/10.1002/jev2.12223.

Long, W., Chen, J., Gao, C., Lin, Z., Xie, X., Dai, H., 2021. Brief review on the roles of neutrophils in cancer development. J. Leukoc. Biol. 109 (2), 407–413.

López-Lago, M.A., Posner, S., Thodima, V.J., Molina, A.M., Motzer, R.J., Chaganti, R.S. K., 2013. Neutrophil chemokines secreted by tumor cells mount a lung antimetastatic response during renal cell carcinoma progression [Internet] Oncogene 32 (14), 1752–1760. Available from: https://www.nature.com/articles/onc2012201.

Maianski, N.A., Geissler, J., Srinivasula, S.M., Alnemri, E.S., Roos, D., Kuijpers, T.W., 2004. Functional characterization of mitochondria in neutrophils: a role restricted to apoptosis. Cell Death Differ. 11 (2), 143–153.

Malm, T., Koistinaho, M., Muona, A., Magga, J., Koistinaho, J., 2010. The role and therapeutic potential of monocytic cells in Alzheimer's disease. Glia 58 (8), 889–900.

Manda-Handzlik, A., Demkow, U., 2019. The brain entangled: the contribution of neutrophil extracellular traps to the diseases of the central nervous system. Cells 8 (12).

Masucci, M.T., Minopoli, M., Carriero, M.V., 2019. Tumor associated neutrophils. Their role in tumorigenesis, metastasis, prognosis and therapy. Front. Oncol. 9 (November), 1–16.

McFarlane, A.J., Fercoq, F., Coffelt, S.B., Carlin, L.M., 2021. Neutrophil dynamics in the tumor microenvironment [Internet] J. Clin. Invest. 131 (6). Available from: https://www.jci.org/articles/view/143759.

McKenzie, S.E., Schreiber, A.D., 1998 [Internet]. Fc Gamma Receptors in Phagocytes, vol. 5. Current opinion in hematology, pp. 16–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9515197.

Middleton, E.A., He, X.-Y., Denorme, F., Campbell, R.A., Ng, D., Salvatore, S.P., et al., 2020. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome [Internet] Blood 136 (10), 1169–1179. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7254017/pdf/main.pdf.

Moulding, D.A., Hart, C.A., Edwards, S.W., 1999. Regulation of neutrophil FcγRIIIb (CD16) surface expression following delayed apoptosis in response to GM-CSF and sodium butyrate. J. Leukoc. Biol. 65 (6), 875–882.

Oberg, H.H., Wesch, D., Kalyan, S., Kabelitz, D., 2019. Regulatory interactions between neutrophils, tumor cells and T Cells. Front. Immunol. 10 (JULY).

Papayannopoulos, V., 2018. Neutrophil extracellular traps in immunity and disease. Nat. Rev. Immunol. 18 (2), 134–147.

Pietronigro, E.C., Della Bianca, V., Zenaro, E., Constantin, G., 2017. NETosis in Alzheimer's disease. Front. Immunol. 8 (MAR), 1–12.

Quail, D.F., Joyce, J.A., 2017. The microenvironmental landscape of brain tumors. Cancer Cell 31 (3), 326–341.

Ramadass, M., Catz, S.D., 2016. Molecular mechanisms regulating secretory organelles and endosomes in neutrophils and their implications for inflammation [Internet] Immunol. Rev. 273 (1), 249–265. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27558339.

Rawat, K., Syeda, S., Shrivastava, A., 2021. Neutrophil-derived granule cargoes: paving the way for tumor growth and progression. Cancer Metastasis Rev. 40 (1), 221–244.

Rice, C.M., Davies, L.C., Subleski, J.J., Maio, N., Gonzalez-Cotto, M., Andrews, C., et al., 2018. Tumour-elicited neutrophils engage mitochondrial metabolism to circumvent nutrient limitations and maintain immune suppression [Internet] Nat. Commun. 9 (1). https://doi.org/10.1038/s41467-018-07505-2.

Richards, D.M., Endres, R.G., 2014. The mechanism of phagocytosis: two stages of engulfment [Internet] Biophys. J. 107 (7), 1542–1553. https://doi.org/10.1016/j.bpj.2014.07.070.

Rodrigues, D.A.S., Prestes, E.B., Gama, A.M.S., de Souza Silva, L., Pinheiro, A.A.S., Ribeiro, J.M.C., et al., 2020. CXCR4 and MIF are required for neutrophil extracellular trap release triggered by Plasmodium-infected erythrocytes. PLoS Pathog. 16 (8), 1–23.

Rørvig, S., Honore, C., Larsson, L.-I., Ohlsson, S., Pedersen, C.C., Jacobsen, L.C., et al., 2009. Ficolin-1 is present in a highly mobilizable subset of human neutrophil granules and associates with the cell surface after stimulation with fMLP. J. Leukoc. Biol. 86 (6), 1439–1449.

Rosales, C., 2018. Neutrophil: a cell with many roles in inflammation or several cell types? [Internet] Front. Physiol. 9, 113. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29515456.

Roth Flach, R.J., Su, C., Bollinger, E., Cortes, C., Robertson, A.W., Opsahl, A.C., et al., 2019. Myeloperoxidase inhibition in mice alters atherosclerotic lesion composition [Internet] PLoS One 14 (3), e0214150. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30889221.

Sadiku, P., Willson, J.A., Ryan, E.M., Sammut, D., Coelho, P., Watts, E.R., et al., 2021. Neutrophils fuel effective immune responses through gluconeogenesis and glycogenesis. Cell Metabol. 33 (2), 411–423.e4.

Saffarzadeh, M., Juenemann, C., Queisser, M.A., Lochnit, G., Barreto, G., Galuska, S.P., et al., 2012. Neutrophil extracellular traps directly induce epithelial and endothelial cell death: a predominant role of histones. PLoS One 7 (2).

Sanders, L.A.M., Feldman, R.G., Voorhorst-Ogink, M.M., De Haas, M., Rijkers, G.T., Capel, P.J.A., et al., 1995. Human immunoglobulin G (IgG) Fc receptor IIA (CD32) polymorphism and IgG2- mediated bacterial phagocytosis by neutrophils. Infect. Immun. 63 (1), 73–81.

Sas, A.R., Carbajal, K.S., Jerome, A.D., Menon, R., Yoon, C., Kalinski, A.L., et al., 2020. A new neutrophil subset promotes CNS neuron survival and axon regeneration [Internet] Nat. Immunol. 21 (12), 1496–1505. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33106668.

Schernberg, A., Nivet, A., Dhermain, F., Ammari, S., Escande, A., Pallud, J., et al., 2018. Neutrophilia as a biomarker for overall survival in newly diagnosed high-grade glioma patients undergoing chemoradiation [Internet] Clin Transl Radiat Oncol 10, 47–52. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2405630817301039.

Schneider, T., Mawrin, C., Scherlach, C., Skalej, M., Firsching, R., 2010. Die gliome des erwachsenen. Dtsch. Ärztebl. 107 (45), 799–808.

Schönrich, G., Raftery, M.J., Samstag, Y., 2020. Devilishly radical NETwork in COVID-19: oxidative stress, neutrophil extracellular traps (NETs), and T cell suppression [Internet] Adv Biol Regul 77, 100741. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32773102.

Schrijver, I.T., Kemperman, H., Roest, M., Kesecioglu, J., de Lange, D.W., 2017. Myeloperoxidase can differentiate between sepsis and non-infectious SIRS and predicts mortality in intensive care patients with SIRS. Intensive Care Med Exp 5 (1).

Sengeløv, H., Follin, P., Kjeldsen, L., Lollike, K., Dahlgren, C., Borregaard, N., 1995. Mobilization of granules and secretory vesicles during in vivo exudation of human

neutrophils [Internet] J. Immunol. 154 (8), 4157–4165. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7535822.
Shaw, S.K., Owolabi, S.A., Bagley, J., Morin, N., Cheng, E., LeBlanc, B.W., et al., 2008. Activated polymorphonuclear cells promote injury and excitability of dorsal root ganglia neurons. Exp. Neurol. 210 (2), 286–294.
Sheshachalam, A., Srivastava, N., Mitchell, T., Lacy, P., Eitzen, G., 2014. Granule protein processing and regulated secretion in neutrophils. Front. Immunol. 5 (SEP), 1–11.
Smyth, L.C.D., Murray, H.C., Hill, M., van Leeuwen, E., Highet, B., Magon, N.J., et al., 2022. Neutrophil-vascular interactions drive myeloperoxidase accumulation in the brain in Alzheimer's disease. Acta Neuropathol Commun 10 (1), 1–17.
Stock, A.J., Kasus-Jacobi, A., Pereira, H.A., 2018. The role of neutrophil granule proteins in neuroinflammation and Alzheimer's disease. J. Neuroinflammation 15 (1), 1–15.
Szczerba, B.M., Castro-Giner, F., Vetter, M., Krol, I., Gkountela, S., Landin, J., et al., 2019. Neutrophils escort circulating tumour cells to enable cell cycle progression [Internet] Nature 566 (7745), 553–557. https://doi.org/10.1038/s41586-019-0915-y.
Tapper, H., Furuya, W., Grinstein, S., 2002. Localized exocytosis of primary (lysosomal) granules during phagocytosis: role of Ca 2+ -dependent tyrosine phosphorylation and microtubules. J. Immunol. 168 (10), 5287–5296.
Tecchio, C., Micheletti, A., Cassatella, M.A., 2014. Neutrophil-derived cytokines: facts beyond expression. Front. Immunol. 5 (OCT), 1–7.
Veras, F.P., Pontelli, M.C., Silva, C.M., Toller-Kawahisa, J.E., de Lima, M., Nascimento, D.C., et al., 2020. SARS-CoV-2-triggered neutrophil extracellular traps mediate COVID-19 pathology [Internet] J. Exp. Med. 217 (12). Available from: http://www.ncbi.nlm.nih.gov/pubmed/32926098.
Verri, W.A., Souto, F.O., Vieira, S.M., Almeida, S.C.L., Fukada, S.Y., Xu, D., et al., 2010. IL-33 induces neutrophil migration in rheumatoid arthritis and is a target of anti-TNF therapy. Ann. Rheum. Dis. 69 (9), 1697–1703.
Vitte, J., Michel, B.F., Bongrand, P., Gastaut, J.L., 2004. Oxidative stress level in circulating neutrophils is linked to neurodegenerative diseases. J. Clin. Immunol. 24 (6), 683–692.
Vogt, K.L., Summers, C., Chilvers, E.R., Condliffe, A.M., 2018. Priming and de-priming of neutrophil responses in vitro and in vivo. Eur. J. Clin. Invest. 48 (June), 1–9.
Vojtechova, I., Machacek, T., Kristofikova, Z., Stuchlik, A., Petrasek, T., 2022, 11. In: Lazear, H.M. (Ed.), Infectious Origin of Alzheimer's Disease: Amyloid Beta as a Component of Brain Antimicrobial Immunity, vol. 18. PLOS Pathog, e1010929. Available from: https://dx.plos.org/10.1371/journal.ppat.1010929.
Volkman, R., Ben-Zur, T., Kahana, A., Garty, B.Z., Offen, D., 2019. Myeloperoxidase deficiency inhibits cognitive decline in the 5XFAD mouse model of Alzheimer's disease. Front. Neurosci. 13 (September), 1–14.
Vono, M., Lin, A., Norrby-Teglund, A., Koup, R.A., Liang, F., Loré, K., 2017. Neutrophils acquire the capacity for antigen presentation to memory CD4+ T cells in vitro and ex vivo [Internet] Blood 129 (14), 1991–2001. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28143882.
Walmsley, S.R., Print, C., Farahi, N., Peyssonnaux, C., Johnson, R.S., Cramer, T., et al., 2005. Hypoxia-induced neutrophil survival is mediated by HIF-1α-dependent NF-κB activity. J. Exp. Med. 201 (1), 105–115.
Wang, S., Song, R., Wang, Z., Jing, Z., Wang, S., Ma, J., 2018. S100A8/A9 in inflammation. Front. Immunol. 9 (JUN).
Ward, R.A., Nakamura, M., McLeish, K.R., 2000. Priming of the neutrophil respiratory burst involves p38 mitogen-activated protein kinase-dependent exocytosis of flavocytochrome b558-containing granules [Internet] J. Biol. Chem. 275 (47), 36713–36719. https://doi.org/10.1074/jbc.M003017200.
Weaver, D.F., 2020. Amyloid beta is an early responder cytokine and immunopeptide of the innate immune system [Internet] Alzheimer's Dement Transl Res Clin Interv 6 (1). Available from: https://onlinelibrary.wiley.com/doi/10.1002/trc2.12100.
Worthen, G.S., Haslett, C., Rees, A.J., Gumbay, R.S., Henson, J.E., Henson, P.M., 1987. Neutrophil-mediated pulmonary vascular injury. Synergistic effect of trace amounts of lipopolysaccharide and neutrophil stimuli on vascular permeability and neutrophil sequestration in the lung [Internet] Am. Rev. Respir. Dis. 136 (1), 19–28. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3300442.
Yang, P., Li, Y., Xie, Y., Liu, Y., 2019. Different faces for different places: heterogeneity of neutrophil phenotype and function. J Immunol Res 2019.
Yipp, B.G., Kubes, P., 2013. NETosis: how vital is it? Blood 122 (16), 2784–2794.
Zenaro, E., Pietronigro, E., Della Bianca, V., Piacentino, G., Marongiu, L., Budui, S., et al., 2015. Neutrophils promote Alzheimer's disease-like pathology and cognitive decline via LFA-1 integrin [Internet] Nat Med 21 (8), 880–886. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26214837.
Zhang, C.C., Sadek, H.A., 2014. Hypoxia and metabolic properties of hematopoietic stem cells. Antioxidants Redox Signal. 20 (12), 1891–1901.