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Battle and balance at mucosal surfaces – The story of *Shigella* and antimicrobial peptides

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ABSTRACT

Shigella is a major cause of morbidity and mortality for children in many developing countries. Emergence of antibiotic-resistance among *Shigella* demands the development of effective medicines. Antimicrobial peptides (AMPs) are expressed in phagocytes and at epithelial surfaces and are important effector molecules of innate immunity. We have found that pathogens are able to turn off the endogenous expression of AMPs, resulting in serious infections such as shigellosis. A therapeutic rationale to prevent microbial invasion would be to strengthen the epithelial line of defence through enhancing AMP expression. We have identified several inducers of AMP-production, including butyrate, phenylbutyrate and vitamin D, which have been investigated in animal models of shigellosis as well as in clinical trials. We believe that the conceptual framework presented here can be applied to additional clinical entities and that this novel approach can be an alternative or complement to traditional antibiotics in the future.

1. Introduction

In the first decade of the nineteenth century Europe was at war, the Napoleonic Wars were reshaping Europe. This was the last time Sweden was involved in a war. As always at wartimes infectious agents can be entitled "the third army" with serious impact on death and suffering among soldiers and civilians. In fact, infectious agents caused death of similar order as those injured or killed directly in battles. A great killer was the bacterium *Shigella,* the causative agent of bacillary dysentery.

The war activities during 1808–1809 were a disaster for the Swedish army and a lack of army surgeons was identified as one major problem. Therefore the king Karl XIII initiated the foundation of Karolinska Institutet, as a training centre for army surgeons. Thus, in retrospect one can claim that *Shigella* was an indirect factor influencing the foundation of the institute.

Now two centuries later at the 200 year anniversary of Karolinska Institutet, *Shigella* can still be a deadly threat with epidemics in developing countries. Furthermore, the impact of bacterial pathogens in general may be difficult to foresee, especially in the face of the global spread of resistance against antibiotics.

From the viewpoint of biology, *Shigella* has served as an important model for studying microbe host interactions. The bacterial response upon contact with host cells has been analyzed as well as the intracellular signaling pathways of infected host cells [1]. Molecular mechanisms of bacterial invasion and immune-escape have been established. *Shigella* infect the host via the oral route, survive the acid of the gastric juice, but also degrading enzymes, and typically invade epithelial cells of the colon from the basolateral side and spread laterally. Classic dysentery caused by *Shigella* is characterized by fever together with mucoid and hemorrhagic stool. The mucosal secretions from gut epithelial cells constitute the first line of defence against *Shigella* and other gastrointestinal pathogens. These secretions contain antimicrobial peptides (AMPs), which are expressed by epithelial cells at mucosal surfaces (Fig. 1A). AMPs have the capacity both to kill microbes and to recruit immune cells to the site of infections. The colonic mucosal barrier consists of a single layer of columnar epithelial cells and normally this barrier is in perfect harmony with the massive microbial community that we refer to as the endogenous flora. However, pathogenic bacteria such as *Shigella* are able to circumvent mucosal defenses and cause invasive disease. The original discovery that *Shigella* could down-regulate the expression of AMPs was made by our research-group in 2001 [2] (Fig 1B). Our initial finding has since been corroborated by other groups [3] and microbial down-regulation of innate defenses appears to be a general phenomenon exploited by other pathogens [4,5].

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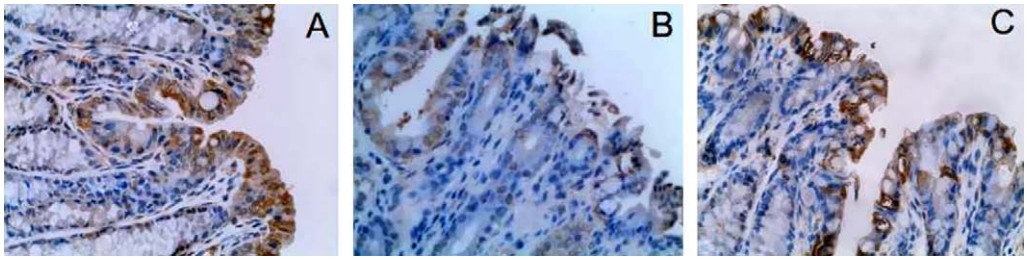

Fig. 1. Immunohistochemical staining of the cathelicidin CAP-18 in paraffin embedded sections of rabbit colon. All sections were counter-stained with hematoxylin (blue/violet). (A) Immuno-reactivity of CAP-18 (brown) in healthy rabbits was mostly located to the surface epithelium. (B) In rabbits infected with *Shigella*, the surface and crypt epithelia had drastic reduction of CAP-18 staining with occasional erosion of the epithelial lining. (C) Reappearance of CAP-18 staining in the surface epithelium in infected rabbits treated with butyrate.

In this paper we will present recent work from our laboratories and others on the pathogenesis of shigellosis in relation to antimicrobial peptides. We will discuss recent progress, where we have utilized small molecules to induce AMP expression at mucosal surfaces. Finally, we present our thoughts on future treatment strategies of infectious diseases.

2. *Shigella* and innate immunity

The *Shigella* bacterium is well defined, the genome is sequenced and many effector proteins have been characterized. *Shigella* utilizes type III secretion system (T3SS), a molecular syringe apparatus for injecting proteins that interfere with host cell function. These proteins promote bacteria to escape into the cytoplasm and avoid vacuole destruction [6]. *Shigella* effectors interfere with important signaling pathways of inflammation and evade host defenses. The *Shigella flexneri* protein effector OspF dephosphorylates p38, Erk1 and Erk2 to their inactive mode, resulting in epigenetic modulation of histone H3. This blocks transcriptional activation of NF-kappa B, a key factor in inflammatory responses [7]. *Shigella* injects IpaH with E3 ligase activity that promotes the degradation of NEMO which also leads to inhibition of NF-kappa B-mediated inflammatory responses [8]. These examples highlight *Shigella*–host cell interaction research with general reference to innate signaling pathways. Other pathogens, e.g., *Listeria monocytogenes, Clostridium perfringens* and *Streptococcus pneumoniae* also use a common strategy by reprogramming host gene expression especially key immunity genes via epigenetic modulation during the spread of infections [9,10].

As little as 10 *Shigella* bacteria can establish an overt clinical disease via contaminated food or water. After the *Shigella* has reached the colon the bacterium approaches the epithelium. Epithelial cells or enterocytes are tightly linked together with tight junctions, controlling the paracellular space and form a physical barrier. Proteins and the protective carbohydrate layer in addition to active antimicrobial components, such as lysozyme, defensins, cathelicidins, RNase A, secretory phospholipase A2 and proteases constitute the chemical defenses of the enterocytes. This is the surface that *Shigella* encounters, some components are very active against *Shigella* such as the cathelicidin peptide LL-37 [2]. Activated neutrophils release neutrophil extracellular traps (NETs), consisting of chromatin laced with AMPs to trap and kill *Shigella* and other pathogens [11].

Shigella invades the epithelial barrier through the microfold cells (M cells), is taken up by enterocytes from the basolateral side and spread laterally in the epithelial lining. During the invasion process, *Shigella* down-regulates the expression of the active components cathelicidin and beta-defensin [2,12] (Fig. 1B) by injecting virulence plasmid-encoded effectors into host cells and hence regulates innate signaling [3].

3. Antimicrobial peptides

Our defense system against pathogens relies partly on AMPs that are synthesized constitutively or induced at epithelial surfaces, where the initial contact with all microbes, from symbionts to pathogens, takes place. There are two major classes of these peptides in mammals; the defensins [13] and the cathelicidins [14,15]. In humans, AMPs include a single cathelicidin, LL-37, together with α-and β-defensins. The peptides are cationic and have affinity to the negatively charged bacterial membrane that they disrupt, resulting in bacterial killing by lysis. Collectively these peptides represent key components at epithelial surfaces, the barrier between the external environment and the interior milieu. This barrier relies on multiple components, with variable mechanisms of action. AMPs are also included in the microbicidal armament of phagocytes and are secreted from neutrophils. Thus, AMPs are present both in the front line and in the first wave of defenses at the site of infections. The expression is both constitutive and induced. The fact that AMPs are widely expressed in our body is well established, however, the exact tissue distribution has not yet been defined. Characterization of the human genome has identified multiple beta-defensin genes [16], indicating a system that is only partially characterized at epithelial surfaces and also in other tissues.

AMPs are multifunctional peptides and examples of established functions are chemotaxis, angiogenesis and activation of immune cells [17]. Thus, AMPs are now considered as key molecules of our immune system.

Coevolution with the microbiota has most likely affected the development of our immune system. The commensal gut flora forms a delicate and constantly changing balance, protecting the intestinal mucosal barrier by preventing attachment of pathogenic micro-organisms. AMPs are a part of this system, shaping the composition of the microflora and maintain the homeostatic balance. It is the composition not the number of bacteria that is the important factor, determining homeostasis and health [18]. This balance is affected by changes in the intestinal environment leading to dysregulation and chronic/acute inflammation. Pathogens take advantage of inflammation by crossing the epithelial barrier and reduce the microflora in order to invade their niche. In addition, pathogens express effectors that modulate inflammation and expression of AMPs [19].

4. Induction of AMPs

4.1. Butyrate and phenylbutyrate

Butyrate, a short chain fatty acid produced in the colon by bacterial fermentation of dietary fibers has the capacity to "override" the down-regulation imposed by *Shigella* and thus to reconstitute AMP expression at the colonic mucosal surface [12] (Fig. 1C). Since

butyrate is a foul-smelling liquid and therefore may be problematic to use therapeutically we have recently investigated if the derivative phenylbutyrate (PBA) exhibits equal potency with regard to AMP-induction [20]. Interestingly, PBA appears to be an even more potent inducer of LL-37 expression in several cell-lines.

4.2. Vitamin D and LL-37 – a sunshine story of tuberculosis

Before the discovery of effective antimycobacterial drugs, vitamin D therapy in the form of cod liver oil and exposure to sunlight were used to treat human tuberculosis. The body produces vitamin D when sunlight hits the skin. The active form of vitamin D (1,25-dihydroxyvitamin D_3) is subsequently generated via two hydroxylation steps in the liver and kidney, respectively. This active form of vitamin D has been demonstrated to be an inducer of the *CAMP* gene encoding the cathelicidin LL-37 [21,22]. The *CAMP* gene is responsive to vitamin D_3 due to the fact that there is a Vitamin D response element (VDRE) in the promoter of the *CAMP* gene. Furthermore, it has been shown that low levels of 25-hydroxyvitamin D_3 in sera of African-American individuals, who are more susceptible to tuberculosis, correspond to lower induction of LL-37 in macrophages [23]. This indicates a connection between low LL-37 levels and susceptibility to tuberculosis and that vitamin D plays a key role in the production of LL-37, which kills the mycobacteria. We have recently shown that PBA and the active form of vitamin D act synergistically in inducing the expression of LL-37 [20], which might be utilized in therapy.

4.3. Lithocholic acid

More recently we have found that lithocholic acid (LCA) also induces antimicrobial peptide expression [24]. LCA has some characteristics of both butyrate and vitamin D_3 [25]. It is a bacterial product, like butyrate, made by bacteria from bile acid in the colon and it is a known ligand to VDR like vitamin D. LCA is known to bind the nuclear receptors; farnesoid X receptor (FXR), pregnane X receptor (PXR) and VDR. Our preliminary results indicate that by binding these receptors LCA can affect surface expression of innate defense-molecules in colon epithelial cells. FXR and PXR have so far mainly been linked to control of bile biosynthesis. Our findings indicate a role of these transcription factors in the communication axis with the native flora that is important for homeostasis in the gut.

5. Extension of the paradigm – novel therapeutic options

Globally there is a need to generate new antibiotics to overcome the problem with bacterial resistance that is spreading within hospitals and society. We are developing a novel strategy to combat infectious diseases by inducing AMPs with small molecules. The multiplicity of AMPs with different mechanism of action, including lysis of the pathogens is the key to restrict the development of resistant bacterial strains. AMPs are degraded in the gastrointestinal tract. Hence, prophylactic or therapeutic use would be based on induction of AMPs at epithelial sites. We have shown that butyrate, phenylbutyrate and phenylbutyrate together with vitamin D are compounds, which exhibit efficient inducing effects both *in vitro* and *in vivo* [12,20].

One major point of critique against therapeutic AMP-induction has been the risk of excess inflammation and tissue damage. However, recent evidence suggests that butyrate dampens intestinal inflammation via a G-protein coupled receptor (GPR43) on neutrophils [26]. Butyrate induces epithelial AMP expression and inhibits inflammation via separate effects on granulocytes. This fact may explain the favorable results of utilizing butyrate in experimental models of gastrointestinal inflammation and in shigellosis. Apart from shigellosis, a lack of AMP expression has been implicated in the pathogenesis of a number of clinical entities, such as cystic fibrosis, Crohn's disease and atopic dermatitis [27–29].

5.1. Regulation of innate responses via the Th17 pathway

An emerging concept is the connection of mucosal AMP expression to the T-cell compartment. The novel T-cell subset of Th17-cells has been shown to play a key role in orchestrating the epithelial immunity against extracellular pathogens [30]. Th17-cells reside in the submucosa where they become activated by dendritic cells and release IL-17 and IL-22. These cytokines bind to receptors on the basolateral side of epithelial cells, which secrete AMPs at the apical surface where the microbial attack occurs. Recently several primary immunodeficiencies in humans, including the hyper IgE syndrome, have been shown to depend on deficient Th17-cells [31–33]. Further, in HIV a rapid depletion of mainly Th17-cells occurs in the gut, which attenuates mucosal integrity and leads to translocation of bacterial components to the systemic circulation [34]. These components (LPS and bacterial DNA) have potent proinflammatory effects, which correlate with viral load and treatment status. Pharmacological depletion of T-cells, which is necessary to avoid acute rejection after transplantation also leads to a lack of Th17-cells [35]. We hypothesize that a lack of Th17-cells leads to deficient AMP expression at mucosal surfaces. If this hypothesis is correct, drugs with the capacity to induce epithelial AMP expression (butyrate, phenylbutyrate and vitamin D) could "by-pass" a deficient Th17-cell compartment.

In conclusion, we present here a novel concept where induction of endogenous antimicrobial peptides may be utilized in prevention and/or treatment of infectious diseases. Small molecule compounds such as vitamin D, butyrate, phenylbutyrate or lithocholic acid have the capacity to induce AMPs and thus strengthen mucosal immunity. Currently we are investigating several of these compounds against *Shigella*-infection, both in animal models and in clinical trials. We believe that the conceptual framework presented here also can be applied to additional clinical entities. Hopefully, this novel approach can be an alternative or complement to traditional antibiotics in the future.

The spread of bacterial resistance against conventional antibiotics is very rapid and there are already reports of "superbugs", being resistant to most – if not all – antibiotics. Thus, without novel strategies of combating infectious diseases a nightmare scenario might send us 200 years back in time to the birth of Karolinska Institutet. At that time there were no antibiotics and shigellosis was a great killer, both in the battle field and in the society. However, we hope that research at Karolinska Institutet and elsewhere may find ways to exploit our endogenous defenses to battle and balance the bacteria around us.

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