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Dissecting the role of fractalkine receptor during experimental autoimmune encephalomyelitis: New approach utilizing a humanized animal model

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Fractalkine is a transmembrane chemokine expressed by neurons and peripheral endothelial cells, which acts both as an adhesion molecule and as a soluble chemoattractant upon proteolytic cleavage. In the CNS, fractalkine functions by signaling through its unique receptor, CX3CR1 expressed by microglia. Fractalkine/CX3CR1 signaling regulates microglia neurotoxicity in models of neurodegeneration. During experimental autoimmune encephalomyelitis (EAE), CX3CR1 deficiency confers exacerbated disease characterized by severe inflammation and neuropathology. Among the CX3CR1 human polymorphisms, the $CX3CR1^{I249/M280}$ variant is present in ~20% of the population and exhibits reduced adhesion for fractalkine conferring defective signaling. However, the role of CX3CR1, microglia function and its effect on neuronal damage during multiple sclerosis remains unsolved. The aim of this study is to assess the effect of weaker signaling through the human $CX3CR1^{I249/M280}$ receptor on EAE disease, axonal damage and expression of ciliary neurotropic factor (CNTF). We hypothesize that dysregulated microglial responses in absence of CX3CR1 signaling enhance neuronal/axonal damage via down-regulation of CNTF, a key survival factor for neurons and oligodendrocytes. We have generated an animal model by inserting the $CX3CR1^{I249/M280}$ human variant into the mouse CX3CR1 locus. Active EAE was induced in humanized mice via $MOG_{(35-55)}$ peptide immunization. Our results show an exacerbated EAE phenotype in mice expressing the human $CX3CR1^{I249/M280}$ receptor, characterized by accelerated disease onset and higher maximum EAE score in comparison to WT mice. These results correlated with severe CNS inflammation, microglia activation and increased demyelination in the cerebellum, a similar phenotype observed in CX3CR1-deficient mice. Interestingly, flow cytometry data showed slight down-regulation of MHC-II and CD68 activation markers in humanized mice, suggesting an alteration in microglia function induced by defective CX3CR1 signaling. Our results provide instrumental validation of defective function of the $CX3CR1^{I249/M280}$ human variant and the foundation to broaden the understanding of microglia dysfunction during neuroinflammation.

Biography

Sandra M Cardona is an Assistant Professor of Research in the Department of Biology at the University of Texas at San Antonio. Her career in neurodegeneration started at the Cleveland Clinic studying the biology of the CX3CR1 receptor in microglia during models of systemic inflammation and Parkinson disease. After receiving her PhD in Cellular and Molecular Genetics in 2006 at Kent State University (Ohio), she continued her Post-doctoral training at The University of Texas at San Antonio where she developed a new autoimmunity model of type-1 diabetes aimed to investigate the role of CX3CR1 receptor during diabetic retinopathy. Currently, she is characterizing humanized mice expressing the human CX3CR1 variant receptor in neuroinflammatory models of multiple sclerosis and diabetes and interested in the role of CX3CR1 in the differentiation and biology of astrocytes. She is author of 12 scientific contributions and Member of ASN, SfN and AHA.

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