TARGETING VERY LONG-CHAIN FATTY ACIDS METABOLISM IN MOUSE MODELS OF MULTIPLE SCLEROSIS

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Background: Multiple sclerosis (MS) is the most prevalent autoimmune disorder of the central nervous system (CNS). Despite the unknown etiology of MS, the typical pathological presentation is demyelination caused by immune cell attack. Over the past decades, most pharmacological interventions of MS have been focused reducing autoimmunity. Although current FDA-approved immuno-modulators have slowed down the MS progression, they fail to stimulate remyelination and promote CNS repair. Thus, there is an unmet need to uncover effective pharmacological approach to orchestrate both remyelination and immune modulation. Using a genetic humanized fly model and in collaboration with clinicians, we previously discovered that accumulation of very long-chain fatty acids (VLCFAs) leads to phenotypes resembling MS pathology, including myelin loss, neuronal loss, and autoimmune response. These observations suggest that aberrant VLCFAs metabolism may be implicated in MS progression, which could be targeted to address both remyelination failure and autoimmunity in MS.

Materials/Methods: Using an established mouse model for human MS (experimental autoimmune encephalomyelitis, EAE), we performed targeted lipidomic analysis of VLCFA in multiple organs. To target VLCFA metabolism in EAE mice, we treated the EAE mice daily with Bezafibrate, a lipid-lowering agent known to inhibit VLCFA synthesis, in combination with FDA-approved immuno-modulating drug Fingolimod, followed by behavior assessment and pathological examination of demyelination, neuronal loss, and immune cell infiltration.

Results: We observed an aberrant VLCFA metabolism in both CNS and immune response organ of EAE mice. Strikingly, there is a significant accumulation of sphingosine-1-phosphate (S1P) in the spinal cord and spleen during the chronic stage of EAE, which is known to mediate immune activation in MS. Furthermore, prophylactic treatment of Bezafibrate reduces systemic VLCFA accumulation, and ameliorates EAE-induced behavioral dysfunction, demyelination, and neuronal loss. Lastly, therapeutically co-treatment of Bezafibrate and Fingolimod synergistically improves EAE-associated pathology and completely restore fine motor function.

Conclusions: Aberrant VLCFA metabolism contributes to EAE progression and provides a potential therapeutic target for MS. Our study not only provides critical insights into the role of VLCFA in glia-immune cell interaction, but also identifies novel therapeutic strategy to address both remyelination failure and autoimmunity in MS.

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