Transcript Details

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Understanding the Role of B Cells in MS Pathophysiology

Announcer Introduction

You're listening to *NeuroFrontiers* on ReachMD. On this episode, sponsored by Novartis, we're joined by Dr. Alessandro Didonna, who's a Research Associate of Neurology at UCSF Weill Institute for Neurosciences. Dr. Didonna is here to share details on the role of B cells in the pathophysiology of multiple sclerosis, or MS for short. Let's hear from him now.

Dr. Didonna:

So it's well known that B cells from MS patients are overactivated because they express higher level of MHC class 2 molecules together with custom stimulatory factors such as CD40 and CD80. We also see an increase in specific signaling pathways such as MAP kinases and the stock cascades that are involved in cell survival and proliferation. However, the mechanism by which B cells are overactivated in MS is not completely understood. Over time, several hypotheses have been proposed, including both environmental and genetic triggers. For example, infection of B cells by specific lymphotropic viruses such as the EBV virus are considered one of the possible causes of this overactivation.

In particular, EBV is a major environmental factor, and we know that EBV can infect the B cells and remain latent for several years but at random times can be randomly activated, and this activation induced the proliferation of infected memory B cells.

There is also evidence that excessive B cell activation can be due by the carriage of specific genetic factors. For example, single nucleotide polymorphism in the gene such as the cell-activating factor of BAF can lead to increased level of these cytokines in the blood of MS patients, which in turn can cause exaggerated B cell activation, proliferation, and anti-immunoglobulin productions.

Another example is the MS risk gene ataxin-1. The toxin group has recently shown to have an immunomodulatory function on the B cell compartment. Lastly, I would like to mention also the importance of epigenetic factors in mediating this overactivation; in particular, there is recent evidence that B cells display extensive DNA hypomethylation, and this epigenetic signature is associated with specific genetic programs controlling B cell differentiation.

So we can envision multiple roles in which these B cells can trigger the disease. One possibility is that B cells can function as potent antigen-presenting cells for CNS-infiltrating T cells. Infiltrating T cells show features of both proinflammatory TH1 and TH17 lineages, therefore representing highly pathogenic B cell subsets.

Another possibility to consider is B cells producing proinflammatory cytokines which can then fit in the inflammatory process and contribute to the disease. For example, one of these cytokines that is IL6 can directly promote the differentiation of TH17, and at the same time, they can block the formation of regulatory T cells. Lastly, B cells can also be involved in tissue injury by producing specific antibodies against immune antigens such as MOG, MBP, or neurophysin. In fact, there is evidence that B cells undergo clonal expansion in the MS brain, and there is also histological evidence of antibody deposition within the demyelinated areas. However, it should be noted that the identification of one or more epitopes consistently associated with the disease is still ongoing.

Lastly, I would like to mention that not all the B cells are pathogenic, but specific B cell subsets exist with anti-inflammatory property that are associated with the production of specific cytokines–such as IL10, IL35—and transforming growth factor-beta. These cytokines are able to limit the pathogenic T cells response and seems to be impaired upon disease. And this is possibly due to an imbalance between the proinflammatory and anti-inflammatory B cell populations.

So the idea that B cells may be involved in MS progression stems from recent evidence of the efficacy of B cell depleting therapies in reducing the accumulation of disability in the progressive form of the disease. While the migration of B cells from the periphery into the CNS is usually associated with relapses, the disease progression seems to be correlated with the formation of follicle-like structure in

the meningeas that resembles the B cell follicles from secondary lymphoid organs.

There are several disease parameters that are associated with the presence of these structures. For example, there is a strong correlation between this structure and the cortical demyelinations. Also, these aggregates are associated with prominent local neuronal damage and also faster cortical thinning.

Lastly, patients with meningeal B cell follicles seem to transition earlier to the most debilitating stages of the disease. I would also like to mention that as immune cell repertoire are rich in B cells in the CSF of MS patients, it's also associated with faster disease progression. Altogether, this evidence suggested that B cells have an active role in the progression of the disease.

Announcer Close

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