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Selective GSK3β inhibition mediates an Nrf2-independent anti-inflammatory microglial response

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ABSTRACT

Glycogen Synthase Kinase 3 (GSK3) is associated with the proinflammatory phenotype of microglia and has been shown to act in concert with nuclear factor kappa B (NF-κB). GSK3 is also a suppressor of nuclear factor erythroid 2-related factor 2 (Nrf2), the principal regulator of redox homeostasis. Agreeing with the oxidative paradigm of aging, Nrf2 is often deregulated in parainflammatory and neurodegenerative diseases. In this study, we aimed to explore a multimodal disease-modifying utility of GSK3 inhibition, beyond neuronal proteopathologies, Furthermore, we aimed to underscore the difference in therapeutic value between the two GSK3 paralogs by isoform-selective chemical inhibition.

The anti-inflammatory effects of paralog-selective GSK3 inhibitors were evaluated as a function of the reductive capacity of each to mitigate LPS-induced activation of SIM-A9 microglia. The Griess method was employed to detect the nitrate-lowering capacity of selective GSK3 inhibition. Real-time PCR was used to assess post-treatment expression levels of pro-inflammatory markers and antioxidant genes; pro-inflammatory cytokines were assayed by ELISA. Nuclear lysates of treated cells were examined for Nrf2 and NF-κB accumulation by immunoblotting. Finally, to infer whether the counter-inflammatory activity of GSK3 inhibition was Nrf2-dependent, DsiRNA-mediated knockdown of Nrf2 was attempted.

Results from our experiments reveal a superior anti-inflammatory and anti-oxidative efficacy for GSK3β-selective inhibition, compared to GSK3α-selective and non-selective pan-inhibition; hence use of selective GSK3β inhibitors is likely to be more propitious than non-selective dual inhibitors administered at comparable doses. Moreover, our results suggest that the anti-inflammatory effects of GSK3 inhibition is not Nrf2 dependent.

BIOGRAPHY

Mohamed H. Yousef has completed his master's degree in 2022 from the American University in Cairo. He is currently a research assistant and a PhD fellow at the Institute of Global Health and Human Ecology at the American University in Cairo. His research interests span exploring the pathophysiological underpinnings of neurodegenerative/neuroinflammatory disorders and exploiting these for developing novel theragnostic platforms.

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