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Pneumococcal pathogenesis: “innate invasion” yet organ-specific damage

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Abstract

Streptococcus pneumoniae encounters a variety of unique cellular situations during colonization of the nasopharynx or invasion into the lungs, the bloodstream, or the central nervous system. The ligand/receptor pairings that enable this progression of disease appear to be shared by many respiratory pathogens suggesting that a primitive “innate invasion” mechanism may underlie the well-known species-specific mechanisms of pathogenesis. That the acute phase of the innate immune response includes elements to interrupt this path supports this concept. However, it also appears that each cell type or organ responds differently to activation of this innate invasion pathway leaving some organs, such as the lung, intact post-infection but others, such as the brain, largely destroyed. This review posits a concept of innate invasion but cautions that organ-specific responses complicate opportunities for a simple approach to protect from organ damage.

Keywords

Pneumococcus; Innate immunity; Bacterial invasion; PAF receptor; Phosphorylcholine

Introduction

The pneumococcus, commonly harbored asymptotically in the nasopharynx, spreads to cause mucosal infections such as pneumonia, sinusitis, and otitis media and invades to cause devastating sepsis and meningitis. This pattern of disease is shared between the historically major pathogens of children, pneumococcus, meningococcus, and *Haemophilus influenzae*, raising the possibility of a shared mechanism for bacterial invasion that progresses through the lung to blood and brain. This review will present an argument for the existence of a common portal of invasion used by many respiratory tract pathogens, a portal that is guarded by the innate immune response but apparently subverted by what might be termed an “innate invasion strategy.” In this context, the well-known, highly variable, species-specific invasion mechanisms, such as those enabled by pili, can be seen to supplement and extend a

primitive, shared invasion mechanism. Despite an underlying similar host cell–bacterial interaction involving ligation of some of the same receptors in each tissue, surprisingly divergent subsequent cellular responses appear to create different damage reactions in infected organs. This is recognized clinically as the characteristic full recovery of the pneumonic lung to apparently normal architecture but irreversible damage sustained by the brain following meningitis.

Common doorway to invasion

The process of bacterial infection, be it in the blood or on a mucosal surface, involves bacterial adherence to host cell surfaces followed by cellular invasion. It would stand to reason that a successful invasion strategy would be broadly and positively selected for resulting in convergence of virulent pathogens onto a small number of vulnerable host receptors. This may be the case for two receptors present on the surface of many cell types, the 37/67 kDa laminin receptor (LR) and the platelet activating factor receptor (PAFr). In studying how pneumococci circulating in the bloodstream interact with the cerebral vascular endothelium to cause meningitis, Orihuela et al. determined that the bacterial adhesin CbpA bound to endothelial LR [1]. A surface-exposed loop of CbpA mediated binding, a loop distinct from that binding to the polymeric immunoglobulin receptor [2,3] and responsible for the translocation of pneumococcus across the nasopharyngeal epithelium [4]. CbpA binding to LR mediated bacterial adherence but not invasion. Importantly, LR was also targeted by *Neisseria meningitidis* and *H. influenzae* and antibody to CbpA crossreacted with and blocked adherence of these meningeal pathogens indicating a shared binding mechanism. LR has also been shown to mediate cell tropism for prions and several neurotropic viruses [5,6]. These findings suggest that a range of pathogens targets LR as a first step in the host pathogen interaction.

Once bound to a host cell surface, extension of disease to other organs requires bacterial dissemination through cellular barriers. The pneumococcus utilizes the interaction between G-protein-coupled PAFr and bacterial surface phosphorylcholine (PCho) to transit both the epithelium of the lung as well as the endothelium of the blood brain barrier [7]. This is a form of molecular mimicry where the PCho decorating the cell wall of the bacterium imitates the bioactivity of PCho on the natural ligand, the chemokine PAF. Subsequent studies indicated that meningococci and *H. influenzae* also display PCho on protein and lipid components of their surfaces, respectively, and interact with PAFr for invasion [8–10]. In all three cases, the amount of PCho on the bacterial surface is modulated by phase variation that in turn modulates bacterial invasion [11–13]. Display of cell surface PCho was further extended to many respiratory bacteria [14], even including myco-plasma. The importance of the interaction of bacterial PCho with PAFr to disease was demonstrated in mice lacking PAFr and in mice treated with PAFr antagonists, both of which proved resistant to progression of pneumonia to sepsis and meningitis [15,16]. This was further supported by studies where modulation or deletion of PCho expression on non-typeable *H. influenzae* or pneumococcus led to significant loss of adherence and invasion or a virtually avirulent phenotype [17,18]. Even the cellular location of PCho on bacterial components can determine pathogenic potential as evidenced by the finding that commensal strains of *Neisseriae*, while expressing PCho on LPS fail to decorate pili with this virulence determinant as do their pathogenic counterparts [19].

In addition to pneumococcus, *Haemophilus*, and meningococcus, many respiratory pathogens display PCho [20–23]. The fundamental importance of PCho–PAFr-directed pathogenesis is suggested by the existence of elements of the innate immune system directed toward preventing interactions with PAFr (Fig. 1). The acute phase response element C-reactive protein (CRP), which binds PCho and can be bactericidal in the presence of

complement, inhibits the PAFr/PCho interaction in vitro and in vivo [24,25]. Similarly, surfactant, which is rich in PCho, and antibody to phosphorylcholine are competitive inhibitors of ligand binding to PAFr and CRP in the lungs [26]. In this setup, innate invasion is counteracted by early response elements in innate immunity (Fig. 1).

Cellular signaling diversifies organ damage by infection

In response to bacterial components, PAFr is known to engender both G protein coupled and uncoupled cellular signaling involving a diverse array of downstream effectors [15]. Investigation of responses to PCho-containing pneumococcal cell wall in a variety of cell types illustrated that the same bacterial ligand host receptor pairing induced different patterns of responses in an organ-dependent fashion [27]. PCho cell wall was taken up into the cytoplasm and nucleus of neurons, cardiomyocytes, and endothelial cells (Fig. 2). This PAFr-dependent process did not trigger toll-like receptor (TLR)-2 or Nod-dependent activation of NF- κ B target genes as determined by micro-array analysis of stimulated cells [27]. PCho wall within endothelial cells induced ERK1/2 activation in a G protein-independent manner, while PCho wall within neurons and cardiomyocytes failed to activate ERK [27]. In contrast, epithelial cells did not take up PCho cell wall and strongly increased phosphorylation of ERK1/2 and activation of NF- κ B through G protein-mediated PAFr signaling. Thus, PCho/PAFr responses varied according to the location of the bacterial component inside or outside of the cell and the activation of ERK. These differences in turn were correlated with differences in cell survival (Fig. 2), indicating that different organs show variation in the impact on organ function of the innate invasion strategy.

A majority of the cell death during pneumococcal infection is the result of apoptosis, particularly in meningitis where both caspase-dependent and caspase-independent pathways lead to apoptotic death of neurons [28,29]. This apoptosis causes severe and permanent neuronal loss consistent with the severe neurological sequelae experienced by patients that survive pneumococcal meningitis which include hearing loss, seizures, cognitive defects, and motor deficits [30,31]. The picture of apoptotic organ damage is paralleled in the heart but not the lung. Cell wall accumulation in the heart causes a rapid and severe decrease in contractility of cardiomyocytes [27]. The pathophysiological consequences of this dysfunction are sufficient to cause death, an endpoint reversible by PAFr antagonists. In contrast, epithelial cells of the lung fail to take up cell wall and remain healthy, a finding consistent with the return of the pneumonic lung to normal architecture post-infection.

PCho/PAFr and inflammation

It is well known that interaction of bacterial subcomponents with TLRs induces a spectrum of inflammatory responses that underlies most bacterial infections. Recent evidence suggests cross talk between TLRs and PCho/PAFr pathways. The role of TLR2 can be extended to bacterial invasion by a process involving p38 and TGF- β signaling that results in migration of pneumococcus and *H. influenzae* between cells in the lung [32]. On the other hand, the role of PCho can be broadened into the inflammatory response to cell wall components engendered by TLRs [27,33]. Cell wall-induced inflammation required PCho as replacement with ethanolamine strongly dampened inflammation. In one model (Fig. 3), large cell wall fragments bearing PCho on teichoic acids ligate PAFr, while peptidoglycan devoid of PCho and teichoic acid binds to TLRs and smaller muramyl peptides bind to NOD proteins. Thus, the size and decoration of a bacterial component influences both the inflammatory response as well as bacterial trafficking.

Conclusion

A number of significant pathogens have been found to sustain disease progression from the lung to other organs by following a common receptor-mediated route of invasion. Elements of the acute phase response are directed at interrupting this pathway setting up an “innate invasion vs innate immunity” dynamic. This basic mechanism is supplemented by the many diverse ligand/receptor strategies that also contribute to invasion in a species-specific fashion for each pathogen. Despite ligating a limited number of receptors expressed broadly in many organs, this simple pathway engenders cell-specific downstream signaling events leading to very different responses in various organs. This is particularly evident for PAFr and has clinical implications. Investigation into why the PCho/PAFr signaling pattern in lung preserves pulmonary structure and function post-infection may indicate strategies to change signaling in the brain and heart and improve outcome in those organs that fail to heal.

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Innate Invasion vs Innate Immunity

Fig. 1. Innate invasion versus innate immunity. Schematic representation of pneumococcal cell wall (green with blue teichoic acid) containing PCho (blue circles on teichoic acids) interacting with PAFr (yellow waves) on eukaryotic cells (tan). This innate invasion interaction is counteracted by innate immune defenses such as C reactive protein (orange arcs) and high PCho-containing surfactant (blue ovals)

Fig. 2.

Organ-specific cell signaling engendered by PCho cell wall binding to PAFr. PAFr can mediate signaling with or without G protein activation. Epithelial cells are distinguished by G protein activation, no cell wall uptake, activation of ERK, and survival of the cell. Cardiomyocytes, neurons, and endothelial cells take up cell wall without G protein activation. Absence of ERK activation in heart and neuron is associated with cell death

Fig. 3.

Schematic model of interaction of PCho cell wall with proinflammatory cascades. Intact PCho-containing cell wall binds to *PcFr* and is taken up into many cell types and causes various host cell responses. Simpler peptidoglycan lacking PCho binds to *TLR2* while muramyl peptides ligate *NOD* proteins. This creates a hierarchy of responses to cell wall components based on size and PCho decoration. Asterisk PCho moiety; plus sign and; minus sign presence or absence of inflammatory activity (see [21])