Abstract:

There is interest in understanding post-translational modifications of proteins in inflammatory disease. Neddylation is the conjugation of the molecule NEDD8 to promote protein stabilization. Cullins are a family of NEDD8 targets important in the stabilization and degradation of proteins, such as hypoxia-inducible factor (HIF, via Cullin-2). Here, we elucidate the role of human deneddylase-1 (DEN-1, also called SENP8) in inflammatory responses in vitro and in vivo and define conditions for targeting neddylation in models of mucosal inflammation. HIF provides protection in inflammatory models, so we examined the contribution of DEN-1 to HIF stabilization. Pharmacological targeting of neddylation activity with MLN4924 (IC50=4.7 nM) stabilized HIF-1α, activated HIF promoter activity by 2.5-fold and induced HIF-target genes in human epithelial cells up to 5-fold. Knockdown of DEN-1 in human intestinal epithelial cells resulted in increased kinetics in barrier formation, decreased permeability and enhanced barrier restitution by 2±0.5-fold. Parallel studies in vivo revealed that MLN4924 abrogated disease severity in murine DSS colitis, including weight loss, colon length and histological severity. We conclude that DEN-1 is a regulator of cullin neddylation and fine-tunes the inflammatory response in vitro and in vivo. Pharmacological inhibition of cullin neddylation may provide a therapeutic opportunity in mucosal inflammatory disease.

Research Category: Basic Science