EXPERIMENTAL CELL RESEARCH 316 (2010) 1408–1414

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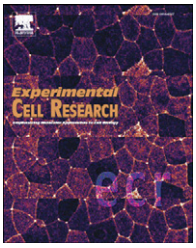

Review

Commensal pathogens, with a focus on *Streptococcus pneumoniae*, and interactions with the human host

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ARTICLE INFORMATION

Article Chronology:
Received 26 February 2010
Accepted 5 March 2010
Available online 19 March 2010

Keywords:
Commensal pathogens
Streptococcus pneumoniae
Host-pathogen interactions
innate immunity

ABSTRACT

Many important pathogens have humans as their normal ecological niche where healthy carriage dominates over disease. The ability of these commensal pathogens, such as *Streptococcus pneumoniae*, to cause disease depends on a series of microbial factors as well as of genetic and environmental factors in the human host affecting the clearing capacity mediated by the innate and adaptive immune system. This delicate interplay between microbe and host affects not only the likelihood for a commensal pathogen to cause disease, but also disease type and disease severity.

Contents

Introduction

Studies on bacterial pathogens and their ability to productively interact with its host and to subvert host defenses have in the past focused on primary pathogens such as the Gram-negative pathogens *Legionella*, *Shigella*, *Salmonella*, *Yersinia*, *Vibrio*, and the Gram-positive *Listeria monocytogenes*. These pathogens do not have humans as their normal habitat, even though asymptomatic carriers of these organisms can be found. Therefore, the ability of these pathogens to cause disease in man must have evolved in other ecological settings such as the marine environment. Indeed, genomic studies on marine organisms from the deep sea [1] reveal

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0014-4827/$ – see front matter
doi:10.1016/j.yexcr.2010.03.003

presence of many virulence-associated gene homologues found in primary pathogens of man, suggesting that these properties may have evolved as microbial tools to retrieve nutrients from marine eucaryotic cells. Studies on primary pathogens have over a 30-year period established a number of important paradigms for bacterial virulence such as the ability of the microbes to evade immediate innate immune defenses, to orchestrate the inflammatory responses, to enter through mucosal barriers, to deliver toxins and/or effector proteins into target cells that might either prevent or facilitate bacterial uptake into cells and facilitate their intracellular replication and survival [2,3].

Many of the most important bacterial pathogens in humans however may normally use humans as their ecological niche without causing any disease. This is certainly the case for *Helicobacter pylori* colonizing the stomach mucosa in up to 50% of the human population. Most *H. pylori* infections are asymptomatic, but infection is predisposing to peptic ulcer disease as well as to gastric cancer. *Escherichia coli* associated with upper urinary tract infections have genetic properties distinguishing them from the true commensal *E. coli* in the gut. Yet, uropathogenic *E. coli* are normally found as part of the human gut flora. *Streptococcus pneumoniae* (pneumococci) colonizes the nasopharynx in up to 60% of all healthy preschool children. Nevertheless, *S. pneumoniae* represents a most important bacterial killer among children below the age of five worldwide, and is also a frequent cause of morbidity and mortality among the elderly. Individuals with underlying diseases such as asthma, cancer, alcoholism, immunodeficiency/HIV, and preceding viral infections particularly influenza virus infection are particularly susceptible to pneumococcal infection. Indeed, current evidence indicates that co-infections with pneumococci during the worst influenza pandemic (1918–1919) were largely responsible for the 150 million deaths that occurred [4].

Tools required for bacteria to adapt and compete in its normal ecological niche may also give insights into the virulence of commensal pathogens

The nasopharynx of preschool children is often colonized by the three commensal pathogens *S. pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis,* as well as by the viridans group of commensal streptococci such as *Streptococcus mitis* that are genetically highly related to *S. pneumoniae* even though they rarely cause disease. An important issue is therefore to identify properties in commensal human pathogens that distinguish them from true commensals.

Colonization of mucosal surfaces by these commensal pathogens may be an initial event in the progression to disease, and it is often a transient process. There are several reasons why pneumococci successfully colonize the nasopharynx, a highly oxygen exposed region. For example, pneumococci like other Gram-positive firmicutes have adopted a special strategy to evade erroneous oxidation of the thiol groups in cysteine residues by excluding this amino acid from exported and cytosolic proteins allowing pneumococci to efficiently handle the oxidizing environment prevailing in the upper airways despite being catalase negative [5]. Another example is that the human mucosa contains a large amount of lysozyme with the ability to degrade the peptidoglycan of bacterial cell walls. However, pneumococci possess peptidoglycan modifying enzymes rendering its peptidoglycan resistant to human lysozyme [6]. Furthermore, pneumococci may also compete with other microbes in its habitat by producing high levels of hydrogen peroxide via a membrane bound pyruvate oxidase that may affect growth of more sensitive catalase negative organisms like *Staphylococcus aureus* [7]. At the same time the vast amounts of hydrogen peroxide produced may have toxic effects on certain types of human cells like $CD4^+$ T-cells (Littman et al, unpublished data).

Further examples on what makes pneumococci successful colonizers are that they are equipped with an arsenal of carbohydrate metabolizing enzymes such as three exoglucosidases that may allow retrieval of carbohydrates from the complex glycans present in the mucosa allowing bacterial growth, but also expose deep carbohydrate receptors for adhesion [8]. Moreover, pneumococci may express a number of adhesive properties believed to promote colonization of the nasopharynx, one being a pilus structure consisting of three subunit proteins joined together by pilus specific transpeptidases or sortases ([9] and Fig. 1). Of these three pilus proteins, RrgA is required to mediate adhesion to respiratory epithelial cells [10]. However, pilus-associated RrgA do not only mediate interactions with epithelial cells, but also with immune cells leading to an increased bacterial uptake. Pilus expression may therefore also be a property affecting bacterial virulence (Dahlberg et al, to be published). Also, pneumococcal adhesion to mucosal surfaces is impaired by the production of its thick antiphagocytic capsule. It has been known for some time that pneumococci isolated from the nasopharynx produce less capsule, and are more prone to form biofilms as compared to isolates from the blood stream. The actual mechanism for this transition, from growth as a colonizer in the nasopharynx to growth as a pathogen in sterile tissues and in the blood stream, is not known.

Human-specific interactions with commensal pathogens

As many commensal pathogens like the pneumococcus and the gastric pathogen *H. pylori* are human adapted microorganisms animal models have limitations even though they may reproduce important aspects of the human disease. Nevertheless, human adapted pathogens may recognize or subvert host receptors and host defense factors that are structurally or functionally different in humans and for example mice. Such well-known examples are host species restricted receptors on epithelial cells for bacterial adhesins and toxins. *H. pylori,* for example, expresses BabA adhesins recognizing fucosylated Lewis blood group antigens that are expressed by gastric epithelial cells of humans and primates but not mice [11,12]. Interestingly, also in the human setting variation in detailed binding specificities of BabA have evolved such that most *H. pylori* isolates express an adhesin that binds A, B, and O antigens, whereas the majority of strains coming from South American Amerindians express BabA variants that preferentially bind blood group O antigens reflecting differences in blood group expression among different ethnic groups [13].

Many bacterial adhesins and toxins recognize sialylated glycoconjugates. Thus, persistent *H. pylori* infection of the human stomach induces an inflammatory response in the gut mucosa that is associated with the formation of sialyl-Lewis x antigens that may be recognized by *H. pylori* Sab adhesins [14]. The most common sialic acid in nature is *N*-acetylneuraminic acid (Neu5Ac) [15]. However, Neu5Ac is in many vertebrates converted into *N*-glycolylneuraminic acid (Neu5Gc) by CMP-Neu5Ac hydroxylase (CMAH) [16], an enzyme that is highly conserved in nature. Intriguingly, unlike other primates this enzyme is inactivated in humans by a mutation [17].