# Combinatory FK506 and minocycline treatment alleviates prion-induced neurodegenerative events via caspase-mediated MAPK-NRF2 pathway

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## Abstract

Transcription factors play a significant role during the symptomatic onset and progression of prion diseases. We previously showed the immunomodulatory and nuclear factor of activated T cells' (NFAT) suppressive effects of an immunosuppressant, FK506, in the symptomatic stage and an antibiotic, minocycline, in the pre-symptomatic stage of prion infection in hamsters. Here we used for the first time, a combinatory FK506+minocycline treatment to test its transcriptional modulating effects in the symptomatic stage of prion infection. Our results indicate that prolonged treatment with FK506+minocycline was effective in alleviating astrogliosis and neuronal death triggered by misfolded prions. Specifically, the combinatory therapy with FK506+minocycline lowered the expression of the astrocytes activation marker GFAP and of the microglial activation marker IBA-1, subsequently reducing the level of pro-inflammatory cytokines interleukin 1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) and increasing the levels of anti- inflammatory cytokines IL10 and IL-27. We further found that FK506+minocycline treatment inhibited mitogen-activated protein kinase (MAPK) p38 phosphorylation, NF-kB nuclear translocation, caspase expression and enhanced phosphorylated cAMP response element-binding protein (pCREB) and phosphorylated Bcl2- associated death promoter (pBAD) levels to reduce cognitive impairment and apoptosis. Interestingly, FK506+minocycline reduced mitochondrial fragmentation and promoted nuclear factor–erythroid2-related factor-2 (NRF2)-heme oxygenase 1 (HO-1) pathway to enhance survival. Taken together, our results show that a therapeutic cocktail of FK506+minocycline is an attractive candidate for prolonged use in prion diseases and we encourage its further clinical development as a possible treatment for this disease.

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Note:- This Work Is Partly Presented 2nd international conference on pathology and surgical pathology July 13-14, 2020 Held At Amsterdam, Netherlands