Karolinska Institutet

Institutionen för Medicinsk Biokemi och Biofysik

Expression and regulation of antimicrobial peptides in mucosal immunity

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Samuelssonsalen, Tomtebodavägen 6, Karolinska Institutet, Campus Solna

Fredagen den 16 november 2012, kl 13.00

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Stockholm 2012

ABSTRACT

Antimicrobial polypeptides (AMPs) are effector molecules of the innate immune defense. AMPs are mainly expressed in epithelial cells and immune cells, providing the first line of defense to infection as direct antimicrobials. In addition, many AMPs display immunomodulatory functions in both the adaptive and innate immune system. Thus, a tight control of AMP-expression is necessary for a functional immune response.

In this thesis the antimicrobial polypeptide armament of neutrophils (PMNs) was evaluated for its activity against four human pathogens *S. aureus*, *H. influenzae*, *M. catarrhalis* and *C. albicans*. We observed a high degree of redundancy in antimicrobial activity for a majority of the AMPs. Still, some polypeptides exhibited a more specific activity against individual pathogens. This suggests that PMNs are equipped with a repertoire of antimicrobial peptides and proteins with broad activities, underscoring the importance of PMNs in the host response.

In a clinical study the expressions of cathelicidin LL-37 and α-defensins HNP1-3 were quantified in nasal fluids of patients with primary immunodeficiencies (PIDs). Healthy controls and most PID patients responded to pathogens with increased levels of AMPs in their nasal fluid. Interestingly, in patients with common variable immune deficiency (CVID) and Hyper IgE syndrome (HIES), the levels of AMPs did not increase in response to pathogens. Thus, there is a dysregulation in AMP-release in CVID and HIES patients, which may explain why these patients suffer from frequent respiratory tract infections.

Furthermore, we have detected an induced expression of AMPs by human breast milk in colonic epithelial cell lines. We isolated and characterized the inducing compound as lactose and noted that the inducing effect of the gene encoding LL-37 (*CAMP*) was dependent on intact p38 mitogen-activated protein kinase and c-Jun N-terminal kinase signaling. A strong synergistic effect on *CAMP* expression in HT-29 cells was observed in stimulations with lactose and phenylbutyrate or butyrate. This synergistic effect was further dissected by a proteomic approach. The subsequent pathway analysis of the proteomic results indicated that eleven pathways were activated. By using the novel *CAMP* gene reporter system we confirmed that the pathways of thyroid hormone receptor and retinoid X receptor (TR/RXR) activation, eicosanoid signaling and steroid biosynthesis were associated with the regulation of *CAMP*.

In summary, AMPs exhibit both a large redundancy and strict specificity with regards to microbial killing. This may be relevant for certain disease conditions, where AMPs are lacking or dysregulated. Endogenous molecules, such as lactose and thyroid hormones are inducers of AMPs. In light of the wide-spread antibiotic resistance, attempts to strengthen epithelial barriers are highly warranted and the data presented here provide a concrete rationale for such studies.

ISBN 978-91-7457-928-4