SOSTM-1/p62: A Novel Therapeutic Target in Infectious and Inflammatory Disease

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Background

IDR-1 (K6RAVAPAVSSL-RH Q62) is a synthetic peptide with no antimicrobial activity that enhances infection control while suppressing inflammation. Treatment of mice with IDR-1 at the time of infectious challenge provides protection from otherwise lethal bacterial infection, and modulates cytokine and chemokine expression downstream of TLR stimulation. Previously, the effects of IDR-1 were postulated to impact several transcriptional pathways, including MAPK, p38 and C/EBP, but the preceding molecular events remained unknown.

In this study, the cytoplasmic protein p62 has been identified as a molecular target of IDR-1. p62 is a multi-domain scaffold ( adaptor) protein, with many known interacting partners, including PKCζ, p38, RIP1, and TRAF6. p62 comprises an N-terminal RING domain that is primarily important for AKP binding, a ZZ domain which interacts with RIP1, and a TBSS sequence domain recognized by TRAF6. Additionally, a C-terminal UBA domain binds to polyubiquitin – a function considered to be the basis of the association between p62 and protein trafficking to the proteasome. Variation in p62 expression levels has been implicated in various disease states but its function in antimicrobial immunity has not yet been investigated.

p62 has recently been recognized as a nodal point in cellular signaling pathways, in particular implicated in regulation of NF-κB. In addition, recent studies demonstrate that p62 expression contributes to regulating macrophage-mediated and cancer-associated inflammation, raising the question as to whether IDR-1 might affect inflammatory responses in the absence of pathogen stimulation.

Results

IDR-1 binds to p62

IDR-1 affects intracellular p62 complexes

IDR-1 modulates p62-mediated signaling

IDR-1 and p62 modulate bacterial replication in vitro and in vivo

Conclusions

• IDR-1 binds to the ZZ domain of p62 to modulate specific protein-protein interactions.
• p62 plays a key role in infection control.
• Therapeutic intervention targeting p62 is capable of both enhancing clearance of infection and suppressing the attendant inflammation, as well as suppressing inflammation in the absence of any infectious challenge.