Immunobiology 225 (2020) 151865

Contents lists available at ScienceDirect

Immunobiology

journal homepage: www.elsevier.com/locate/imbio

The emerging role of neutrophils in neurodegeneration

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ARTICLE INFO

Keywords:
Neutrophils
Neurodegenerative diseases
Multiple sclerosis
Alzheimer's disease

ABSTRACT

Neutrophils are the first line of defense in the innate immune system, helping to maintain tissue homeostasis as well as eliminating pathogens and self-components. The traditional view of neutrophils as simple phagocytes has been revised over the last decade as new research reveals their unappreciated complexity. Neutrophils are phenotypically and functionally heterogeneous, allowing them to act as modulators of both inflammation and immune responses. During acute inflammation, neutrophils perform a variety of beneficial effector functions, but when inflammation is induced by injury (sterile inflammation) the benefits of neutrophils in tissue repair are more controversial. In several pathological conditions, including cancer and autoimmune diseases, neutrophils can trigger harmful tissue damage. Interestingly, neutrophils are also key players in neuroinflammatory disorders, during which they transmigrate in the central nervous system, acquire a toxic phenotype, home in on neurons, and release harmful molecules that compromise neuronal functions. In this review, we discuss recent data that redefine the cell biology and phenotype of neutrophils, focusing on the role of these cells in multiple sclerosis and Alzheimer's disease, both of which feature strong neuroinflammatory components.

1. Introduction

Neutrophils, basophils and eosinophils together comprise the polymorphonuclear leukocytes (PMNs), also known as granulocytes because of their abundant cytoplasmic granules (Roitt et al., 2001). These exceptionally sensitive leukocytes are the first line of defense in the innate immune system, with key roles in the maintenance of tissue homeostasis (Mantovani et al., 2011), and the elimination of pathogens and self-components, including nucleic acids and the products of sterile tissue damage (Kolaczkowska and Kubes, 2013).

Until about 10 years ago, neutrophils were considered to be a homogenous population of short-lived, nonproliferative and terminally differentiated cells with reduced transcriptional capacity, producing a limited panel of cytokines, and with no ability to recirculate from tissues to blood, suggesting highly conserved specialized functions. However, more recent research based on powerful high throughput technologies and computing data analysis methods has revealed unexpected phenotypic plasticity and diversity in terms of neutrophil trafficking and functionality. Their role is now understood to include not only homeostasis but also inflammation and tissue damage that, if not resolved, could lead to autoimmune diseases and chronic inflammatory conditions (Nemeth et al., 2016; Ley et al., 2018).

During acute inflammation caused by infection, the effector functions of neutrophils are generally beneficial to the host. However, when injury induces sterile inflammation, the effect of neutrophils is more complex, and can include chronic tissue damage in patients with cancer and autoimmune disorders (Kubes, 2018). Neurodegenerative diseases are also exacerbated by neutrophils, which produce inflammatory messages when they infiltrate the central nervous system (CNS) and make contact with neuronal cells, leading to a complex series of events that ultimately result in neuronal death. Notably, neutrophils play a pivotal role in several sterile neuroinflammatory diseases, such as trauma, cerebral ischemia, demyelinating syndromes but also in infectious conditions such as viral and bacterial encephalitis (Miller et al., 2015; Kenne et al., 2012; Holmin et al., 1998). Once extravasated in the CNS parenchyma, neutrophils likely contact neuronal cells and release damaging molecules that may impair neuronal physiology (Allen et al., 2012). Limiting neutrophil migration and/or activity could therefore ameliorate neurodegeneration by reducing neuronal injury (Miller et al., 2015; Kenne et al., 2012; Zenaro et al., 2015, 2017).

Neurodegenerative conditions, including Alzheimer's disease (AD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and Parkinson's disease (PD), are characterized by uncontrolled neuronal death that leads to a progressive decline in brain functions, such as cognition and locomotor control. The affected brain areas may differ between disorders, leading to a wide spectrum of clinical

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https://doi.org/10.1016/j.imbio.2019.10.014
Received 27 September 2019; Accepted 30 October 2019
Available online 09 November 2019
0171-2985/

manifestations. However, the growing incidence of neurodegenerative diseases represents an increasing burden on health care systems worldwide due to the limited availability of effective therapies. Neurodegenerative diseases such as AD and ALS are currently untreatable, and future treatment strategies will require the simultaneous targeting of multiple pathogenic components in order to reduce neuronal loss. Neurodegenerative diseases also have a complex etiology, with multiple risk factors contributing to susceptibility including aging, genetic factors and environmental triggers. Our understanding of the specific pathways and molecular mechanisms involved in these disorders remains rudimentary at best, and a more comprehensive understanding of neurodegenerative pathology will require a broadening of the current neurocentric viewpoint.

The role of neuroinflammation in neurodegenerative diseases indicates that the dysregulation of the immune system is an important etiological factor. There is a large body of evidence that MS is associated with aberrant gene expression in cells of the innate and adaptive immune systems (Hellings et al., 2002; Hernandez-Pedro et al., 2013), but such associations have only recently been reported for the other neurodegenerative diseases discussed above (Gagliano et al., 2016; Yokoyama et al., 2016). For example, a recent genome-wide association study (GWAS) involving MS, PD, ALS and AD patients revealed strong associations between PD and genes expressed in adaptive immune cells (such as T cells), whereas MS and AD were associated with genes expressed in the adaptive and innate immune systems, the latter including *CD14* in monocytes and *CD15* in neutrophils (Gagliano et al., 2016). Although AD and MS have distinct clinical symptoms, they share similar immune cell signatures characterized by the involvement of neutrophils in pathogenesis.

This review brings together recent data that redefines neutrophil biology and phenotype, focusing on the roles of neutrophils in neurodegenerative diseases with a chronic neuroinflammatory component. We summarize what is known about the involvement of neutrophils in the pathogenesis and maintenance of MS, AD, PD and ALS by focusing on their detrimental effects, particularly the exacerbation of brain injury.

2. The complexity of neutrophils

2.1. Neutrophil biology

Neutrophils are the most abundant leukocytes in mammalian blood, representing 50–70% of all leukocytes in humans and 10–25% in mice (Mestas and Hughes, 2004). As well as neutrophils in the circulation, another population of mature neutrophils is found in a marginated state, slowly transiting in the vascular compartments of bone marrow sinusoids, the spleen, liver, and lungs, and in some interstitial tissues (Summers et al., 2010). More than 50 years ago, it was estimated that 49% of human neutrophils were found in the blood and 51% as marginated cells (Athens et al., 1961), whereas in mice only 1–2% of neutrophils are found in the circulation and the remainder as marginated cells or cell stored in the bone marrow hematopoietic compartment (Semerad et al., 2002). Neutrophils are normally short-lived cells with a circulating half-life of 8–12.5 h in mice (Pillay et al., 2010a,b, Lord et al., 1991; Basu et al., 2002) and 5 h to 5.4 days in humans (Pillay et al., 2010a,b, Lahoz-Beneytez et al., 2016; Pillay et al., 2012). However, recent studies suggest that the activation of neutrophils during inflammation increases their longevity, allowing them to carry out more complex activities than previously understood (Deniset and Kubes, 2016).

In adult bone marrow under basal conditions, neutrophils mature from common hematopoietic $CD34^+$ stem cells (Lahoz-Beneytez et al., 2016) in a process called granulopoiesis, which takes ~5 days (Athens et al., 1961; Lahoz-Beneytez et al., 2016; Dancey et al., 1976; Macallan et al., 1998). Under these conditions, the generation rate is $5–10 \times 10^{10}$ cells per day, to compensate for the short half-life in circulation (Roitt et al., 2001; Summers et al., 2010). Granulopoiesis is a multi-step process involving three main stages of developmental commitment: (i) the undifferentiated stem cell pool, consisting of hematopoietic stem cells and pluripotent progenitors; (ii) the intermediate lineage-committed mitotic pool, comprising actively proliferating myeloblasts, promyelocytes, and myelocytes; (iii) and the post-mitotic pool, mainly comprising fully-differentiated, mature neutrophils (Summers et al., 2010; Semerad et al., 2002). Neutrophil development involves the condensation and hyper-segmentation of the nucleus and the formation of cytoplasmic granules, both of which are useful morphological markers that identify mature neutrophils. In contrast, immature neutrophils are characterized by a kidney-shaped nucleus in humans, and a ring-shaped nucleus in mice (Rausch and Moore, 1975; Lemez and Kacirkova, 2014; Pillay et al., 2013). Granulopoiesis is regulated by several cytokines and growth factors released from hematopoietic and stromal cells, particularly granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), stem cell factor (SCF), interleukin 3 (IL-3), IL-6, and FMS-like tyrosine kinase 3 ligand (FLT3-L) (Manz and Boettcher, 2014), together with reactive oxygen species (ROS) (Zhu et al., 2017). Under physiological conditions, G-CSF is the principal regulator of neutrophil production and release from the bone marrow (Summers et al., 2010; Bugl et al., 2012). The retention or release of neutrophils from bone marrow depends on the expression of certain CXC-motif chemokine receptors (CXCR family) on the surface of neutrophils and their interaction with secreted CXC ligands (CXCL family). Neutrophil storage is maintained when receptor CXCR4 binds CXCL12/stromal cell-derived factor 1 (SDF-1) produced by hematopoietic stem cells and bone marrow stromal cells (Furze and Rankin, 2008). Neutrophil release is promoted when CXCR4 is replaced with CXCR2, following peripheral attraction by chemokines (Martin et al., 2003; Eash et al., 2010; Devi et al., 2013; Christopher et al., 2009). In this context, G-CSF induces neutrophil mobilization by suppressing the expression of CXCR4 and inhibiting the production of CXCL12 by stromal cells (Semerad et al., 2002; De La Luz Sierra et al., 2007; Kim et al., 2006). Mature neutrophils leave the hematopoietic parenchyma for the blood stream primarily by transcellular migration through the tight-fitting pores of sinusoidal endothelial cells (Burdon et al., 2008).

Under basal conditions and during inflammation, apoptotic neutrophils are removed from clearance sites by macrophages, which destroy them by phagocytosis (Serhan and Savill, 2005). Given the efficiency with which the hematopoietic compartment continuously produces and releases large numbers of neutrophils, it is evident that efficient clearance is necessary for homeostasis. Studies in mice and human volunteers have shown how radiolabeled circulating neutrophils are captured and subsequently destroyed by reticular endothelial macrophages in the spleen, liver and bone marrow, each of them contributing equally (~30% each) to neutrophil clearance (Furze and Rankin, 2008; Thakur et al., 1977; Saverymuttu et al., 1985; Lovas et al., 1996; Suratt et al., 2001; Rankin, 2010; Shi et al., 2001). However, the bone marrow makes the greatest contribution to homeostatic neutrophil clearance under steady-state conditions (Furze and Rankin, 2008). In the spleen and liver, the reticular endothelial system is precisely located to ensure the direct capture of circulating apoptotic cells, whereas senescent neutrophils in the bone marrow reach stromal macrophages that are located within the hematopoietic tissue by active migration through the sinusoidal endothelium (Martin et al., 2003). Pre-apoptotic senescent circulating neutrophils display high levels of CXCR4 and low levels of CXCR2, which reduces their ability to follow peripheral chemokines such as CXCL1, CXCL2, CXCL5 and CXCL8 (Christopher et al., 2009) while enhancing their CXCL12-dependent migration in the hematopoietic compartment (Martin et al., 2003; Nagase et al., 2002). Intriguingly, whereas efferocytosis stimulates resolution processes during the clearance of cells from inflammatory sites (Serhan and Savill, 2005; Fadok et al., 1998), the destruction of senescent neutrophils in the bone marrow stimulates resident stromal

macrophages to secrete GCSF, increasing the circadian release of hematopoietic progenitors into the circulation during homeostasis (Casanova-Acebes et al., 2013). In healthy subjects, the neutrophil count is maintained by homeostatic equilibrium between production, storage, mobilization (from bone marrow or intravascularly marginated pools) and clearance (Bugl et al., 2012). G-CSF is mainly responsible for neutrophil homeostasis, not only by controlling granulopoiesis and mobilization, but also by regulating neutrophil trafficking and lifespan (Semerad et al., 2002; Basu et al., 2002; Lieschke et al., 1994).

Many environmental factors, including drugs, physical exercise, prolonged inflammation and infections affect the maturation, activation status and lifespan of neutrophils (Summers et al., 2010; Bugl et al., 2012). During infection and/or inflammation, neutrophils are rapidly mobilized from bone marrow, increasing their abundance in the circulation by up to 10-fold within a matter of hours. Chemokines that are released locally at sites of inflammation and regulate the recruitment of circulating leucocytes into tissues also promote neutrophil mobilization (Kobayashi, 2006). Studies in animal models have shown that high plasma levels of several chemokines (including CXCL1, CXCL2 and CXCL8) and other chemotactic factors (including leukotrienes B4 and C5a) induce neutrophilia by inducing rapid neutrophil mobilization from the bone marrow (Burdon et al., 2008; Terashima et al., 1998; Wengner et al., 2008; Jagels et al., 1995; Jagels and Hugli, 1992). Mobilization is also enhanced by the indirect effect of G-CSF, which reduces the availability of CXCL12 and the expression of CXCR4, thus freeing neutrophils to respond to peripheral chemoattractants (Martin et al., 2003). Systemic infections, prolonged inflammation or conditions that trigger myeloablation can rapidly induce bone marrow to release immature neutrophils from the post-mitotic pool, which accounts for 95% of the total neutrophil population (Summers et al., 2010; Semerad et al., 2002). This process of accelerated neutrophil production is known as emergency granulopoiesis, and the immature neutrophils are directly stimulated following the recognition of microbial associated molecular patterns (PAMPs) or damage associated molecular patterns (DAMPs) (Manz and Boettcher, 2014, Bugl, et al., 2012, Balmer et al., 2014). However, these immature circulating neutrophils do not contain the full complement of granules (Rausch and Moore, 1975), and they are less active than mature neutrophils, producing lower quantities of ROS and antimicrobial peptides, and with a lower capacity for phagocytosis, chemotaxis and tissue migration (Kolaczkowska and Kubes, 2013; Suratt et al., 2001; Evrard et al., 2018; Pedersen et al., 2016).

Once mobilized, a proportion of the neutrophil population is enlisted as the marginated pool, which disappears from the bloodstream, whereas the remaining neutrophils passively circulate in the blood to be recruited immediately after infection or injury based on their priming by circulating DAMPs, PAMPs, cytokines and chemokines (Hallett and Lloyds, 1995). Circulating cells are attracted to peripheral tissues by local chemokines that orchestrate their adhesion, transmigration and chemotaxis at the injury or infection site (Roitt et al., 2001; Kobayashi, 2006). Chemokine signaling activates integrins found in great abundance on the neutrophil plasma membrane, such as lymphocyte function-associated antigen-1 (LFA-1) and macrophage-1 antigen (Mac-1), allowing the firm arrest of neutrophils on vessel endothelial cells (Kolaczkowska and Kubes, 2013). The neutrophils then extend pseudopods to scan the endothelium, seeking an appropriate site for transmigration through endothelial cell–cell junctions (paracellular transmigration) (Jenne et al., 2013). Following this process of extravasation, neutrophils follow a second, more attractive chemotactic gradient to reach the site of inflammation (Phillipson and Kubes, 2011; Foxman et al., 1997). Local microbes and/or tissue stress factors then induce signaling pathways in the neutrophils, triggering their antimicrobial defense and pro-inflammatory programs. The corresponding effector functions include phagocytosis, the release of neutrophil extracellular traps (NETs) (Brinkmann et al., 2004) followed by auto-phagocytosis and intracellular digestion (Mitroulis et al., 2010; Mihalache and Simon, 2012), the production and release of ROS, antimicrobial peptides and serine proteases, and the secretion of pro-inflammatory cytokines and chemokines (Teng et al., 2017). Furthermore, inflammasome activation by chemokines and DAMPs also triggers neutrophil infiltration during sterile inflammation, where they can induce acute or chronic inflammatory responses (McDonald et al., 2010).

At the site of inflammation, many neutrophils undergo apoptosis and are cleared by macrophages and dendritic cells (DCs), leading to the resolution of acute inflammation and the restoration of tissue homeostasis (Savill et al., 1989). Neutrophils also contribute actively to resolution by the degradation of local inflammatory cytokines, the clearance of DAMPs, the production of cytokines (such as IL-1Ra, IL-10, IL-1β and IL-6) and lipid mediators, and the secretion of chemokines such as monocyte chemoattractant protein-1 (MCP-1), which attracts circulating monocytes and induces a regulatory M2 phenotype in macrophages (Kolaczkowska and Kubes, 2013; Soehnlein et al., 2009; Langereis et al., 2011; Wang and Arase, 2014; Butterfield et al., 2006; Kobayashi, 2015; Headland and Norling, 2015). Furthermore, many recent studies have reported that neutrophils can return to the blood after tissue migration (reverse transmigration), and that such cells exhibit a pro-inflammatory phenotype, characterized by the strong expression of intercellular adhesion molecule-1 (ICAM-1), which correlates with the depletion of junctional adhesion molecule C (JAM-C) in endothelial cells (Woodfin et al., 2011; Buckley et al., 2006; Shelef et al., 2013; Colom et al., 2015). Interestingly, reverse-transmigrating cells are resistant to apoptosis, and this prolonged lifespan may influence their phenotype and function, thus contributing to neutrophil heterogeneity (Buckley et al., 2006). The purpose of reverse transmigration is not clearly understood: although it may preserve neutrophils when they are not needed to fight infection, cells re-entering the circulation could disseminate inflammation to other organs, eventually leading to damage and/or chronic inflammation (Kolaczkowska and Kubes, 2013). Alternatively, activated neutrophils may leave infected/inflamed tissues by migrating to secondary lymphoid organs through the lymphatic and circulatory systems (Abadie et al., 2005; Chtanova et al., 2008; Duffy et al., 2012; Gorlino et al., 2014; Hampton et al., 2015; Yang et al., 2010; Yang and Unanue, 2013). Neutrophils that egress from tissues to the circulation or emigrate into secondary lymphoid organs have a prolonged lifespan and a different phenotype, explaining their heterogeneous characteristics. Furthermore, during infection and sterile inflammation, cytokines, PAMPs, DAMPs and other microenvironmental factors such as serpins may regulate the longevity of neutrophils by inhibiting apoptosis (Summers et al., 2010; Geering et al., 2013; Sundqvist et al., 2013; Baumann et al., 2013; Loison et al., 2014). Indeed, in several chronic inflammatory diseases (such as asthma and acute coronary syndrome), neutrophil longevity is associated with more severe symptoms and a negative prognosis (Uddin et al., 2010; Garlichs et al., 2004). The extended lifespan of neutrophils during inflammation may allow phenotypic and functional changes that underpin the observed heterogeneity in this population (Peyssonnaux et al., 2005; Thompson et al., 2014; Laval et al., 2013; Makam et al., 2009). Although the transcriptional plasticity of neutrophils was traditionally considered rather limited (Cassatella, 1995), recent studies have reported the inducible genetic and epigenetic modulation of neutrophil gene expression (Tecchio et al., 2014; Yost et al., 2004), and the association of both mechanisms with disease susceptibility (Naranbhai et al., 2015; Coit et al., 2015). Neutrophils secrete a wide range of chemokines and cytokines either constitutively or in response to different local stimuli (Tecchio et al., 2014; Cassatella et al., 1992). This reveals that neutrophils show significant functional diversity in terms of recruitment, the regulation of controlled sequential migration, and the activation of other innate and adaptive immune cells such as monocytes, macrophages, DCs, natural killer (NK) cells, and subsets of helper T cells, such as Th17 (Mayadas et al., 2014; Jaillon et al., 2013; Scapini and Cassatella, 2014; Sadik et al., 2011; Pelletier et al., 2010).

Neutrophils may not only attract other cell types but also modulate their activity, thereby playing a key role in the control of adaptive

immune responses (Mantovani et al., 2011; Scapini and Cassatella, 2014; Mocsai, 2013). Neutrophils not only activate antigen presenting cells (APCs) and T cells by secreting pro-inflammatory cytokines and chemokines (Mantovani et al., 2011; Wright et al., 2010), but may also function directly as APCs (Hampton et al., 2015; Yang et al., 2010; Yang and Unanue, 2013; Cross et al., 2003). In the synovial fluid of rheumatoid arthritis patients, neutrophils were found to express high levels of major histocompatibility complex (MHC)-II and costimulatory molecules such as CD80 and CD89, which enabled them to stimulate T cell proliferation in vitro (Cross et al., 2003). Furthermore, if neutrophils are prevented from migrating to the lymph nodes in mouse disease models, the proliferation of T cells is inhibited, suggesting that neutrophils can initiate early adaptive immune responses (Hampton et al., 2015; Yang et al., 2010; Yang and Unanue, 2013). Other studies have proposed that neutrophils with internalized microbes may act as "Trojan vectors" for macrophages (Coombes et al., 2013; Peters et al., 2008). Some circulating neutrophils, now defined as B cell helper neutrophils (N_{BH}), have been shown to colonize the spleen and induce immunoglobulin class switching, somatic hypermutation, and T-cell-independent antibody production in B cells by secreting B-cell activating factor (BAFF), IL-21 and a proliferation-inducing ligand (APRIL) (Puga et al., 2011; Huard et al., 2008; Cerutti et al., 2013). Moreover, murine neutrophils can secrete B lymphocyte stimulator (BLyS), thus prolonging B cell and plasma cell survival (Scapini et al., 2005). There appear to be inter-species differences in the role of splenic neutrophils because the above mechanisms identified in mice do not always occur in humans (Nagelkerke et al., 2014; Scapini and Cassatella, 2017).

The discovery of different subpopulations of neutrophils that polarize macrophages in opposite directions indicates that these cells may not only induce but also suppress immune responses. A subtype of murine neutrophils with a suppressive phenotype has been identified (Tsuda et al., 2004). In a mouse model of leishmaniasis, apoptotic neutrophils that have phagocytosed the parasite were co-localized with DCs suppressing the adaptive immune response (Peters et al., 2009; Ribeiro-Gomes et al., 2012). In addition, a subtype of human neutrophils acting as granulocytic myeloid-derived suppressor cells (G-MDSCs) was found to reduce T cell and NK cell proliferation (Youn and Gabrilovich, 2010; Munder et al., 2005; Kraaij et al., 2010; Nagaraj et al., 2013). Another neutrophil subtype that inhibits the proliferation of T cells was identified in patients with systemic inflammation (Pillay et al., 2012).

Given the prominent role played by neutrophils during infection, their large array of receptors for the recognition of PAMPs, and the proposed co-evolution of microbes and immune cells, it is not unlikely that microbes influence multiple aspects of neutrophil biology. For example, commensal microbes may control the production of neutrophils and their capacity for phagocytosis, raising the opportunity that these factors also affect the ageing of peripheral neutrophils (Zhang et al., 2015). Furthermore, neutrophil diversity induced by microbial products in mice can also affect pathological states. For example, neutrophils were shown to become more active following the activation of Toll-like receptors (TLRs) and Myd88, which mediate microbiome-driven neutrophil ageing. The microbiome may therefore support the balanced activation status of neutrophils, justifying the evolutionary pressure to maintain an energy-consuming short lifespan as a mechanism to refine the balance between highly active neutrophils and the risk of tissue injury (Zhang et al., 2015). We therefore speculate that the imbalanced microbiome (dysbiosis) associated with many neurodegenerative diseases (Jangi et al., 2016; Fung et al., 2017; Marizzoni et al., 2017) may cause homeostatic neutrophils to be overrun with more active and/or aging neutrophils, with deleterious effects.

Despite the growing literature drawing attention to the role of sex-on immune system, most studies have focused on the adaptive immune system and innate immune cells such as neutrophils have been largely overlooked (Pennell et al., 2012; Giefing-Kroll et al., 2015; Tan et al., 2015; Klein and Flanagan, 2016; Gubbels Bupp et al., 2018). Interestingly, a recent study using a bacterial model of prostate inflammation indicated that testosterone promotes the recruitment of malfunctioning neutrophils that amplify and prolong the inflammatory response, with the persistence of their toxic products destroying cellular components and generating a pathogenic environment (Scalerandi et al., 2018). The authors clearly showed that testosterone inhibits the bactericidal potential of neutrophils by reducing myeloperoxidase (MPO) activity and promoting the expression of the anti-inflammatory cytokines IL-10 and transforming growth factor 1β (TGF-β1), a neutrophil phenotype previously reported only in the tumor microenvironment (Scalerandi et al., 2018).

Taken together, these studies indicate that neutrophils can display environmental-specific phenotypic and functional plasticity that underpins their pleiotropic effects during homeostasis, but also has the potential to induce chronic inflammation and/or tissue damage. Although the diversity of neutrophil subtypes remains unclear, neutrophils are now known to be key players in the development of many chronic inflammatory diseases, including chronic low-grade adipose tissue inflammation, insulin resistance mediated by the secretion of elastase, atherosclerosis, rheumatoid arthritis, systemic lupus erythematosus, anti-neutrophil cytoplasmic antibody-related vasculitis, deep vein thrombosis, chronic obstructive pulmonary disease, cystic fibrosis, and animal models of MS (Mantovani et al., 2011; Miller et al., 2015; Caielli et al., 2012; Talukdar et al., 2012; Chmelar et al., 2013). The pathological significance of the neutrophil subtypes as well as their regulatory networks, urgently need to be clarified.

2.2. Neutrophil heterogeneity

Neutrophils are a heterogeneous population of cells that rapidly change their characteristics and behavior when they are activated, as they age, or when they enter new environments. This is a fundamental property for the cells, allowing functional specialization and environmental adaptation. The subpopulations of neutrophils are defined by a combination of features such as the expression of surface markers, maturity, density, morphology and anatomical site.

When neutrophils leave the bone marrow and enter the peripheral circulation, integrin α4β1, also known as very late antigen 4 (VLA-4) or CD49d, and CXCR4 are downregulated, whereas CXCR2 and TLR-4 are upregulated (Grieshaber-Bouyer and Nigrovic, 2019). Mature human neutrophils express the neutrophil lineage markers CD15 and CD66b, along with high surface levels of CD16 (FcγRIII), CD62 L (L-selectin), and CD10 (neutral endopeptidase) (Elghetany, 2002, Marini, et al., 2017). Neutrophils change their phenotype following activation, which involves the surface translocation of pre-formed intracellular pools of membrane proteins such as β2 integrin CD11b/CD18 (Mac-1), and in some individuals CD177 (Elghetany, 2002; Goldschmeding et al., 1992; Videm and Strand, 2004). Activated neutrophils also display complement surface receptors such as CR1 (CD35), which mediates the binding and phagocytosis of C3b-coated particles and immune complexes (Videm and Strand, 2004; Berends et al., 1993). Other surface markers are lost during activation, including CD62 L. Under conditions of immune stress, immature neutrophils released from bone marrow also become $CD16^{lo}$ and $CD10^{lo}$ (Marini et al., 2017; Pillay et al., 2010a,b). In the mouse, a recent report distinguished neutrophil subsets during inflammation by identifying CD101 (Igsf2) as a marker of mature neutrophils (Evrard et al., 2018). Indeed, circulating mature neutrophils are defined as $Ly6G^{+}$ $CXCR2^{+}$ $CD101^{+}$, whereas immature neutrophils are defined as $Ly6G^{lo/+}$CXCR2– CD101–, and are rare in the circulation under baseline conditions (Evrard et al., 2018).

Aged neutrophils are known to upregulate CXCR4, leading to their return to the bone marrow for clearance, but they downregulate L-selectin and CD47, an inhibitor of phagocytosis (Adrover et al., 2016). In mice, the neutrophil marker Ly6G is less abundant in older cells (Zhang et al., 2015; Rosales et al., 2017). Recently, the surface expression of other molecules has also been found to increase during neutrophil

aging, including CD11c, CD24, CD45, and molecules involved in cell migration and intercellular interactions (CD11b and ICAM-1) (Zhang et al., 2015; Rosales et al., 2017). Interestingly, ICAM-1 also identifies neutrophils with enhanced effector functions in murine models of endotoxemia and MS (Whittaker Hawkins et al., 2017; Woodfin et al., 2016). Neutrophils undergo morphological changes during aging, becoming smaller, containing fewer granules, and displaying a granular multi-lobular nucleus (Casanova-Acebes et al., 2013; Rosales et al., 2017). Functionally, these cells appear hyper-activated, with the induction of several signaling pathways distinct from those in activated neutrophils, including TLRs, NOD like receptors (NLRs), and the transcription factor NF-κB, leading to the production of more ROS and the formation of NETs (Zhang et al., 2015; Adrover et al., 2016). Some studies have shown that aged neutrophils migrate efficiently to sites of inflammation (Uhl et al., 2016), whereas others have described impaired migration and reduced pro-inflammatory activity in neutrophils that have been aged in vitro (Rankin, 2010; Whyte et al., 1993). Furthermore, brain injury in a model of induced ischemic inflammation was only exacerbated in mice enriched with fresh neutrophils, not in mice with constitutive aged neutrophils, suggesting that fresh neutrophils preferentially migrate during brain inflammation contributing to tissue injury (Adrover et al., 2016). A further subtype of neutrophils displaying a $CD49d^{hi}$ $CXCR4^{hi}$ profile is efficiently recruited to non-vascularized tissues under hypoxia, where they support angiogenesis (Christoffersson et al., 2012; Massena et al., 2015), like the neutrophils that promote tumor vascularization (Jablonska et al., 2010), further complicating the classification of neutrophil subtypes based on the expression of surface markers.

Analysis of the role played by tumor-associated neutrophils in a variety of human cancers revealed a heterogeneous population with phenotypes ranging from inflammatory and anti-tumor (N1) to suppressive and pro-tumor (N2), mirroring the nomenclature of macrophages with similar activity (Smith and Trinchieri, 2018; Grecian et al., 2018). N1 neutrophils can kill tumor cells via hypochlorus acid produced from ROS, via release of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), or via tumor necrosis factor-α (TNF-α) expression (Dallegri et al., 1991; Andzinski et al., 2016; Tecchio et al., 2004). In contrast, N2 neutrophils promote tumor growth by increasing the deposition of extracellular matrix and suppressing the anti-tumor immune response. However, the binary N1/N2 classification is now considered an oversimplification, with evidence of greater plasticity and heterogeneity, and context-dependent differentiation and/or activation states reflecting the tissue environment, the inflammatory trigger, and interactions with other cell types (Smith and Trinchieri, 2018; Silvestre-Roig et al., 2016; Jones et al., 2016; Singhal et al., 2016; Sagiv et al., 2015; Mishalian et al., 2017).

Looking more specifically at the tissue environment, the lung is populated by large numbers of neutrophils under steady-state conditions, with cells adhering to the vascular lumen and interstitial spaces (Devi et al., 2013; Zemans et al., 2009). These cells are strategically positioned in the lungs either to supply the circulation or respond to injury. Their retention is mediated by CXCR4 signaling, and release into the blood can therefore be triggered by CXCR4 antagonists or epinephrine (Devi et al., 2013). Alternatively, they promptly infiltrate the interstitium and airspaces during inflammatory conditions (Kreisel et al., 2010). It is unknown whether similar strategies are adopted elsewhere, but neutrophils populating other tissues are also endowed with homeostatic functions. As stated above, neutrophils can interact with T cells in the lymph nodes (Hampton et al., 2015), and a subpopulation of human and mouse neutrophils is known to express functional CCR7, a chemokine receptor involved in the migration of neutrophils to secondary lymphoid organs (Beauvillain et al., 2011). Neutrophil migration to lymph nodes also relies on receptors that are upregulated in aging cells, such as CD11b and CXCR4 (Gorlino et al., 2014). Interestingly, neutrophils (like T and B cells) can enter lymph nodes from the peripheral circulation by crossing high endothelial venules in the context of infection or antigen challenge (Gorlino et al., 2014; Kamenyeva et al., 2015; Brackett et al., 2013), and intravital microscopy has identified neutrophils migrating within the lymphatic vessels of inflamed skin, and localizing to draining lymph nodes in response to the injection of microbes (Hampton et al., 2015). Neutrophils are also involved in T cell-mediated responses through contact-dependent inhibition and the local delivery of ROS (Pillay et al., 2012). Notably, low doses of endotoxin trigger the appearance of a T cell-suppressive population of neutrophils in the human peripheral circulation, and this subtype displays morphological features such as nuclear hypersegmentation and the expression of the surface markers $CD62L^{lo}$, $CD11b^{hi}$ and $CD11c^{hi}$ (Pillay et al., 2012) that resemble aged neutrophils in the mouse (Casanova-Acebes et al., 2013; Zhang et al., 2015). Similarly, large numbers of neutrophils are also found in the spleens of healthy mice and humans. Human N_{BH} cells display a $CD15^{int/lo}$ $CD16^{int/lo}$ $CD11b^{hi}$ phenotype, whereas the equivalent population in mice are a mixture of immature $Ly6G^{lo}$ cells, which retain their proliferative capacity but have limited mobility and phagocytic capacity, and mature $Ly6G^{hi}$ cells that are highly motile and phagocytic (Puga et al., 2011; Scapini and Cassatella, 2017; Deniset et al., 2017). Splenic neutrophils adopt a distinct $CD62L^{lo}$ $CD11b^{hi}$ $ICAM\text{-}1^{hi}$ phenotype and are found near B cells in the marginal zone, where they have the tendency to produce NETs and secrete cytokines to induce somatic hypermutation and antibody production (Puga et al., 2011; Cerutti et al., 2013).

The density of neutrophils in healthy human subjects is > 1.080 g/mL, which is slighter greater than the density of peripheral blood mononuclear cells (PBMCs), such as lymphocytes (1.073–1.077 g/ml) and monocytes (1.067–1.077 g/ml) (Zipursky et al., 1976). Neutrophils isolated from the blood by discontinuous density gradient form a red cell pellet, often described as the high-density or normal-density layer, and a low-density layer of PBMCs. Normal-density neutrophils (NDNs) are generally the most abundant cell type in the pellet, but in cancer patients and individuals with autoimmune diseases, systemic and local infection, dermatomyelosis, malaria or asthma, there is an expanded population of neutrophils in the low-density layer, known as low-density neutrophils (LDNs), which can be further defined by maturity and/or morphology (Galdiero et al., 2018; Carmona-Rivera and Kaplan, 2013; Villanueva et al., 2011; Singh et al., 2014; Zhang et al., 2017; Rocha et al., 2015; Fu et al., 2014; Cloke et al., 2012). LDNs tend to be large and are either immature with banded/ring nuclei or mature with segmented nuclei, they have a tendency to produce NETs, and an enhanced pro-inflammatory profile characterized by the synthesis of cytokines such as IL-6, IL-8, TNFα, and interferon (IFN) type I, meaning they contribute to neutrophil recruitment and chronic inflammation (Villanueva et al., 2011; Denny et al., 2010; Kanamaru et al., 2018). In mice, NDNs can be converted into a distinct LDN subpopulation that appears to be transient in self-resolving inflammation but accumulates in animals with tumors (Sagiv et al., 2015).

Overall, these data suggest that neutrophil functionality is determined not only by surface markers but also, independently, by the anatomical site and inflammatory milieu. Insight into the pathological role of neutrophils therefore requires a deep characterization of their functional phenotype. We currently know little about neutrophil heterogeneity, hallmark effects, and the detection of mediators that trigger the conversion from physiological tissue repair and regeneration to pathological tissue damage. Given the exceptional sensitivity of these cells to external stimuli, the selection of procedures to analyze neutrophils isolated from the blood or tissue environment may influence their phenotype and/or functional properties, thus contributing to the increasingly complex and confounding identification of neutrophil subtypes (Rebecchi et al., 2000; Pallister et al., 2006).

The field will continue to expand, there is far more to be learned about neutrophils that do much more than simply get sent into the circulation to capture and digest microbes. This multifaced cell support homeostasis as well as complex disease states, and display regulatory

properties that extend beyond their lifetime in the circulation.

3. Neutrophils in MS

MS is a chronic inflammatory disease of the CNS with an autoimmune origin. It involves progressive myelin degradation by cells of the immune system, which slows and disrupts the transmission of nerve impulses (Tillery et al., 2017). MS pathology is also characterized by well-defined inflammatory infiltrates, the activation of microglia, the proliferation of astrocytes, gliosis, and variable degrees of axonal degeneration (Kaskow and Baecher-Allan, 2018; Constantinescu et al., 2011). This results in clinical manifestations such as changes in sensation, mobility, balance, sphincter function, vision, and cognition. MS clinical manifestation is heterogeneous, ranging from a mild illness to a rapidly evolving, incapacitating disease demanding profound lifestyle adjustments and with major individual and socioeconomic consequences (Aktas et al., 2010; Bishop and Rumrill, 2015; Kobelt et al., 2019). Globally, MS affects ~2.5 million people in early to middle adulthood (mean age at onset = 30 years), and is the most common chronic demyelinating disease, with a higher prevalence in countries further from the equator (Dendrou et al., 2015).

Based on the initial disease course, MS can be classified as relapsing-remitting (RRMS) or primary progressive (PPMS). The most frequent form of MS is RRMS, affecting more than two-thirds of patients. It typically affects young adults and features episodes of neurological dysfunction (relapses) lasting at least 24 h in the absence of fever or infection, alternating with periods of remission, which can be variable and incomplete. One of the hallmarks of RRMS is the presence of focal inflammatory lesions leading to demyelinated CNS plaques that can be detected by magnetic resonance imaging (MRI). Most RRMS patients present with lesions primarily disseminated in the brain, whereas a small proportion have lesions primarily disseminated in the spinal cord (Bot et al., 2004; Thorpe et al., 1996; Nociti et al., 2005). RRMS affects women three times more frequently than men (Brownlee et al., 2017). After 10–15 years, most RRMS cases evolve into secondary progressive MS (SPMS), during which there is a gradual loss of ability, with or without relapses (Dendrou et al., 2015; Lublin et al., 2014; Ontaneda et al., 2017). The remaining 15% of MS patients present with PPMS, in which there is a continuous and gradual worsening of neurological symptoms over time, usually without relapses. In contrast to RRMS, in which gadolinium-enhancing MRI lesions are common, PPMS patients present with progressive brain atrophy (Filippi et al., 1997). The final acute MS phase usually lasts no more than 1 year before death.

Both environmental and genetic factors seem to be involved in MS. There is a broad consensus that the disease is multifactorial and the MS-prone genotype results from multiple independent or interacting polymorphic genes, with risk alleles common in the population, and each exerting a small or at most moderate effect. GWAS have identified more than 100 common genetic variants associated with MS, mostly in loci related to the adaptive immune system (Hemmer et al., 2015). Moreover, environmental risk factors affecting the immune system, such as prior infection with Epstein-Barr virus, smoking, and low sunlight exposure/vitamin D deficiency, play a role in the development of MS (Tillery et al., 2017; Salvetti et al., 2009). The broad heterogeneity in terms of pathological features and clinical development suggests that multiple pathogenic pathways contribute to the disease. Two main hypotheses have been proposed to explain the role of the immune system in the development of lesions. The “outside-in” hypothesis suggests that a peripheral antigen-specific immune response, triggered by foreign antigens, spreads to the initially unaffected CNS. In contrast, the “inside-out” hypothesis suggests that MS is triggered within the CNS, leading to the activation of resident microglia followed by the amplification of the immune response due to the recruitment of ancillary adaptive and innate immune cells (Henderson et al., 2009). In the latter case, the triggering factor might be a mutation that causes the death of oligodendrocytes, resulting in the activation of microglial cells (Hemmer et al., 2015). Inflammation is known to cause tissue damage in the early stages of the disease because anti-inflammatory and immunosuppressive therapies can ameliorate RRMS but not the progressive forms of the disease (Mahad et al., 2015).

The “outside-in” hypothesis was developed based on studies in mice with experimental autoimmune encephalomyelitis (EAE), the most widely used experimental model of the disease. C57BL/6 J and SJL mice are widely used for the induction of EAE, but different clinical signs are observed in each strain. SJL mice immunized with the peptide PLP139-151 develop a disease similar to RRMS, where remission can be complete or partial depending on the severity of the symptoms (McRae et al., 1995; Vanderlugt et al., 2000). In contrast, C57BL/6 J mice immunized with peptide MOG35-55 in complete Freund’s adjuvant (CFA) manifest a chronic and sustained form of EAE (Bannerman et al., 2005). Pathogenesis is closely related to the trafficking of autoreactive immune cells into the CNS via an increasingly dysfunctional blood–brain barrier (BBB). Myelin-reactive T cells (particularly subtypes Th1 and Th17) are the principal cell populations that attack myelin sheaths (Korn et al., 2007; Langrish et al., 2005).

Neutrophil infiltration has been investigated in C57BL/6 J mice immunized with MOG35-55. Immunohistochemistry and flow cytometry revealed that neutrophils were the most abundant population immediately before and at the onset of disease, whereas their number and percentage dropped at the disease peak, when they were found also in the CNS parenchyma (Fig. 1), and during the phase of recovery (Soulika et al., 2009; Steinbach et al., 2013; Christy et al., 2013; Simmons et al., 2014; Rumble et al., 2015; Wu et al., 2010; Aube et al., 2014). Interestingly, neutrophils appear in meningeal and perivascular inflammatory foci shortly before the onset of clinical symptoms in the CNS of mice with active EAE (Steinbach et al., 2013; Christy et al., 2013). At the disease peak, neutrophils were observed in CNS regions within areas of vascular leakage, demyelination and axonal damage (Soulika et al., 2009; Wu et al., 2010), suggesting their detrimental role in the CNS during the development of EAE. Furthermore, the spinal cord showed evidence of massive neutrophil accumulation in the center of and in close proximity to demyelinated areas and sites of axonal loss or degeneration during the early stages of EAE, but no neutrophil infiltration was observed in the CNS of naïve mice (Wu et al., 2010). These findings suggest that neutrophils promote inflammation during the onset and progression of EAE, as well as demyelination and axonal damage during the acute phase of the disease. Notably, in an EAE model induced in rhesus monkeys (very similar to human MS pathology), neutrophils consistently infiltrated the CNS as the disease developed (Bajramovic et al., 2008).

EAE can be attenuated by the direct targeting of neutrophils, interference with their mobilization from the bone marrow, or by blocking the mechanism of neutrophil recruitment in the inflamed CNS (Steinbach et al., 2013; Rumble et al., 2015; McColl et al., 1998; Carlson et al., 2008; Woodberry et al., 2018). Interestingly, neutrophil depletion attenuates the disease before (but not after) onset or relapse, suggesting a role for neutrophils in the early phases of lesion development (Steinbach et al., 2013; McColl et al., 1998; Carlson et al., 2008). G-CSF is indirectly responsible for neutrophil mobilization in response to inflammation (Sadik et al., 2011; Nauseef and Borregaard, 2014), and this molecule accumulates in the CNS and periphery of EAE mice during the preclinical disease phase, correlating with the greater number of neutrophils in the bone marrow and bloodstream (Soulika et al., 2009; Rumble et al., 2015). Mice deficient for the G-CSF receptor show evidence of neutropenia and are resistant to the induction of EAE (Rumble et al., 2015). Moreover, treatment with G-CSF prior to the onset of EAE and during remission aggravates the disease (Verda et al., 2006). In agreement with these data, the symptoms of MS are also aggravated in human patients treated with G-CSF (Openshaw et al., 2000; Burt et al., 2001). The massive infiltration of neutrophils into CNS lesions occurs following the induction of EAE by the passive transfer of myelin-specific Th2 and Th17 cells, which secrete GM-CSF

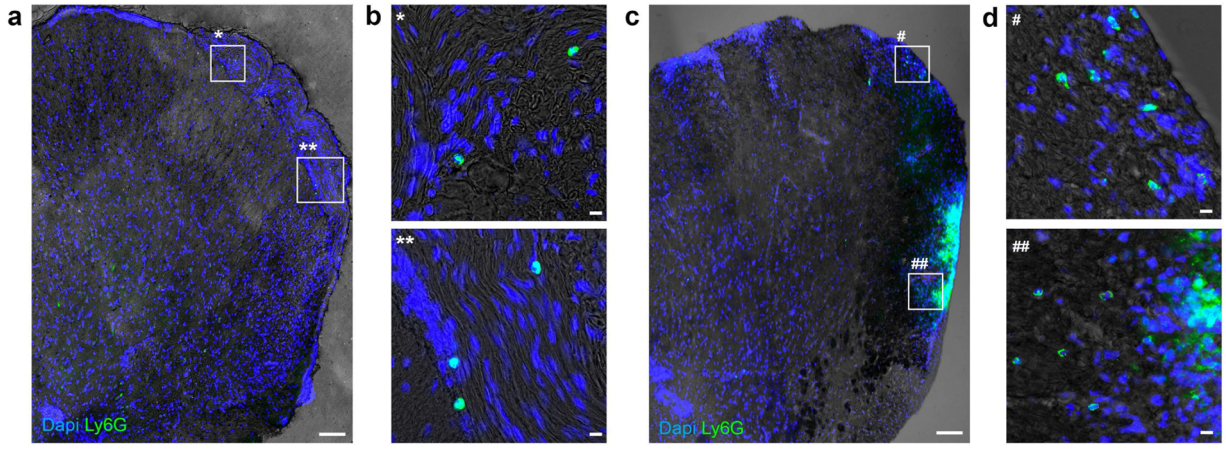

Fig. 1. Neutrophils infiltrate the spinal cord of EAE mice at onset and peak of disease. Representative images of Ly6G$^+$ neutrophils accumulating in the spinal cord at the onset of disease (a, b), and at the disease peak (b, c). Immunofluorescence staining of the spinal cord in EAE mice using antibodies against Ly6G (green) and counterstaining with the nuclear dye DAPI (blue). The outlined area in a and c (magnification 20x) is shown at higher magnification (40x) in the adjacent panels b and d. Scale bar = 200 μm (a, c), 10 μm (b, d). Images were acquired using an Axio Imager Z2 (Zeiss, Germany). *These figures are unpublished data from G. Constantin's laboratory.*

and IL-17, respectively (Woodberry et al., 2018; Lafaille et al., 1997; Herges et al., 2012). In agreement with these results, EAE can be ameliorated by neutrophil depletion, achieved by inhibiting CXCR2-dependent migration, or by blocking IL-17 and GM-CSF (key mediators of neutrophil recruitment) (Woodberry et al., 2018).

Although there is no direct experimental evidence showing that CNS-infiltrating neutrophils can become APCs (Steinbach et al., 2013; Carlson et al., 2008), neutrophils can induce the maturation of resident APCs during active EAE by producing pro-inflammatory cytokines such as TNFα, IFNγ, IL-6, IL-1β and IL-12/23 p40, thus confirming their key role in pathogenesis (Steinbach et al., 2013; Levesque et al., 2016). However, the ability of NETs to activate plasmacytoid DCs (Garcia-Romo et al., 2011; Lande et al., 2011) and myeloid DCs (Sangaletti et al., 2012) appears to play an important role in some autoimmune diseases, such as type I diabetes (Diana et al., 2013), systemic lupus erythematosus (Garcia-Romo et al., 2011; Lande et al., 2011; Barrat et al., 2005; Means et al., 2005) and psoriasis (Lande et al., 2007), arguing against a direct role of neutrophil NETosis in the activation and maturation of resident or migrating APCs in the CNS during EAE. In agreement with this hypothesis, neutrophils isolated from the CNS of EAE mice can induce the maturation of in vitro differentiated DCs by secreting an unidentified soluble factor (Steinbach et al., 2013). Specifically, neutrophil depletion impaired the maturation of both microglia and macrophages into professional APCs, reducing the amplification of early CNS inflammation (Steinbach et al., 2013), a key step in the development of autoimmune disease via the local re-activation of myelin-specific T cells (Kawakami et al., 2004). ICAM-1 was recently identified as a surface marker that distinguishes between intravascular crawling neutrophils and extravascular CNS-infiltrating neutrophils, highlighting how molecular changes lead to functional plasticity after extravasation (Whittaker Hawkins et al., 2017). Once they have extravasated in the CNS, neutrophils acquire macrophage-like immunostimulatory and antigen presentation properties in close physical contact with T and B cells, suggesting a direct role in chronic inflammation. The pro-inflammatory enzyme aspartic peptidase retroviral-like 1 (ASPRV1) is only expressed by neutrophils inside the CNS, correlating with the progression from acute to chronic inflammation during EAE (Whittaker Hawkins et al., 2017). However, it is unclear whether neutrophils modulate (or are modulated by) lymphocytes during disease progression.

Another potential mechanism by which neutrophils contribute to EAE pathology is by facilitating the disruption of the BBB (Steinbach et al., 2013; Aube et al., 2014). Neutrophil perivascular infiltration has been observed in hyper-acute MS lesions, which are associated with areas of BBB leakage (Aube et al., 2014), suggesting that neutrophil infiltration in the CNS of MS patients may represent an early trigger for inflammation leading to BBB damage. Such cytotoxic effects may be contact-dependent or may involve the secretion of cytokines (Levesque et al., 2016), ROS (Wright et al., 2010; Larochelle et al., 2011), proteases such as MMP9 (Rosenberg, 2002; Agrawal et al., 2006), and NETs (Allen et al., 2012), as postulated for other neuroinflammatory conditions (Rosales et al., 2017; Woodberry et al., 2018). Moreover, in MS patients with active lesions, the abundance and activity of MMP9 increased in the serum and cerebrospinal fluid (CSF) associated with BBB leakage (Vafadari et al., 2016). Larger numbers of NETs were found in the blood of some RRMS patients, supporting a role for neutrophils in MS pathogenesis, although there was no correlation with disease severity (Naegele et al., 2012; Tillack et al., 2013). Furthermore, inhibiting the production of ROS (which stimulate the release of NETs) reduced the severity of EAE and modulated the immune response (Choi et al., 2015). Neutrophil infiltration has also been reduced by inhibiting neutrophil elastase and depleting MPO, two enzymes involved in NETosis, attenuating the clinical symptoms of EAE (Herges et al., 2012; Yu et al., 2018). However, in other studies with MPO-deficient mice and mice treated with inhibitors of neutrophil elastase, the course of EAE was not affected in comparison to control mice (Steinbach et al., 2013). Interestingly, when peripheral neutrophils were depleted before the induction of EAE, inflammatory cells accumulated in the perivascular space without infiltrating the parenchyma. This suggests that neutrophils may boost leukocyte recruitment during EAE, facilitating cell migration from the perivascular space to the brain parenchyma probably by increasing the permeability of the glia limitans (Simmons et al., 2014).

Phagocytosis by activated macrophages is the major cause of neuron demyelination during EAE (Rawji and Yong, 2013), but recently-published 3D ultrastructural data indicate that neutrophils can also take up myelin debris via this process (Yamasaki et al., 2014). The molecular and pathophysiological significance of neutrophil phagocytosis in demyelination is still unclear, but CCR2-deficient mice develop EAE because neutrophil extravasation fulfils the same role as macrophage infiltration and the resulting macrophage-dependent phagocytosis and damage in the CNS (Gaupp et al., 2003; Saederup et al., 2010).

As discussed earlier, neutrophils range in function from pro-inflammatory to suppressive, and the presence of the latter in EAE is supported by the fact that nitric oxide (NO) released by neutrophils inhibits the proliferation of encephalitogenic T cells in response to

Table 1
Summary of experimental evidences of neutrophils involvement in MS.

Study design	Main findings concerning neutrophils	Putative neutrophil involvement	References
Autopsy material from acute MS patients	Neutrophil perivascular infiltration is observed in hyper-acute MS lesions associated to BBB leakage.	CNS neutrophils infiltration represents an early phenomenon in the inflammatory reactions in MS patients.	Aube et al., 2014
MS patient and MS pediatric patients	Early-diagnosed MS subjects and early-onset pediatric patients present CSF neutrophilia.	Neutrophils are most relevant in MS pathogenesis during preliminary stages. prior to onset or relapses.	Chabas et al., 2010; Kostic et al., 2014
MS patients	MS patients are characterized by a high neutrophil-lymphocyte ratio (NLR) in the blood, that ratio tends to increase during relapses or with the worsen of disability.	Elevated number of peripheral neutrophils contributes to MS exacerbation and relapses. NLR must be investigated as novel marker of disease activity in RRMS.	Demirci et al., 2016; Bisgaard et al., 2017
RRSM, SPSM and PPSM patients	RRMS patients have elevated number of circulating neutrophils exhibiting a primed state based on reduced apoptosis, higher expression of TLR-2, CD11b/CD18, CD10, CD13, fMLP receptor, IL-8 receptor and CD43, enhanced degranulation of elastases and proteases, ROS production and higher levels of NETs in serum.	Elevated number of primed peripheral neutrophils increases BBB permeability, CNS inflammation and tissue injury contributing to MS exacerbation and relapses.	Aoki et al., 1984; Guarnieri et al., 1985; Ziaber et al., 1998; Naegele et al., 2012; Tillack et al., 2013
RRMS patients	Plasma levels of CXCL5 are elevated during acute lesion formation. Systemic expression of CXCL1, CXCL5, and neutrophil elastase correlate with measures of MS lesion burden and clinical disability.	Neutrophil-related molecules must be investigated as novel biomarkers in MS.	Rumble et al., 2015
EAE	Neutrophils represent the most abundant CNS infiltrating leukocytes in the in the effector phase of EAE development.	CNS infiltrating neutrophils are one of the major sources of inflammatory cells in the early EAE development having a role in EAE initiation.	Wu et al., 2010; Rumble et al., 2015
EAE	CNS infiltrating neutrophils reduction (depleting circulating neutrophils or inhibiting neutrophils mobilization or interfering with neutrophil CNS recruitment) inhibits or attenuates EAE.	CNS infiltrating neutrophils have a role in preparing local inflammation.	McColl et al., 1998; Carlson et al., 2008; Steinbach et al. 2013; Rumble et al., 2015
EAE	CNS infiltrating neutrophils correlate with axonal damage in acute subpial and perivascular lesions.	CNS infiltrating neutrophils contribute to axonal loss in the earlier stages of EAE.	Soulika et al., 2009
EAE	Neutrophils promote blood-CSF barrier breakdown in the EAE-initiating events.	CNS infiltrating neutrophils allow initial cells migration into the meninges promoting vascular permeability.	Christy et al., 2013; Aube et al., 2014
EAE	Neutrophils differently migrate in brain and spinal cord: Il-17 promotes ELR-motif CXC chemokines expression on neutrophils and their recruitment in the brain while IFN-γ promotes their ELR-motif CXC chemokines mediated migration in the spinal cord.	Brain and spinal cord exhibit distinct sensitivities to cellular mediators of tissue damage: brain but not in spinal cord, is neutrophil infiltration dependent.	Simmons et al., 2014
EAE	ICAM-1 + neutrophils are preferentially recruited in the CNS during EAE. Neutrophils once extravasated in the CNS acquire macrophage-like immunostimulatory and antigen presentation properties in close physical contact with T and B lymphocytes Proinflammatory enzyme ASPRV1 is only expressed by neutrophils inside the CNS and correlates to the progression from acute to chronic inflammation.	ICAM1 + macrophage–like neutrophils have a direct role in antigen presentation and in perpetuation of chronic inflammation via ASPRV1 activity.	Whittaker et al. 2017
EAE	CNS-infiltrating neutrophils mature bone marrow-derived DCs by proinflammatory molecules secretion *in vitro*. Depletion of neutrophils impaired maturation of microglia and macrophages into professional APCs during EAE.	CNS infiltrating neutrophils promote resident APCs maturation and the development of EAE through the local re-activation of myelin-specific T cells.	Steinbach et al., 2013
EAE	CCR2 deficient mice are susceptible to EAE induction because inflammation and demyelination are supported by neutrophils that infiltrate CNS in a high number to compensate inhibited monocyte recruitment.	CNS infiltrating neutrophils contribute to demyelination.	Gaupp et al., 2003
EAE	IL-1R1 and IL-1β deficient mice are resistant to EAE; adoptive transfer of WT IL-1β producing neutrophils restores IL-1R1 deficient mice to sensitivity in EAE induction.	IL-1β producing activated neutrophils stimulate CNS vascular endothelium to produce cytokines and chemokines promoting a positive feedback in the recruitment of neutrophils and monocytes in the CNS.	Levesque et al., 2016

myelin antigen (Zehntner et al., 2005). Moreover, the adoptive transfer of suppressive neutrophils (G-MDSCs) from the spleen inhibited T cell activation in the lymph nodes via Programmed death-ligand 1 (PD-L1)-dependent signaling (Ioannou et al., 2012).

Neutrophils are typically absent from brain samples representing the most common forms of MS, and the outmoded idea that neutrophils do not significantly influence the course of this disease are therefore likely to reflect a sampling bias. The marked increase in the abundance of neutrophils during the early stages of EAE suggests that these cells may be more relevant before the clinical manifestation of MS, whereas tissue sections from MS patients tend to be analyzed long after the disease is established (Rumble et al., 2015). Accordingly, CSF neutrophilia has been reported in studies involving recently-diagnosed MS subjects and pediatric patients with early-onset MS, respectively (Chabas et al., 2010; Kostic et al., 2014). The CSF of children with early-onset MS contained a much greater number of neutrophils compared to pediatric patients with later-onset MS, suggesting that neutrophils increase the severity of the disease (Chabas et al., 2010). Several indirect observations also link neutrophils to other demyelinating conditions (Casserly et al., 2017). Infiltrating neutrophils have been observed in Marburg's MS patients with diffuse demyelination and active vasculitis (Elenein et al., 2011), and in the spinal cords of patients with optico-spinal MS and active lesions of Devic's neuromyelitis optica (Aube et al., 2014; Lucchinetti et al., 2002; Ishizu et al., 2005).

Although CNS tissue samples from most MS patients feature subacute or chronic lesions, blood is characterized by a higher neutrophil–lymphocyte ratio (NLR) than healthy blood, and the ratio tends to increase during relapses or with worsening symptoms (Demirci et al., 2016, Bisgaard et al., 2017). Larger numbers of circulating neutrophils with a primed phenotype (such as greater resistance to apoptosis and

enhanced effector mechanisms) were observed in RRMS patients compared to healthy controls (Rumble et al., 2015; Naegele et al., 2012). Circulating neutrophils in MS patients also produce more ROS (Naegele et al., 2012), secrete greater amounts of the protease medullasin and neutrophil elastase (Guarnieri, et al., 1985, Aoki et al., 1984), and express higher levels of CD11b/CD18, CD10, CD13 (Ziaber et al., 1998), TLR-2 and N-formylmethionyl-leucyl-phenylalanine receptor (Naegele et al., 2012; Hertwig et al., 2016) as the disease becomes more severe. Neutrophils may therefore trigger disease progression not only after invading the CNS but also from the periphery. Neutrophil activation within the bone marrow during MS could promote the mobilization of monocytes and neutrophils themselves in the bloodstream, thus increasing the number of myeloid cells ready to migrate to the CNS (Singh et al., 2012). Accordingly, serum from MS patients contains significantly higher levels of the neutrophil chemoattractant CXCL8/IL-8, supporting a role for neutrophil recruitment in the disease (Campbell et al., 2010). During relapses, the plasma of MS patients contains higher levels of CXCL1, CXCL5, neutrophil elastase and CD11b/CD18 compared to patients in remission, healthy controls and patients with non-inflammatory neurological diseases (Aoki et al., 1984; Ziaber et al., 1998). The pathogenicity of human neutrophils in autoimmune demyelinating diseases is also suggested by the exacerbation of symptoms in patients with optico-spinal MS and neuromyelitis optica when treated with recombinant G-CSF, which is known to mobilize neutrophils from the bone marrow (Openshaw et al., 2000; Jacob et al., 2012). As described above for EAE, circulating neutrophils with a suppressive phenotype have also been detected during MS. Granulocytic myeloid derived suppressor cells (G-MDSCs) are more abundant in RRMS patient compared to healthy controls, and increased during relapses (Ioannou et al., 2012). Although their immunoregulatory mechanisms are not yet understood, G-MDSCs may contribute to MS clinical recovery.

In conclusion, the data summarized above suggest that the interactions between neutrophils and cells of the adaptive immune system play a key role in the pathogenesis of EAE (Aube et al., 2014) and MS (Rumble et al., 2015). The data from MS and EAE models demonstrate the potential harmful nature of neutrophils (Table 1), highlighting the need to understand their role in more detail and suggesting that interfering with neutrophil-dependent tissue damage may offer a promising therapeutic approach for MS patients.

4. Neutrophils in AD

AD is the most common neurodegenerative cause of dementia in the elderly, accounting for 72% of cases (Querfurth and LaFerla, 2010; Calderon-Garciduenas and Duyckaerts, 2017). Sporadic AD usually occurs in elderly people, whereas familial AD tends to begin before 60 years of age. Both the familial and sporadic forms of AD share a common phenotype converging towards similar neuropsychiatric symptoms, emotional disturbance, and the progressive impairment of normal activity, resulting in dependence, disability and mortality (Cummings, 2004). With the progression of the disease, neuronal loss occurs in the most affected areas, and macroscopic atrophy becomes evident in the entorhinal area and hippocampus, amygdala, and associative regions of the neocortex. AD pathogenesis is characterized by numerous features such as the accumulation of aggregated β-amyloid peptides (Aβ), the intracellular aggregation of hyperphosphorylated tau to form neurofibrillary tangles, oxidative stress, inflammation, and changes in innate immune signaling. There is currently neither a cure nor adequate clinical treatment for AD and it remains unclear how AD originates and propagates through the brain.

AD was traditionally viewed as a primary neurodegenerative disorder that specifically affects the CNS, but there is now evidence that brain dysfunctional is closely associated with peripheral inflammatory signals (Morris et al., 2014; Wang et al., 2017a). AD-related inflammation develops in the blood and the brain, separate compartments that make contact via the BBB. Notably, the BBB clears potentially neurotoxic molecules from the cerebral parenchyma to the blood, and regulates the passage of essential nutrients and leukocytes into the CNS (Zenaro et al., 2017; Abbott et al., 2006; Zlokovic, 2008, 2011). In patients with early cognitive dysfunction, the BBB breaks down in the hippocampus, which is critical for learning and memory (Nation et al., 2019). Thus, the BBB impairment hampers the conventional clearance of Aβ that accumulate in the brain (Zlokovic, 2011) and in the vessel walls, inducing the upregulation of adhesion molecule expression on brain endothelial cells and the release of inflammatory mediators such as complement system peptides, chemokines and cytokines, likely promoting the leukocyte recruitment. Tau protein may also play a part in the BBB breakdown, and its dysfunction correlates with perivascular tau accumulation in main blood vessels in hippocampus in vivo (Forman et al., 2005; Kovac et al., 2009; Blair et al., 2015). Additionally, misfolded protein tau modifies the endothelial properties of the BBB, facilitating blood-to-brain cell transmigration (Majerova et al., 2019; Zilka et al., 2009). These findings suggest that neuro-inflammation triggered by tau and Aβ promotes the expression of leukocyte-binding receptors on the endothelial cell surface and damages the cells of the neurovascular unit, disrupting the integrity of the BBB and the permeability of blood vessels that facilitate the infiltration leukocytes into the brain, contributing to disease progression and neurodegeneration (Zenaro et al., 2015; Banks, 2015; Di Marco et al., 2015; Sweeney et al., 2018).

Activated resident sentinel cells in the CNS, such as microglia and astrocytes, may release tissue danger signals, cytokines and chemokines that recruit leukocytes from the peripheral circulation to inflammation areas in the CNS (Zenaro et al., 2017; Abbott et al., 2006; Zlokovic, 2008, 2011; Heneka et al., 2015). A combination of experimental and clinical evidence, including our own research, suggests that T cells and neutrophils migrate into the AD brain (Zenaro et al., 2015; Togo et al., 2002; Town et al., 2005; Ferretti et al., 2016). Although neutrophils may play a key role in AD, few studies have directly investigated this phenomenon (Zenaro et al., 2015; Pietronigro et al., 2017; Cruz Hernandez et al., 2019; Baik et al., 2014). Circulating neutrophils from AD subjects express higher levels of CD11b in comparison to healthy subjects, indicating that the adhesion of neutrophil and their brain infiltration may correlate with the severity of the disorder (Scali et al., 2002). Recent clinical data revealing greater numbers of neutrophils or a higher NLR associated with AD suggest that changes in the neutrophil population could be used as markers of AD-related peripheral inflammation (Kuyumcu et al., 2012; Shad et al., 2013; Rembach et al., 2014). Peripheral blood neutrophils in AD patients also produce greater quantities of ROS than controls, suggesting that neutrophils may exist in a more activated state during AD (Vitte et al., 2004). In agreement with these findings, a recent pilot study aiming to characterize the phenotype of human peripheral neutrophils at different stages of AD revealed a greater neutrophil hyper-activation state in fast-decliner compared to slow-decliner patients (Dong et al., 2018). In these patients, the ratio between the harmful aged neutrophils ($CXCR4^{hi}$ $CD62L^{lo}$) and the $CD16^{bright}$ $CD62L^{dim}$ immunosuppressive neutrophil subsets rose during the later stage of the disease, indicating changes that may play an instrumental role in establishing systemic chronic inflammation (Dong et al., 2018). These data strongly suggest that the hyper-reactive phenotype of circulating neutrophils correlates with the rate of cognitive decline, potentially offering a prognostic blood biomarker in AD patients (Dong et al., 2018). Other studies reported the higher expression of αM CD11b integrin, HLA-DR and COX1 in the neutrophils of AD patients (Scali et al., 2002; Fiala et al., 2005), also

supporting the hypothesis of neutrophil hyper-activation. These data have been confirmed in patients with a diagnosis of mild AD, where the neutrophils were shown to upregulate CD177 (Le Page et al., 2017), a Ly6/uPAR family member and well-known marker of neutrophil activation (Xie et al., 2015; Stroncek et al., 2004; Hu et al., 2009). Interestingly, CD177 is known to associate with β2 integrins and actively bind CD31 (PECAM-1) expressed by endothelial cells, thus probably stimulating neutrophil transmigration (Stroncek, 2007; Sachs et al., 2007; Bai et al., 2017). These results also suggest that the interaction between CD177 and CD31 could serve to recruit neutrophils into the brain parenchyma of AD patients, in a manner similar to that reported for ICAM-1 and LFA-1 (Zenaro et al., 2015).

Amyloid precursor protein (APP) was recently shown to be expressed at higher levels in the granulocytes of AD subjects compared to healthy subjects, whilst there was no statistically significant variation in peripheral blood mononuclear cells, indicating that the high expression of APP in granulocytes could be utilized for the early detection of disease (Wang et al., 2016). Others recently published that neutrophil functions and granulocyte density from AD subjects differ compared to healthy controls, thus proposing the characterization of blood neutrophils as the opportunity to discover new AD biomarkers (Jaremo et al., 2013; Le Page et al., 2015). Notably, this activated phenotype of neutrophils in the peripheral circulation may promote their interactions in the vasculature and brain parenchyma, as shown in multiple mouse models of AD (Zenaro et al., 2015; Cruz Hernandez et al., 2019; Baik et al., 2014). We found that integrin LFA-1 controls the intraparenchymal motility and intravascular adhesion of neutrophils in the cerebral microcirculation of 3xTg-AD transgenic mice, a prominent animal model of AD (Zenaro et al., 2015). The blockade of the integrin LFA-1 in 3xTg-AD mice during the early disease phase prevented neutrophil adhesion and brain infiltration, and reduced the neuropathological hallmarks of AD, hence re-establishing cognition. Our data also revealed that early treatment with anti-Gr1, anti-Ly6G or anti-LFA-1 antibodies, which deplete neutrophils or inhibit their adhesion, led to a persistent improvement in cognitive performance (Zenaro et al., 2015). Of note, the temporary blockade of the integrin LFA-1 during the first disease phase improve cognitive function also in older mice, thus indicating that the early therapeutic intervention to inhibit neutrophil recruitment may extend beneficial effects in subjects with AD. In addition, the genetic depletion of the integrin LFA-1 in 3xTg-AD mice showed amelioration in behavioral test performance and in the severity of microgliosis in comparison to wild-type control mice (Zenaro et al., 2015). Neutrophil may damage brain tissue through several independent mechanisms, such as premature activation during migration, extracellular release of toxic products or failure to terminate inflammatory responses. However, the functions of neutrophils in AD remain elusive, and deserve a deeper investigation to elucidate new mechanisms by which neutrophils might contribute to AD. Interestingly, massive neutrophil accumulation in the brains of 3xTg-AD mice coincides with the onset of memory loss in cognitive tests at 6 months of age (Zenaro et al., 2015), but neutrophils also infiltrate the brain at 8–10 months of age, suggesting that neutrophils play a role in the induction of cognitive decline as well as in disease progression. In agreement with our data, the inhibition of neutrophil adhesion using anti-Ly6G antibodies in APP/PS1 mice with established cognitive impairment (at 15–16 and 21–22 months of age) rapidly improved cerebral blood flow and performance in short-term memory tasks, suggesting neutrophils also play a role in disease progression (Cruz Hernandez et al., 2019).

$Gr1^+$ cells infiltrate the brain parenchyma and migrate toward Aβ plaques in the 5xFAD transgenic mouse model of aggressive amyloidosis (Zenaro et al., 2015; Baik et al., 2014). Our two-photon laser-scanning microscopy experiments in this model revealed neutrophil swarming in blood vessels adjacent to Aβ plaques, and neutrophil extravasation inside the cerebral parenchyma preferentially in Aβ-rich areas, suggesting that Aβ might be involved in neutrophil recruitment and movement inside the brain parenchyma (Zenaro et al., 2015). Neutrophils typically access sites of infection or tissue damage via the circulation by following multiple chemoattractant cues and responding to local inflammatory mediators. The Aβ accumulating in the brain may represent an 'end-target' chemoattractant binding to the FPR1 receptor prevailing over 'intermediate' chemokines in the recruitment of neutrophils, likely providing the directional bias observed for many neutrophils infiltrated in the brains of AD mouse models (Zenaro et al., 2015; Phillipson and Kubes, 2011; Tiffany et al., 2001). The association of neutrophils with Aβ deposits was first reported 30 years ago, when Aβ deposits in the brain parenchyma and cerebral blood vessels of AD patients were shown to be associated with cells expressing the neutrophil-specific protease cathepsin G, confirming neutrophil accumulation in the CNS of AD patients (Savage et al., 1994). Aβ in AD patients was also proposed to trigger the expression of CAP37, an inflammatory mediator constitutively expressed in neutrophils, but the link with neutrophils was not discussed (Pereira et al., 1996, Grammas, 2000; Brock et al., 2015). CAP37 was specifically detected in brain regions that experience the greatest atrophy during AD (temporal, parietal and frontal lobes) (Serrano-Pozo et al., 2011), but not in age-matched controls or patients with other neuropathological conditions such as Pick's disease, Binswanger's disease, supranuclear palsy or PD, thus underlining the strict association of neutrophils with AD pathogenesis (Pereira et al., 1996; Grammas, 2000; Brock et al., 2015). CAP37 was also detected in the hippocampal cerebral microvasculature of AD patients (Pereira et al., 1996), and it is well known that CAP37 released

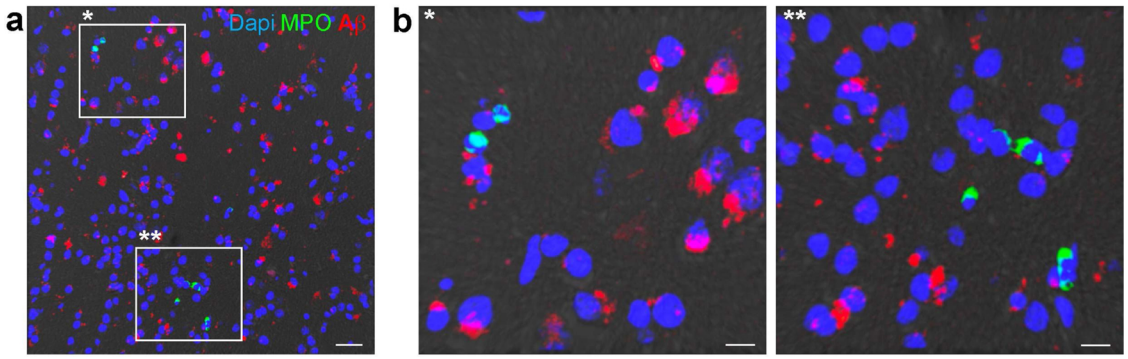

Fig. 2. Infiltrating MPO^+ cells in the human AD brain. Immunofluorescence staining of the hippocampus of a human AD patient, using antibodies against Aβ (red) and MPO (green), counterstained with the nuclear dye DAPI (blue). The outlined area in (a) (magnification 20x) is shown at higher magnification (40x) in the adjacent panel (b). Scale bar = 30 μm (a), 15 μm (b). Images were acquired using an SP5 tandem confocal microscope (Leica, Germany). *These figures are unpublished data from G. Constantin's laboratory.*

from the azurophil granules of activated neutrophils may attach to vascular endothelial cells to prepare the neutrophil for its extravasation into infected or injured tissue (Morgan et al., 1991). While attached to the proteoglycans on vascular endothelial cells, CAP37 recruits and activates monocytes, and increases the expression of adhesion molecules on endothelial cells. This promotes the adherence and extravasation of additional neutrophils and monocytes, thus perpetuating their recruitment into the AD brain.

We recently identified MPO^+ cells infiltrating the brain parenchyma of AD patients, followed by their localization typically within 50 μm of Aβ plaques (Zenaro et al., 2015) (Fig. 2). Like CAP37, MPO is a major protein in the azurophil granules of neutrophils. The distribution of MPO^+ cells in brain tissue was non-random, suggesting that Aβ may play a chemoattractant role by establishing a favorable microenvironment for the brain infiltration of neutrophils, thus favoring their pro-inflammatory function (Zenaro et al., 2015). Neutrophils actively release MPO by degranulation, but the enzyme is also released during cell death (van der Veen et al., 2009). MPO activity produces hypochlorous acid and other chlorinated species, which are effective microbicidal agents but also cytotoxic, thus contributing to neuropathology and disease progression (Ray and Katyal, 2016). Interestingly, the recent comparison of various brain regions in neurologically healthy individuals and AD patients revealed MPO^+ cells in brain regions affected by neuronal death, thus supporting a role for this enzyme in neurodegeneration (Gellhaar et al., 2017).

We have previously used various stains to confirm the presence of neutrophils in the brains of AD mice and human AD patients (and not in age-matched controls), including (i) hematoxylin and eosin staining to highlight the presence of the characteristic polysegmented nuclei in cells that have migrated perivascularly or within the parenchyma (Zenaro et al., 2015), (ii) napthol AS-D chloroacetate esterase staining to confirm the presence of cells of the granulocytic lineage (Uchida et al., 2009; Khandoga et al., 2009), and (iii) staining for the neutrophil-specific marker CD66b (Zenaro et al., 2015). The brains of human AD patients also show evidence of intraparenchymal migrated neutrophils releasing MPO, neutrophil elastase and citrullinated histone H3, which are required for NETosis (Zenaro et al., 2015). Our findings were also confirmed by a recent pilot study showing that the harmful hyper-reactive neutrophil phenotype in the peripheral circulation of AD patients is associated with the increased production of ROS and intravascular NETs (Dong et al., 2018). These data suggest that NETs may represent a neutrophil-dependent disease mechanism that potentially causes bystander damage in patients with AD.

The highly reactive phenotype of extravasated neutrophils can cause chronic collateral tissue damage even if only a few cells migrate within tissues during a low-grade chronic sterile inflammation. Notably, intravascular adhesion *per se* in the absence of transmigration through the BBB is sufficient to induce endothelial injury (Fabene et al., 2008; DiStasi and Ley, 2009; Zarbock and Ley, 2008). Our data support this assumption, in fact the blockade of the integrin LFA-1, known to regulate the intravascular adhesion of neutrophils, restore cognitive impairment and neuropathological lesions in murine models of AD (Zenaro et al., 2015). In agreement, a recent report in APP/PS1 mice showed that an anti- Ly6G antibody removed capillary stalls resulting from the intravascular accumulation of neutrophils, improving spatial and working short-term memory within 3 h from the onset of treatment (Cruz Hernandez et al., 2019).

Overall, AD is now recognized as a complex systemic disorder characterized by chronic inflammation involving both the innate and adaptive immune systems, highlighting the need to investigate the role of circulating leukocytes in the management of the disease. The role of neutrophil functional plasticity in AD (Table 2) requires future longitudinal studies to discover new therapeutic approaches for the treatment of early symptoms and to monitor disease progression.

Table 2
Summary of experimental evidences of neutrophils involvement in AD.

Study design	Main findings concerning neutrophils	Putative neutrophils involvement	References
Autopsy material from AD patients	CNS infiltrating neutrophils releasing MPO, NE and citrullinated histone H3, essential components involved in NETosis.	CNS neutrophils infiltration represents a phenomenon in the inflammatory reactions in AD patients.	Zenaro et al., 2015
AD patients	CNS infiltrating neutrophils express inflammatory mediator CAP37.	Infiltrating neutrophils promote perpetuating recruitment of additional neutrophils and monocytes, into the brain by CAP37 contributing to neuronal injury in AD.	Pereira et al., 1996; Brock et al., 2015
AD patients	AD patients are characterized by a high neutrophil-lymphocyte ratio (NLR) in the blood, that ratio tends to increase during relapses or with the worsen of disability.	Elevated number of peripheral neutrophils contributes to AD neurodegeneration and pathogenesis. NLR must be investigated as markers of AD-related peripheral inflammation.	Kuyumcu et al., 2012
AD patients	AD patients have high number of circulating neutrophils exhibiting a primed state based on over expression of CD11b, CD177, HLA-DR, COX-2 and NETs and elevated levels of ROS production. Activation markers in neutrophils positively correlate with disease severity and progression rate of mental decline.	Elevated number of activated peripheral neutrophils increases BBB permeability, CNS inflammation contributing to neurodegeneration and clinical progression of AD. Neutrophils activation markers must be investigated as biomarkers of AD-related peripheral inflammation.	Scali et al., 2002; Vitte et al., 2004; Fiala et al., 2005; Shad et al., 2013; Dong et al., 2018; Le Page et al., 2017
AD patients	AD patients have high expression of APP in circulating neutrophils.	APP expression level in peripheral blood granulocyte is a potential biomarker for early diagnosis of AD.	Wang et al., 2016
AD patients	In the blood of AD patients harmful aged neutrophils (CXCR4high/CD62Llow) and immunosuppressive neutrophil (CD16bright/CD62Ldim) ratio increases in the later stage of the disease.	Aged related changes in neutrophils phenotype and activity, plays a role in establishing systemic chronic inflammation during AD.	Dong et al., 2018
Mouse models	Neutrophils infiltrate the CNS where they produce NETs and IL-17.	CNS infiltrating neutrophils are one of the major sources of inflammatory cells in the early AD-like development.	Zenaro et al., 2015
Mouse models	Neutrophils are attracted from the blood vessels into CNS by chronic Aβ deposition and accumulated preferentially in Aβ-rich areas.	Neutrophil responses to senile plaques influence the progress of AD.	Baik, et al., 2014; Zenaro et al., 2015
Mouse models	Brain infiltrating neutrophils reduction (depleting circulating neutrophils or interfering neutrophil CNS recruitment by LFA-1 inhibition) reduce AD-like neuropathology and improve memory.	CNS infiltrating neutrophils have a role in preparing local inflammation contributing to AD-like pathogenesis and cognitive impairment.	Zenaro et al., 2015
Mouse models	Prevent neutrophil adhesion on cortical capillaries (depleting circulating neutrophils) restore cerebral blood flow and improve memory.	Neutrophils indirectly promote cognitive impairment of AD-like adhering in brain capillary segments occluding or reducing cerebral blood flow.	Cruz Hernandez et al., 2019

5. Neutrophils in other neurodegenerative diseases

PD is a long-term disorder of the CNS classically associated with Lewy bodies and the loss of dopaminergic neurons in the substantia nigra of the midbrain. Like AD and MS, systemic chronic inflammation may also play an important role in pathogenesis and progressive neurodegeneration (Ferrari and Tarelli, 2011). PD is not restricted to the dopaminergic system, indeed it involves extensive regions of the nervous system, and is characterized by protein aggregates other than Lewy bodies (Kalia and Lang, 2015). Disease symptomatology is heterogeneous, with clinically significant non-motor features. The diagnosis of PD is challenging, and new biomarkers are therefore needed. The NLR is a widely used marker to detect subclinical inflammation, and the NLR is higher than normal in PD patients and correlates with serum levels of C-reactive protein, another marker of peripheral inflammation (Akil et al., 2015). However, in one of the few studies evaluating different types of PD (idiopathic, akinetic-rigid and tremor-dominant), there was no statistically significant difference in the NLR (Atac Ucar et al., 2017). Accordingly, a recent report involving early-stage PD patients found no changes in immune responses of circulating innate leukocytes, with neutrophil and lymphocyte adherence, chemotaxis, phagocytic capacity, and NK cytotoxic activity similar to age-matched healthy subjects (Vida et al., 2019). However, MPO was shown to be upregulated in damaged areas (ventral midbrain) in human PD patients and mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a common animal model of induced PD (Choi et al., 2005). The same authors also demonstrated that ventral midbrain dopaminergic neurons in *MPO*$^{-/-}$ knockout mice are more resistant to MPTP-induced cytotoxicity than in wild-type controls, suggesting that MPO inhibitors may provide a protective benefit in PD. In agreement, MPO^{+} cells were shown to accumulate in brain regions affected by neurodegeneration in PD, supporting a role for MPO in neuronal toxicity (Gellhaar et al., 2017). However, more evidence is needed to establish the role of neutrophils in the development and progression of PD in order to identify the mechanism of pathogenesis as well as potential therapeutic targets.

ALS is another motor neuron disease with a strong neuroinflammatory component, but the inflammatory mechanisms influencing peripheral motor axon degeneration remain largely unknown (Chiot et al., 2019). ALS is perhaps the most devastating neurodegenerative condition because of its insidious onset, rapid progression, and inevitable endpoint. Only 5–10% of ALS cases are familial, and the etiology of the majority sporadic cases remains to be defined (Zufiria et al., 2016). A prospective cohort study involving ALS patients revealed systemic low-grade inflammation, detected as significant increases in the erythrocyte sedimentation rate, fibrinogen levels, C-reactive protein concentrations, leukocyte counts and NLR, correlating with the degree of disability (Keizman et al., 2009). Changes in CD4^{+} T cell and neutrophil counts also correlate with rapid disease progression, suggesting that these leukocytes may contribute to the pathologic features of ALS (Murdock et al., 2017). These results were also supported by blood profiling, which identified low-grade neutrophilia and hypoxia as new biomarkers for the disease (Swindell et al., 2019). Interestingly, mast cells and neutrophils accumulate around motor axons in the extensor digitorum longus muscle, sciatic nerve, and ventral roots of symptomatic SOD1G93A rats (an animal model of ALS), indicating that leukocyte infiltration extends along the entire peripheral motor pathway (Trias et al., 2018).

More work is required to define the profile of immune cell subpopulations during the course of PD and ALS to identify suitable biomarkers and therapeutic targets.

6. Conclusion

Neutrophils were once regarded as simple phagocytic cells of the innate immune system, but are now understood to be an important component of the effector and regulatory circuits that control the magnitude and quality of an immune response. A large body of evidence indicates that neutrophils contribute to neural damage in neurodegenerative disorders, particularly MS and AD. However, the mechanisms of neutrophil transmigration, accumulation and tissue damage inside the CNS parenchyma during neurodegeneration are largely unknown. The phenotype and functional characteristics of neutrophils in neurodegenerative disorders remain to be established, partly because it has been difficult to identify neutrophils selectively until the last 10 years. The growing capacity for single-cell analysis in immune cell populations and recent platforms for multicolor flow cytometry and next-generation sequencing will therefore provide important insights into the heterogeneity of neutrophils in neurodegenerative disorders.

The heterogeneity and plasticity of neutrophils and their access to the inflamed CNS represent opportunities for therapeutic intervention, which may apply to MS and AD but also to other neurodegenerative diseases. This diversity of neutrophil phenotypes may allow the selective targeting of pathogenic neutrophils without perturbing those engaged in antimicrobial defense. Further understanding of neutrophil biology will provide new opportunities for the selective manipulation of this lineage, as recently explored in the treatment of cancer. Indeed, several studies involving experimental tumor models have contributed to our understanding of neutrophil functions in cancer progression, which may lead to the development of therapies that block the migration of suppressive neutrophils to the tumor (Movassagh et al., 2017; Xie et al., 2017), disrupt their reprograming (Sahakian et al., 2017; Wang et al., 2017a,b), or exploit their spontaneous migration to the tumor for the delivery of anti-cancer drugs (Kang et al., 2017; Chu et al., 2017).

Neutrophil phenotyping and the investigation of neutrophil dynamics following their recruitment to the CNS during the development and progression of neurodegenerative diseases will therefore offer the opportunity to determine the mechanisms of pathogenesis and to identify novel therapeutic targets.

Declaration of Competing Interest

All authors declare to have no conflicts of interest.

Acknowledgement

We would like to thank Jessica Arioli and Dr. Enrica Caterina Pietronigro for tissue sectioning, staining and acquisition of the images included in the present manuscript.

This work was supported by the European Research Council grant 695714 IMMUNOALZHEIMER (to GC).

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