DOI:
10.1038/nrd2319

INFECTION

New peptide modulator of innate immunity

Owing to the continuing emergence of 'superbugs', multiple antibiotic-resistant bacteria, novel antibacterial strategies are urgently needed. Reporting in *Nature Biotechnology*, Scott and colleagues now demonstrate that a small synthetic peptide, modelled on naturally occurring host defence proteins, can protect mice against a lethal bacterial challenge in different models of aggressive bacterial infection. As the peptide acts on the cells of the immune system, development of bacterial resistance in this approach is unlikely.

The innate immune system is composed of an intricate network of components, including neutrophils, monocytes, macrophages, complement, cytokines, chemokines and host defence proteins, which provides the first line of defence against infectious agents. Immunomodulatory approaches to boost innate immunity are an attractive option; however, drug development efforts have been limited, as excessive or prolonged triggering can induce massive damage and death by sepsis. Based on a recent demonstration that small cationic peptides can have immunomodulatory properties, Scott and colleagues have now developed a 13 amino-acid peptide IDR-1 (innate defence regulator peptide-1) — a peptide that proved protective in several mouse models of bacterial infection, but lacked toxic side effects.

Administered locally or systemically, either 48 or 24 h before, or 4 h post-bacterial challenge, IDR-1 substantially decreased bacterial counts and mortality of mice infected with *Staphylococcus aureus, Enterococcus* or *Salmonella enterica*. Common bacterial resistances did not lower peptide protection, as demonstrated by decreased lethality in MRSA (methicillin resistant *S. aureus*) and VRE (vancomycin resistant *Enterococcus*) models. Furthermore, combinations of subeffective doses of IDR-1 and a common antibiotic increased protection compared with either agent alone. As neutropaenic and B- and T-cell deficient mice can still be protected by IDR-1, but depletion of macrophages and/or monocytes abrogates the effect, IDR-1 is likely to trigger a protective response with macrophages/monocytes as central players.

Microarray analysis of human monocytes treated with IDR-1 revealed an approximately 30% overlap in gene expression signature with LL-37, a natural host defence protein. Further gene and protein expression analysis revealed that IDR-1 selectively modulates the innate immune response. By stimulating several signalling pathways — including mitogen-activated protein kinase (MAPK), phosphoinositide-3-kinase (PI3K) and, transiently, nuclear factor-κB (NF-κB), — and transcription factors (including CCAAT/enhancer binding protein-β (C/EBP)), it induces the expression of key chemokines, and the anti-inflammatory mediator interleukin 10 (IL10). Further, it suppresses lipopolysaccharide-induced pro-inflammatory cytokines such as tumour-necrosis factor-α (TNFα). Overall, this results in enhanced recruitment of monocytes/macrophages and more efficient bactericidal activity, while inflammation is kept under control.

Compared with other host defence proteins, IDR-1 is small and easy to manufacture, and lacks the known toxicities of natural host defence proteins. IDR-1 could be a valuable complement to antibiotic treatment, and its prophylactic efficacy might render it useful in situations in which there is a high risk of infection. Importantly, as it does not display any direct microbicidal activity, it is not expected to contribute to the emergence of resistant superbugs.

Alexandra Flemming

ORIGINAL RESEARCH PAPER Scott, M. G. *et al.* An anti-infective peptide that selectively modulates the innate immune response. *Nature Biotech.* **4**, 465–472 (2007)
FURTHER READING Bowdish, D. M. *et al.* Immunomodulatory activities of small host defense peptides. *Antimicrob. Agents Chemother.* **47**, 1727–1732 (2005)