Background

IDRs are novel class of synthetic peptides with no antimicrobial activity that enhance microbial infection control while suppressing inflammation. Treatment of mice with IDRs enhanced their survival in bacterial infection models and reduced bacterial burden. The anti-infective effect of IDRs was maintained in animals depleted of neutrophils, but abolished in animals depleted of macrophages/monocytes, indicating an important role for macrophages in IDR mediated host protection. IDRs have been shown to increase chemokine levels at the site of infection (CCL2 and CXCL10), enhance macrophage recruitment to the site of infection and improve the resolution of bacterial infection alone or in conjunction with antibiotics. IDRs have also been shown to modulate pathogen-free inflammation, where levels of pro-inflammatory cytokines were also reduced. Collectively, these data suggest that IDRs modulate innate immune responses by enhancing macrophage recruitment while suppressing inflammatory pathways. The recent identification of the intracellular target of IDR, s62 (sequestosome-1), which is ubiquitously present in the body and known to modulate inflammatory pathways in macrophages, suggests further possibilities for the therapeutic application of IDRs. Recently in Phase 1 a study with a lead IDR, IMX942, has demonstrated the safety of this novel, first-in-class, therapeutic approach.

IDRs recruit macrophages in vivo

IDRs modulate cytokines/chemokines in vivo

IMX942 shifts inflammatory status in healthy human

Conclusions

- IDRs target host to provide protection from bacterial infection
- Macrophages, but not neutrophils, are required for IDR-mediated host protection
- IDRs modulate inflammatory responses
- IMX942 is well tolerated by human
- IMX942 shifts inflammatory status in human