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Spotlight

How BspC from *Streptococcus agalactiae* Interacts with Host Vimentin during Meningitis

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***Streptococcus agalactiae* meningitis is a frequent neonatal disease associated with high mortality and permanent neurological damage. Deng *et al.* (*PLoS Pathog.*, 2019) now show that interactions between the bacterial protein BspC and host cell vimentin participate in the process of invasion of the meninges by this bacterial pathogen.**

Before the late 1960s *Streptococcus agalactiae* (group B *Streptococcus* or GBS) was almost exclusively known as a cause of mastitis in cows, since invasive infections in humans were rarely reported. By the 1980s, however, GBS had rapidly emerged as the main agent of sepsis and meningitis in neonates, due to the global diffusion of bacterial lineages with an increased ability to colonize human tissues and to cause disease. Today, GBS disease continues to increase in incidence, affecting a wider range of age groups and exhibiting a more diverse spectrum of clinical presentations, including skin, soft tissue, bone/joint, heart valve, and urinary tract infections [1]. Meanwhile, the incidence of GBS disease in neonates aged between 7 and 90 days (i.e., 'late onset' disease) remains high, and meningoencephalitis persists as a frequent cause of mortality and permanent neurological impairment in this age group. The development of novel methods to prevent the disease requires better understanding of the mechanisms by which blood-borne GBS breaches the blood–brain barrier (BBB). The latter is predominantly made up of specialized endothelial cells (brain microvascular endothelial cells, or BMECs) that are sealed together by tight junctions and form the wall of small blood vessels. Adherence of GBS to the endothelium, which is a first and necessary step in breaking through the BBB, is the end result of numerous interactions between bacterial surface proteins and their cognate BMEC receptors (Figure 1). These receptors consist primarily of extracellular matrix components such as plasminogen, fibrinogen, and fibronectin, present on the BMEC surface. Several GBS proteins, including fibrinogen-binding proteins (e.g., Srr1/2 and FbsC), the plasminogen-binding protein PbsP and the fibronectin-binding protein SfbA, were shown to play nonredundant roles in brain invasion by GBS, using experimental meningitis models [2–6].

These nonredundant players in the neurotropism of GBS are now joined by a 'new kid on the block', the Antigen I/II (AgI/II) family protein BspC, as reported by Deng *et al.* in a recent article [7]. They find that deletion of the *bspC* gene impairs the ability of GBS to adhere to BMECs *in vitro*, and to infect the brain in a murine model of meningitis. Notably, it was found that BspC enables GBS to exploit vimentin, a new target for these bacteria, on the surface of BMECs. Mice lacking vimentin were less susceptible to GBS-induced meningitis and exhibited less inflammation in the central nervous system, in association with lower levels of proinflammatory cytokines. Moreover, BspC interacts directly with vimentin, as shown by Deng *et al.* using a number of elegant techniques such as bidimensional far-western blot, immunofluorescence, thermophoresis, and a bacterial two-hybrid system [7]. This study is important because it shows a unique requirement for vimentin in the pathogenesis of GBS meningitis. It is intriguing that other frequent agents of neonatal meningitis, such as *Escherichia coli* K1 and *Listeria monocytogenes*, also highjack vimentin to promote their pathogenesis, as found in previous studies [8,9]. Vimentin is present in the cytosol of mesenchymal cells (e.g., endothelial cells, phagocytes, and platelets, but not epithelial cells) as a major constituent of the type III intermediate filaments that participate in cytoskeleton formation. Besides its intracellular location, vimentin can be expressed on the cell surface of mesenchymal cells where it can function as a receptor for a wide variety of bacterial and viral pathogens [10]. A crucial question in the pathogenesis of neonatal meningitis is how adherence to vimentin on the luminal side of BMECs enables bacterial pathogens to cross the endothelial layer. After adhering, pathogens can be internalized by BMECs and transmigrate within membrane-bound vesicles to the brain interstitium by exploiting the physiological process of transcytosis. In the Deng *et al.* study it is noteworthy that BspC–vimentin interactions clearly promoted adherence of GBS to BMECs, but not bacterial invasion of these cells. This is at variance with findings with *E. coli* and *L. monocytogenes* that suggest a major role for vimentin in bacterial internalization by BMECs [8,9]. It is possible that this discrepancy is linked to differences in the molecular regions of vimentin targeted by *E. coli* and *L. monocytogenes*, on one hand, and by GBS BspC on the other [7]. A growing number of novel functions of this protein are attracting attention, including its ability to influence the organization and expression of other surface molecules [10]. It is likely that vimentin acts initially to support bacterial attachment to facilitate the subsequent recruitment of other adhesin/receptor systems mediating internalization, such as those involving extracellular matrix proteins [2–6]. Future studies are needed to clarify this point and to identify more precisely the mechanisms by which vimentin promotes crossing of the BBB by GBS.

Interestingly, Deng *et al.* also note that BspC–vimentin interactions can lead

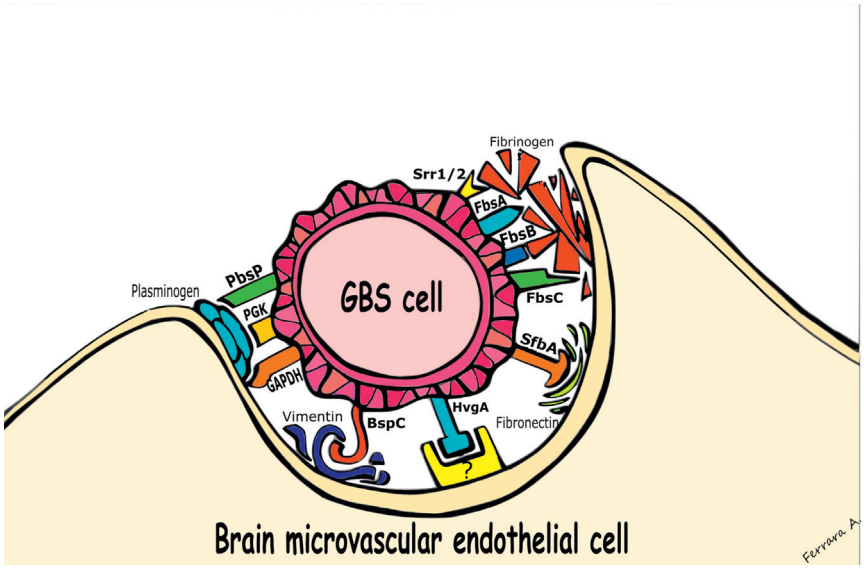

Figure 1. Interactions between Receptors on Brain Endothelial Cells and Cell-Wall Adhesins of *Streptococcus agalactiae* (GBS). Abbreviations: BspC, group B *Streptococcus* surface protein C; FbsA, FbsA, FbsC, fibrinogen-binding surface protein A, B, C; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; HvgA, hypervirulent GBS adhesin; PbsP, plasminogen-binding surface protein; PGK, phosphoglycerate kinase; SfbA, streptococcal fibronectin-binding protein A; Srr1/2, serine-rich repeat proteins 1 and 2.

under certain circumstances to immune signaling, resulting in activation of NF-κB and the production of neutrophils attracting chemokines CXCL-1 and interleukin (IL)-8. This is an intriguing observation that deserves further investigation, particularly in view of the ability of vimentin to activate the ERK kinase pathway, as shown in a previous study using *E. coli* [8]. The authors note that proinflammatory cytokine/chemokine levels are lower in the brains of mice infected with a GBS *bspC* deletion mutant, but the interpretation of these data is difficult since they might simply reflect the lower bacterial load in the organs. Similarly, the slightly lower chemokine levels observed in BMEC cultures stimulated with the *bspC* deletion mutant might reflect the lower number of cell-associated bacteria. Also, the doses of recombinant BspC used to stimulate cells *in vitro* is rather high (10–20 mg), and further investigations are warranted to ascertain whether these concentrations are attainable in the proximity to immune cells *in vivo*. Despite these limitations, the new data raise important questions on the role of vimentin in innate immune responses against GBS.

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https://doi.org/10.1016/j.tim.2019.07.001

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Forum

Fluidic Force Microscopy Captures Amyloid Bonds between Microbial Cells

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Fluidic force microscopy (FluidFM) is a recent force-controlled pipette technology that enables manipulation of single cells. FluidFM can be used for quantification of forces between single cells, and a novel mode of cell–cell adhesion was uncovered: amyloid-like interactions that mediate homophilic adhesion in the fungal pathogen *Candida albicans*.

Single-Cell Manipulation of Pathogens

Single-cell microbiology is a fast-growing research field. It uses single-cell manipulation tools for studying the behavior of individual cells to unravel cellular properties and interactions in an unprecedented manner. The past decade has witnessed exciting progress in the use of atomic force microscopy (AFM) for single-cell