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Stress granules modulate spleen tyrosine kinase to cause microglial dysfunction in Alzheimer's disease

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Microglial cell is the primary immune cell of the central nervous system and maintains the brain homeostasis. In Alzheimer's disease brain, microglial cell are recruited to amyloid beta (Aβ) plaques and exhibit an activated phenotype, but are defective for plaque removal by phagocytosis. To explore the molecular basis for these phenomena, we hypothesized that defect in the functions of the protein-tyrosine kinase SYK, which is important both for macrophage activation and phagocytosis, might underlie much of this observation. Recent evidence from our lab indicates that SYK can associate with stress granules, ribonucleoprotein particles that form in stressed cells and contain inactive translation initiation complexes. In our study, we found that microglial cell line and primary mouse brain microglia, when stressed by exposure to sodium arsenite or Aβ(1-42) peptides or fibrils, form extensive stress granules to which SYK is recruited. SYK enhances the formation of stress granules as evidenced by the inhibition of stress granule formation by small molecule inhibitors, knockdown of SYK expression by shRNA and SYK haplo-insufficiency in mouse microglial cells. SYK is active within the resulting stress granules where it catalyzes the phosphorylation of stress granule-associated proteins on tyrosine. SYK-dependent stress granule formation stimulates the production of reactive oxygen and nitrogen species. These are toxic to neuronal cells as demonstrated by a co-culture assay using stressed microglial cells and HT22 neuronal cells. The ability of microglial cells to phagocytose *E. coli* is blocked by SYK inhibitors. The sequestration of SYK into stress granules inhibits the ability of microglial cells to phagocytose either *E. coli* or Aβ fibrils. Microglial cells from aged mice are more susceptible to the formation of stress granules than are cells from young animals. Stress granules containing SYK and phosphotyrosine are prevalent in the brains of patients with severe Alzheimer's disease, suggesting that the sequestration of SYK into stress granules is part of the pathology of the disease. Phagocytic activity can be restored to stress microglial cells by treatment with IgG independent of the epitope specificity, suggesting a mechanism to explain the therapeutic efficacy of intravenous IgG.

Biography

S Ghosh is currently pursuing his Postdoctoral research at Washington School of Medicine, St. Louis, USA. His research interest lies in understanding the neuro-immune signaling pathways that are disrupted during neurodegenerative diseases and autoimmune disorders in the brain. He has received his Bachelor's degree in Technology in Genetic Engineering from SRM University, India. He has pursued his PhD at Purdue University, USA in kinase signaling examining the role of different kinases such as CDK5 in neuronal cell death, Aurora A kinase in breast and ovarian cancer and spleen tyrosine kinase in microglial cell activation.

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