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Editorial

# Role of Innate Immunity in Multiple Sclerosis

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## Editorial

Multiple sclerosis (MS) is a chronic demyelinating inflammatory disease of the central nervous system (CNS) affecting prevalently young adults and with multi-factorial pathogenesis that includes genetic and environmental factors [1-3]. The pathogenesis of MS has been long attributed to self-reactive T cells but recently the relevant role of B cells, another component of adaptive immunity, has been recognized [4]. It has been demonstrated that innate immunity also contributes significantly to MS pathogenesis both in the initial and in the advanced stages of the disease [5-8]. In particular, activation of microglial cells, which physiologically act as cleaners of the brain microenvironment in response to injury and infections, has been widely reported in both white matter and gray matter tissue in MS [3]. Microglial activation in the absence of lymphocytes or myelin phagocytosis, has been observed in early MS lesions [9,10], expression of a primary involvement of innate immunity. Likewise, predominant microglia activation into newly formed cortical lesions has been detected in the progressive MS phase [11]. Widespread damage of normal appearing white matter (NAWM) seems to be related to chronic microglial activation with marked expression of i-NOS and myeloperoxidase [3]. Moreover, it has been hypothesized that the progressive phase of MS could be mainly driven by the innate immune system contributing to the neurodegenerative changes of the disease [7]. In vivo positron emission tomography studies using radioligands that selectively target the translocator protein (TSPO), expressed in activated microglia and macrophages, have recently demonstrated increased TSPO expression in NAWM and cortex of patients from the earliest to the progressive MS stages [12].

Innate immunity represents the immediate, nonspecific defense against infections and dangerous agents. Adaptive immunity develops a specific immunological memory after the first contact with a pathogen, exponentially enhancing its successive responses [13]. There are close interrelationships between both types of immunity, and innate immunity stimulates and modulates the adaptive one. Innate immunity acts through its essential processes such as inflammation and blood coagulation [14-17]. The coagulation cascade has had primordially the function of limiting invasiveness of potential pathogens by trapping them in the fibrin network [15]. Physiologically, coagulant processes are balanced by the natural anticoagulant system needed to limit the host damage, and the lack of homeostatic interactions between these systems leads to thrombosis [14-17]. This could occur in people with genetic or environment-induced impaired anti-coagulant, and/or anti-oxidative system or during prolonged inflammatory-thrombotic processes. In any case, the presence of thrombotic events indicates an excessive activation of innate immunity.

Since extensive reviews have already described in detail the involvement of innate immunity cells in MS and in experimental allergic encephalomyelitis (EAE) [2,5-8], this editorial aims to emphasize also the important role of the coagulant component of innate immunity in MS and EAE. It is not negligible that such component could be an easily reachable target for a possible therapeutic intervention.

In fact, while many efforts have been aimed to better define the function of innate immune cells in MS [6,7], the role and impact of the coagulant component of innate immunity are still unclear, though there is ample literature on the presence of systemic thrombosis in MS [18-23]. Furthermore, recent studies provided evidence for involvement of platelets [24-26] and complement [27-29] in MS, which participate in the innate immune response by linking inflammation and coagulation.

In addition to systemic thrombosis, several data in the literature have shown the presence of brain thrombotic processes in MS and in EAE. In 1935, Putnam had already considered the role of venule thrombosis in CNS demyelination [30]. A pathological study in acute MS reported fibrin deposition on endothelial cells in many thin veins and capillaries, with some thrombosed vessels, in areas without myelin damage or reactive parenchyma changes [31]. The areas of microglial activation associated with fibrin deposition were found in acute or early MS and in rat EAE, representing a first stage of tissue injury before active demyelination and massive T-cell infiltration [9]. Coagulation proteins were highlighted within the chronic active plaque in MS by the proteomic analysis [32]. In vivo, some proteins involved in coagulation such as β2glicoprotein I, fibrinogen and complement C4, were found in most abundant quantities in the cerebrospinal fluid of fulminant MS compared to controls [33]. Another paper reported an increase of soluble thrombomodulin in relapsing-remitting MS, released from the surface of damaged cerebrovascular endothelial cells, reducing their normal function in promoting the activation of anticoagulant protein C [34]. This leads to a reduction in the inhibitory function of protein C on inflammatory cell migration across the blood-brain barrier (BBB).

Also in EAE, fibrin deposition preceded and regulated inflammatory demyelination, while its genetic or pharmacologic depletion ameliorated both clinical symptoms and inflammatory response [35]. It has been demonstrated that early perivascular microglial clustering, triggered by fibrinogen leakage after BBB disruption, contributed to axonal damage in EAE before myelin loss or paralysis onset, and that this process was blocked by anticoagulant




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treatment or by genetic deletion of fibrinogen [36]. Likewise, hirudin or recombinant activated protein C (rAPC) improved EAE and suppressed pro-inflammatory T-helper1 and T-helper17 cytokines in astrocytes and immune cells [32]. Both anticoagulant and signaling functions of rAPC have been demonstrated necessary for improving EAE [32].

Chapman stressed the importance of thrombin in inflammatory brain diseases [37,38]. Thrombin converts circulating fibrinogen to fibrin, and has numerous hormone-like functions affecting, among others, microglia and astrocytes [39]. The activity of thrombin in the brain is regulated by endogenous thrombin inhibitors such as serum antithrombin III, expressed in the liver and less in the brain, and brain protease nexin-1 (PN-1) secreted by glial cells and neurons [37,38]. It has been demonstrated that the plasma thrombin-antithrombin complexes were associated with EAE severity, increasing immediately prior to EAE symptoms and decreasing in relation to their improvement [40]. Similarly, an increase of brain PN-1 has been shown at the preclinical stage in mouse EAE [41]. The suppression of EAE by dermatan sulfate [42] or low doses of heparins [43] has been also demonstrated, as a result Chapman proposed thrombin as a therapeutic target in MS [37].

In conclusion, involvement of the coagulant component of innate immunity in MS is largely supported by several studies in EAE and MS. Therapeutic targeting of innate immunity, both its cellular and coagulant components, could be a promising approach for treating MS.

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