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Glial receptors for extracellular mitochondrial transcription factor A (TFAM): Potential new therapeutic targets in the treatment of neurodegenerative diseases

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Neuroinflammation contributes to the progression of neurodegenerative disorders including Alzheimer's disease. Evidence indicates that over-activation and dysregulation of microglia, which are the primary immune effector cells of the brain, contribute to neuronal death. Microglial activation in Alzheimer's disease could be triggered not only by amyloid peptides, but also by other endogenous molecules including damage-associated molecular patterns (DAMPs), which are released upon cellular stress and damage. We hypothesized that mitochondrial transcription factor A (TFAM) could function as a DAMP in the brain since in addition to its intracellular role as a regulator of mitochondrial DNA transcription, extracellular TFAM has been implicated as a DAMP in the peripheral tissues. Our preliminary data indicated that TFAM induced pro-inflammatory and cytotoxic responses of human microglia. In this study, using an *in vitro* human cell culture system we show that the cellular effects of TFAM are partially mediated by the receptor for advanced glycation endproducts (RAGE) and macrophage-1 antigen (Mac-1). RAGE was implicated by experiments that showed heparin attenuating TFAM-induced human monocytic THP-1 cell toxicity towards SH-SY5Y neuronal cells. Furthermore, heparin decreased the release of monocyte chemoattractant protein (MCP)-1 from activated THP-1 cells. Blockade of the Mac-1 receptor by a specific antibody also attenuated the toxicity of THP-1 monocytic cells towards SH-SY5Y neuronal cells. Identifying the receptors and the intracellular signaling pathways that mediate glial effects of extracellular TFAM could help develop novel therapeutic strategies for neurodegenerative diseases, such as Alzheimer's, which are characterized by cell damage and associated sterile neuroinflammatory responses.

Biography

Stephanie M Schindler completed her BSc at the University of British Columbia Okanagan and is currently completing her MSc at University of British Columbia Okanagan. She has published 5 papers in the field of neuroscience.

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