Autoimmunity Reviews 16 (2017) 294–307

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

Review

Neutrophil perversion in demyelinating autoimmune diseases: Mechanisms to medicine

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ARTICLE INFO

Article history:
Received 18 November 2016
Accepted 29 November 2016
Available online 2 February 2017

Keywords:
Demyelination
Autoimmunity
Acute disseminated encephalomyelitis
Granulocytes
Polymorphonuclear leukocytes
Disease-modifying therapies

ABSTRACT

Neutrophils are essential to a healthy life, yet pose a threat if improperly controlled. Neutrophil perversion is well documented in a variety of inflammatory disorders (e.g. arthritis, lupus, psoriasis), but is only beginning to be demystified in autoimmune demyelination, the most common cause of neurological disability in young adults. Using the animal model experimental autoimmune encephalomyelitis (EAE), several molecules that help neutrophils invade the central nervous system (CNS) have been identified. Mechanisms by which neutrophils may contribute to demyelination have also been proposed (e.g. secretion of endothelial/leukocytic modulators, antigen presentation to T cells, myelin degradation and phagocytosis). In human, neutrophils are seen in the CNS of people with neuromyelitis optica spectrum disorder and other severe variants of autoimmune demyelinating diseases. At the time of autopsy for multiple sclerosis (MS) — often many years after its onset — neutrophils appear to have escaped the scene of the crime. However, new clues implicate neutrophils in MS relapses and progression. This warrants further investigating 1) the differential importance of neutrophils among demyelinating diseases, 2) the largely unknown effects of current MS therapies on neutrophils, and 3) the potential of neutrophil proteins as clinical biomarkers or therapeutic targets.

Contents

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http://dx.doi.org/10.1016/j.autrev.2017.01.013
1568-9972/

1. Introduction

Demyelinating autoimmune diseases are afflictions of the nervous system involving destruction of the myelin sheath that surrounds nerve fibers. This occurs through cellular and/or humoral immune responses directed against glial antigens (e.g. peptides from oligodendrocytes, Schwann cells, astrocytes). By far, the most common of these diseases is multiple sclerosis (MS) (Table 1), but there are others such as neuromyelitis optica spectrum disorder (NMOSD, previously called Devic's disease or opticospinal MS), acute disseminated encephalomyelitis (ADEM) and their variants. Although these diseases share clinical, radiological and histopathological features that can complicate the initial diagnosis, they involve different immunological processes and most often produce distinctive spatiotemporal patterns of inflammatory lesions (Table 1). While decades of research have led to several variably effective treatments for these conditions [1,2], scientists are still struggling to identify root causes, biomarkers to distinguish disease forms and predict response to treatment, and molecular mechanisms that could be targeted for better clinical outcomes.

Much of our knowledge on autoimmune demyelination comes from an animal model studied for over 80 years, experimental autoimmune encephalomyelitis (EAE) [3,4]. This disease model can be induced in mammals in three different ways: by immunization with myelin antigens and adjuvants (active EAE), by adoptive transfer of myelin-reactive T cells (passive EAE), or by transgenic expression of myelin-specific T cell receptors (TCRs) (e.g. 2D2 and 1C6 mice) [5,6]. The mechanisms and symptoms of EAE vary with the method of induction and animal species used [5]. EAE differs in many respects from MS and other human demyelinating diseases. Nevertheless, EAE is indispensable not only for studying evolutionarily conserved immunological processes that are difficult to dissect in human, but also for pre-clinical testing of anti-inflammatory medications [7].

The immune cascade responsible for EAE is still the subject of intense research. As reviewed elsewhere [6,8–10], the prevailing view is that EAE is triggered when a self-reactive naïve $CD4^+$ T helper (T_h) cell escapes tolerance mechanisms and recognizes a myelin peptide through its TCR. This occurs in lymphoid tissue, with the aid of a dendritic cell (DC), on which the peptide is loaded onto MHC class II molecules (MHCII). Depending on the context, the T_h cell can be induced to proliferate and differentiate into two subsets of effector cells: IFNγ-secreting T_h1 cells and IL-17-secreting T_h17 cells. Both cell types acquire the mandate to search for their cognate antigen throughout the body. Upon finding it on antigen-presenting cells (APCs) stationed in strategic locations, such as the meninges and perivascular areas of the central nervous system (CNS), APCs release proinflammatory cytokines (e.g. IL-12, IL-23). In response, T_h cells proliferate and secrete growth factors (e.g. GM-CSF) and chemokines (e.g. CCR2 ligands) that mobilize classical monocytes ($Ly6C^{hi}$) from the bone marrow and recruit them to inflammatory foci. These monocytes give rise to macrophages that initiate demyelination through phagocytosis [11]. They also give rise to $CD11c^+$ DCs that amplify and perpetuate the immune response [12–17]. As if that was not enough, B cells and autoantibodies can get invited to the party [18,19].

Discoveries made over the last eight years have added a new piece to the EAE puzzle in revealing the involvement of another type of immune cell: the neutrophil. Belonging to the myeloid — granulocytic lineage, neutrophils are characterized by a multilobed nucleus and four types of cytoplasmic granules containing proteases and antimicrobial agents [20]. They are among the most abundant leukocytes in blood and are also the first to be deployed to sites of inflammation, where they die in combat after a brief lifespan (typically <1 day). In mice, but not in humans, neutrophils can be unequivocally marked using a monoclonal antibody (clone 1A8) against the cell surface protein Ly6G [21]. This antibody was first used in 2008 to conclusively demonstrate the presence of neutrophils in the CNS of EAE mice [22]. Years earlier, this presence had been proposed on the basis of less specific staining with chemical dyes [23–29] or an anti-Ly6G antibody (Gr1 or RB6-8C5) [30–34] that also recognizes Ly6C on both neutrophils and some monocytes [21,35]. Since 2008, interest to investigate neutrophils in EAE has steadily grown.

Studies on injury and infection tell us that neutrophils quickly invade the affected tissues to execute different functions (e.g. phagocytosis, degranulation, production of reactive oxygen species, extracellular trap formation, antigen presentation [20]). Is the same true in the context of demyelinating autoimmune diseases? In this review, we take a comprehensive look at how neutrophils gain access to the CNS and contribute to demyelination in EAE. We highlight the importance of neutrophils in human diseases, such as MS and NMOSD, and propose clinical directions. Finally, we outline future challenges in this emerging area of research.

2. Mechanism of neutrophil recruitment in EAE

Under normal physiological conditions, neutrophils, like most other leukocytes, are excluded from the CNS parenchyma by the blood-brain barrier (BBB) [36], which primarily consists of specialized endothelial cells interconnected by tight junctions [37]. Nevertheless, the CNS vasculature is constantly being patrolled by leukocytes that crawl on its luminal surface. Discovered in 2003 [38], this population of sentinels has been characterized in the mouse using conventional histological methods [39–42] and intravital video microscopy [39,43,44]. It comprises approximately 25% neutrophils ($CD11b^+Ly6G^+$) and 75% monocytes ($CD11b^+Ly6G^-$) [40]. Most of these cells have a rod shape attributable to their passage through narrow capillaries and exhibit a bipolar morphology typical of migrating cells [38,39]. Indeed, their movement on the endothelium is driven by a leading edge (where actin polymerizes to push the cell front forward) and by a uropod (where microtubules reorganize to allow retraction of the rear edge) [45,46]. While a few monocytes ultimately cross the endothelium and its basal membrane to renew the pool of perivascular macrophages [39], neutrophils do not take up residence in the healthy CNS [36].

Upon inflammation, neutrophils adhere to the CNS vasculature in greater numbers and can also infiltrate the parenchyma in some circumstances. The population of intravascular rod-shaped neutrophils is roughly four times higher than normal in the CNS of EAE mice [40]. A similar increase occurs in mice intraperitoneally injected with bacterial agents such as pertussis toxin (PTX) [40], which is commonly used as an adjuvant to induce EAE [47]. This recruitment of neutrophils at the blood-CNS interface appears to be a non-specific innate immune response that can be triggered by diverse inflammatory stimuli of local or systemic origin. In contrast, the infiltration of neutrophils into the CNS parenchyma is a more specific event that occurs in EAE, but not in acute toxin exposure. In the CNS of mice with active EAE, neutrophils appear in meningeal and perivascular inflammatory foci shortly before the onset of clinical symptoms [22,48,49]. At the peak of disease, they are observed in the CNS parenchyma within areas of demyelination and axonal damage [50,51]. CNS infiltration of neutrophils is also observed in passive EAE, but only when transferring IL-23-driven T_h17