FUNCTIONAL DUALISM OF ANTIMICROBIAL HOST DEFENCE PEPTIDES

Akademisk avhandling

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av
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Avhandlingen baseras på följande arbeten:

I. Fu H, Björstad Å, Dahlgren C, Bylund J. **A bactericidal cecropin-A peptide with a stabilized alpha-helical structure possess an increased killing capacity but no proinflammatory activity.** *Inflammation. 2004 Dec;28(6):337-43.*

II. Björstad Å, Fu H, Karlsson A, Dahlgren C, Bylund J. **Interleukin-8-derived peptide has antibacterial activity.** *Antimicrobial Agents and Chemotherapy 2005 Sep;49(9):3889-95.*

III. Björstad Å, Askarieh G, Brown KL, Christenson K, Forsman H, Önnheim K, Li H, Teneberg S, Maier O, Hoekstra D, Dahlgren C, Davidson DJ, Bylund J. **The host defence peptide LL-37 selectively permeabilises apoptotic leukocytes.** *Antimicrobial Agents and Chemotherapy 2009. 53(3). In Press.*

IV. Björstad Å, Önnheim K, Karlsson J, Rabiet MJ, Dahlgren C and Bylund J. **LL-37 mediated activation of human leukocytes - characterisation of receptor usage.** *Manuscript.*

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Abstract: Antimicrobial host defence peptides are central to innate immunity and many possess direct antimicrobial actions on bacteria as well as indirect immunomodulatory functions on human leukocytes. Different variants of the bifunctional *Helicobacter pylori* peptide, Hp(2-20), were synthesised and inhibition zone assays and chemiluminescence systems were employed for determination of direct antimicrobial action and superoxide release (immunomodulatory) from human neutrophils, respectively. α-helically stabilised peptides displayed increased antimicrobial action, while destabilised peptides were impaired. Only native Hp(2-20) had the capability to induce superoxide production from neutrophils, this representing a sequence-specific feature. The well known chemokine interleukin-8 (IL-8) contains a C-terminal part with many similarities to α-helical antimicrobial peptides. The C-terminal part of IL-8 was synthesised and displayed antibacterial activity but was incapable of inducing neutrophil superoxide production and chemotaxis, prominent activities of the native protein. IL-8 could thus be viewed as a bifunctional molecule with the two effects residing in different parts of the molecule. A prominent example of a human host defence peptide exhibiting functional dualism is LL-37 that permeabilises microbial membranes. LL-37 also selectively permeabilised apoptotic human leukocytes leaving viable leukocytes intact, as measured by flow cytometry. The activity was reminiscent of its antimicrobial activity; it was rapid, independent of known surface receptors and/or active cell signalling. Selectivity was probably related to changes in membrane composition of apoptotic cells. Permeabilisation of apoptotic leukocytes by LL-37 was accompanied by leakage of cytoplasmic and intragranular molecules that may shift the balance between pro- and anti-inflammatory signals and by this be of importance for the termination of acute inflammation. LL-37 also interacted with different receptors present on viable leukocytes. Neutrophil- and monocyte NADPH-oxidase activation by LL-37 was studied and shown to depend on the FPRL1 receptor. Also, the rise of intracellular Ca^{2+} triggered by LL-37 was FPRL1 dependent, but the peptide was a rather weak FPRL1 agonist. However, L-selectin shedding from neutrophils was independent of FPRL1, suggesting the presence of another receptor on neutrophils for LL-37. The dual action of host defence peptides makes them especially important for handling infections; fighting the pathogen directly as well as indirectly by alarming the immune system.

Keywords: antimicrobial, apoptosis, cathelicidin, host defence peptide, interleukin 8, LL-37, permeabilisation

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