to healthy donors, thus indicating a role for this factor in human MS pathogenesis.[7] In particular, besides hemostasis, FXII leads to the activation of the contact system, hereby initiating the release of the proinflammatory peptide hormone bradykinin (BK). Reports on the function of BK in MS and EAE remain contradictory since genetic or pharmacological inhibition of one distinct BK receptor (BK receptor 1 (B1R)) leads to an amelioration of EAE, while another study revealed enhanced inflammation.[8,9] For MS patients, B1R has been shown to have a detrimental effect, as it is upregulated on T-lymphocytes in patients with either relapsing-remitting or secondary progressive MS during active relapse.[10]

Overall, it becomes increasingly clear that the deposition of different coagulation factors in the CNS tissue may trigger exacerbation of neurodegenerative inflammation, thereby limiting regenerative mechanisms crucial for disease recovery. A prominent role besides fibrinogen is especially described for the coagulation proteins prothrombin, FX, and FXII. Since the interplay between inflammatory CNS processes and the coagulation system is eminent, the major challenge for MS research now is to elucidate the exact role of the coagulation cascade and its multiple factors for MS pathophysiology and pick up on the promising leads to identify safe and effective targets for disease intervention. Thus, we should shift our research focus from a detailed examination of only fibrinogen and broaden the picture to include in-depth investigations of other coagulation factors in order to produce more creative and promising therapeutic approaches.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Brain fibrinogen deposition plays a key role in MS pathophysiology – Commentary

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Multiple Sclerosis Journal
2019, Vol. 25(11) 1437–1439
DOI: 10.1177/1352458519863125

Numerous studies focused on the proinflammatory functions of several clotting components have recently highlighted the role of coagulation system in experimental autoimmune encephalomyelitis (EAE) and multiple sclerosis (MS) pathogenesis.[1] The contributions from Davalos et al.[2] and Göbel and Meuth[3]

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in this controversy look at these data from different angles.

Davalos et al.[2] underline the pathogenetic role of brain fibrinogen deposition in MS. Fibrinogen enters and spreads in the central nervous system (CNS) after blood–brain barrier disruption, rapidly converting to fibrin and persisting in the parenchyma.[4] Perivascular fibrinogen deposits are observed in post-mortem studies in pre-active, active, chronic active and chronic inactive MS lesions prevalently in white but also in deep grey matter. Likely due to fibrinolysis, fibrinogen spreads even more in the brain when active white matter lesions evolve into chronic lesions and remains scattered in the re-myelinated lesions and in the cortex of patients with progressive MS. In the early phase, fibrinogen deposits appear attached to axonal nodes and co-localize with activated microglia, prior to peripheral immune cell infiltration or any detectable tissue damage. Fibrinogen induces microglial clustering and promotes chemokine secretion and recruitment of peripheral macrophages and myelin-specific Th1 cells into the CNS.[5] It impairs tissue repair by inhibiting oligodendrocyte precursor cell differentiation and inducing NADPH/ROS-mediated neurodegeneration. Treatment with a monoclonal antibody specifically targeting the inflammatory but not the clotting function of fibrinogen can prevent and treat EAE.[6]

On the other hand, Göbel and Meuth argue that the role of fibrinogen could be overvalued in MS pathophysiology because other coagulation proteins are shown to be dysregulated in both brain and blood of MS patients.[3] In particular, circulating levels of several coagulation factors such as prothrombin (Factor II), thrombin, factor X and Factor XII are significantly increased in relapsing-remitting and secondary progressive MS patients compared to healthy controls, and this rise is correlated with disease activity.[7,8] The thrombin increase, similar to fibrinogen deposition, precedes demyelination and clinical signs in EAE. EAE ameliorates either after thrombin inhibition by anticoagulant hirudin due to a decrease in both immune cell proliferation and cytokine secretion or after FX inhibition with rivaroxaban leading to a decrease in microglial activation and reduced T-cell infiltration as well as after FXII inhibition by recombinant human albumin tagged infestin-4. Thrombin acts not only by cleaving fibrinogen but also by activating a proinflammatory signalling cascade through protease-activated receptors widely expressed in the CNS. Yet, the authors considered FXII as a critical trigger of autoimmune inflammation, which acts by shifting the cytokine profile of dendritic cells necessary to induce the differentiation of interleukin-17A-producing effector T-helper cells.[9]

In our opinion, even if fibrinogen is the key element of a complex chain, other procoagulant factors including antiphospholipid antibodies and platelets as well as anticoagulants factors and fibrinolysis play an important role in MS and EAE pathogenesis.[1] These observations are in line with recent evidence that no longer considers coagulation system and innate immunity as separate entities.[10] So far only a few of the many molecular and cellular pathways linking coagulation/inflammation and the innate immune system were studied. The role of the endothelial cells expressing anticoagulant and procoagulant molecules as well as of several cell surfaces and intracellular signalling pathways should be better understood.[10] The vision of these systems as almost inseparable would lead to a more complete and objective aetiopathogenetic understanding of this complex multifactorial disease. As a subsequent step, it will be necessary to design a convenient treatment approach that can complement available MS anti-inflammatory therapies.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: T.K. has received research grant from Italian Ministry of Health. M.S. has received research support and speaking honoraria from Biogen, Novartis, Sanofi, Merck, Teva and Roche.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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