The Protective Role of NRF2 Signaling Against NLRP3 Inflammasome Activation in Brain

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The NLRP3 inflammasome is a multiprotein complex that activates caspase-1 and triggers the release of the proinflammatory cytokines IL-1β and IL-18 in response to diverse signals and consequent cell death, named pyroptosis. Although inflammasome activation plays critical roles against various pathogens in host defense, overactivation of inflammasome contributes to the pathogenesis of inflammatory diseases, including psychiatric conditions, acute brain injuries, and chronic neurodegenerative disorders. Microglial cells are the primary mediator of NLRP3 inflammasome activation in the brain. Therefore, our studies are mainly related to microglial immune responses in cell culture and animal models. To test the protective role of NRF2, we have utilized protective molecules with NRF2 activating capacities, such as Sulforaphane, Melatonin, and Dimethyl Fumarate. Our studies have revealed that Sulforaphane, Melatonin, and Dimethyl Fumarate protected microglial cells from NLRP3 inflammasome activation and pyroptotic cell death. On the other hand, using a small molecule inhibitor or siRNA of NRF2 reversed the protective roles of Sulforaphane, Melatonin, and Dimethyl Fumarate. Thus, we conclude that NRF2 signaling mediates the protective functions of Sulforaphane, Melatonin, and Dimethyl Fumarate against NLRP3 inflammasome activation in the brain.

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