Study identifies biomarker and potential therapy target in multiple sclerosis

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Researchers from Benaroya Research Institute at Virginia Mason (BRI) have found that proteins in the IL-6 signaling pathway may be leveraged as novel biomarkers of multiple sclerosis (MS) to gauge disease activity and as a target for new therapies. The research, which investigated how several components involved in immune response differ between MS patient and control samples, was conducted by a team of researchers at BRI led by Dr. Jane Buckner in collaboration with Dr. Mariko Kita at Virginia Mason Medical Center and was published today in *Science Translational Medicine*.

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system affecting an estimated 400,000 people in the United States. MS is more prevalent in the Northwest region of the U.S. than almost anywhere else in the world. In the Northwest, the likelihood of being diagnosed with MS (2 in 1,000) is double that across the U.S. (1 in 1,000).

Under normal circumstances, effector T cells protect us from infection and cancer and it is the job of regulatory T cells to keep the effector T cells from attacking healthy tissue, thereby preventing autoimmune diseases such as MS. MS occurs when the immune system's effector T cells mistakenly attack myelin, which surrounds and protects the central nervous system. When the myelin is damaged, nerve impulses are not transmitted quickly or efficiently, resulting in symptoms such as numbness, weakness, vision problems, cognitive impairment or fatigue, among others. In Relapsing Remitting MS (RRMS), individuals

experience episodes of active disease, which include attacks of neurologic dysfunction, followed by periods of improvement.

Buckner's group found that the T cells of RRMS patients with active disease were able to avoid suppression by regulatory T cells, while those from patients with mild or well controlled MS did not exhibit this resistance to suppression. These results suggest that the presence or absence of T cell resistance to regulatory T cells could provide patients and physicians with valuable information about an individual's disease activity level and the potential for disease progression. The researchers also discovered that resistance to T cell suppression in RRMS patients was correlated with increased sensitivity to IL-6, a protein that is produced by the immune system that has been shown to contribute to the resistance of effector T cells to suppression. Buckner's group demonstrated that the patient samples that exhibited T cell resistance to suppression also were more sensitive to IL-6. Furthermore, when the signals generated by IL-6 were blocked in these T cells, the resistance to suppression was reversed, suggesting that therapies targeting the IL-6 pathway could potentially be used to modulate T cell resistance to suppression.

"These findings are an exciting step toward better understanding why MS occurs. They will help us to better assess the degree of disease activity in MS patients and lead us to consider new therapeutic approaches for MS" noted Dr. Buckner. "Therapies that target the IL-6 pathway are already available for treatment of other autoimmune diseases and should now be tested in MS."

Future research directions will include investigation of the role of T cell resistance to suppression and IL-6 signaling in MS onset and whether the IL-6 signaling components can be used as biomarkers to predict the severity of disease at the time of diagnosis or anticipate flares and disease progression. The samples used in this study were obtained

through the BRI's Translational Research Program's Biorepository. Research funding was provided by Life Sciences Discovery Fund and JDRF.

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