influence AD onset and/or development. Recently, we demonstrated that 5-LO is also directly involved in corticosteroid-dependent amyloid-β (Aβ) formation in vitro and in vivo.[6] Compared with controls, 5-LO protein levels are increased in AD postmortem brain tissues, and its genetic absence results in a significant reduction of Aβ levels in the brains of a transgenic model of AD-like amyloidosis.[7,8]

All of these data, together with our current report that 5-LO modulates endogenous levels of Aβ by translational regulation of the γ-secretase complex, without the toxicity of Notch inhibition, make any specific and selective 5-LO inhibitor drug a novel potential therapeutic candidate for a trial in MCI or early AD.

However, we need to take into consideration the finding that there is a significant polymorphism in the human 5-LO promoter region, with implications for 5-LO activity and levels, as well as the pharmacologic response to drugs targeting 5-LO.[9] As a result, if an inhibitor of this enzyme system is to be investigated in MCI or early AD, it would be very important to include the characterization and analysis of the genetics of subjects' 5-LO system in these studies.

In summary, we feel that, although the primary target of minocycline is not completely clear, the finding that this drug may target a new pathway that lowers Aβ generation, and simultaneously reduces early AD neuroinflammation, is of potentially significant therapeutic value.

Potential Conflicts of Interest

Nothing to report.

Department of Pharmacology, Temple University, Philadelphia, PA

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Interferon-beta and Toll-Like Receptor-9 Processing

Hamid Zahednasab, MSc,[1] and Seyed Amir Bahreini, MSc[2]

Although genetics and some environmental factors are implicated in the pathogenesis of multiple sclerosis (MS),[1] the precise etiology of MS is still unclear. Several viruses are suspected to play a role in the development of MS; however, their potential roles in the etiopathogenesis of MS have not been explained.[2] We read with interest the recent study by Balashov and colleagues,[3] which sought to evaluate the inhibitory role of interferon (IFN)-beta in the processing of Toll-like receptor 9 (TLR9).

Plasmacytoid dendritic cells (pDCs) express TLR7, TLR8, and TLR9, but not other TLRs. Moreover, interferon regulatory factor 7 (IRF7) is constitutively expressed in pDCs, but not in other types of cells, which accounts for the ability of pDCs to produce huge amounts of type I IFN rapidly in response to TLR7/8 and TLR9 ligands. Thus, it seems that the inhibition of TLR-9 processing alone would not decrease the amount of IFN-alpha in pDCs.[4]

It is not clear whether patients in this study with relapsing remitting MS were in the relapse or remission phase of the disease course. Some antigens of viruses are expressed only in disease relapse and are undetectable in remission.[5] It is plausible that TLR9 signaling would be altered in relapse and remission stages of the disease. In addition, we would not have included clinically-isolated syndrome (CIS) in this study cohort. Approximately 80% of patients with CIS develop MS while the rest do not.[6]

IFN-beta has a wide range of mechanisms in the amelioration of MS, from inhibition of T-cell activation to potential antiviral activity.[7] Although it appears IFN-beta can inhibit processing of TLR9, it seems unlikely that inhibition of TLR-9 processing alone can cause decreases in type I IFN secretion by pDCs. Further studies are needed to elucidate the inhibition of TLR9 processing in improving the course of MS.[7]

Potential Conflicts of Interest

Nothing to report.

[1]*Department of Clinical Biochemistry, Faculty of Medical Sciences, University of Tarbiat Modares, Tehran, Iran. E-mail: h.zahednasab@modares.ac.ir*
[2]*Department of Biology, Faculty of Sciences, University of Isfahan, Isfahan, Iran*

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Reply

Howard Weiner, MD

Human plasmacytoid dendritic cells (pDCs) are the major cells of the human immune system expressing TLR9.[1] TLR9 has a dominant role in recognition of Epstein-Barr virus (EBV), a human DNA virus, implicated in multiple sclerosis (MS) pathogenesis[2–5] by human pDCs.[6] Based on our results, interferon (IFN)-beta inhibits TLR9 processing and TLR9-mediated pDC responses, including production of IFN-alpha, interleukin-6, tumor necrosis factor-alpha, CCL3, CCL4, and CCL5, and decreases TLR9 ligand-induced chemokine receptor CCR7 expression.[7,8] Those molecules have been implicated in generation and Th1 and Th17 responses, chemotaxis of Th1 cells, and migration of cells from the peripheral blood into the central nervous system. Thus, it would be expected that IFN-beta inhibits EBV-induced pathological inflammatory processes linked to demyelination in MS and experimental autoimmune encephalomyelitis, the animal model of MS.

We agree with Dr Zahednasab that TLR9 is not the only pattern recognition receptor (PRR) involved in activation of pDCs by pathogen-associated molecular patterns. More PRRs and their ligands are being discovered almost every year.[9] We expect new studies to be published soon addressing the role of other PRRs, including TLR7, in MS.

As stated in our article, patients experiencing MS clinical attack were excluded. However, it is very likely that many patients were experiencing subclinical radiological MS attacks. Brain magnetic resonance imaging (MRI) under optimal conditions may detect up to 30× more new MS lesions compared with the number of clinical relapses.[10] However, brain MRI carries a high cost and could not be performed simultaneously with blood drawing for the majority of patients included in the study.

As noted by Dr Zahednasab, both patients with clinically isolated syndrome and relapsing–remitting MS (RRMS) were included in our article. When TLR9 processing in pDCs was analyzed separately in patients with RRMS, it was also significantly decreased ($p = 0.003$) in IFN-beta–treated patients.[8]

We agree with the comment by Dr Zahednasab that IFN-beta has a wide range of mechanisms in the amelioration of MS, from inhibition of T-cell activation to potential antiviral activity, and further studies are needed to elucidate the inhibition of TLR9 processing in improving the course of MS.

Potential Conflicts of Interest

Nothing to report.

Department of Neurology, Brigham and Women's Hospital, Boston, MA

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