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The role of microbial polysaccharides in host-pathogen interaction

David Corbett and Ian S Roberts*

Address: Faculty of Life Sciences, University of Manchester, Michael Smith Building, Dover Street, Manchester M13 9PT, UK

* Corresponding author: Ian S Roberts (i.s.roberts@manchester.ac.uk)

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Abstract

Bacteria are capable of expressing a diverse range of cell surface polysaccharides from capsules and lipopolysaccharides through teichoic acid molecules to lipoarabinomannans. This review will focus on the expression of capsular polysaccharides and their interaction with the host. In particular, it will focus on the role of capsular polysaccharides as immunomodulatory molecules.

Introduction and context

The polysaccharide capsule coats the outside of the bacterial cell and as a consequence plays an intimate role in mediating interactions between the bacterium and its immediate environment. A capsule is a discrete structure that is defined as a layer of polysaccharide that either is physically attached to, or remains tightly associated with, the cell surface of the bacterium. This is in contrast to slime, which has a loose association with the surface of the bacterium and often is shed in large amounts into the surrounding environment.

Major recent advances

Capsules and interactions with the host

From the pioneering experiments of Griffith on encapsulation in pneumococci [1] there is a considerable body of data indicating that encapsulation is an absolute requirement for effective systemic infection by human and animal pathogens [2]. For many years, the perceived role of the capsule in these diseases was resistance to host innate defences, in particular resistance to complement-mediated killing and phagocystosis [3–5]. Recent studies have indicated that, in both cases, the capsule is predicted to function as a shield masking underlying cell surface structures [6]. As such, encapsulation reduces both the generation and effectiveness of the membrane attack complex and the level of opsonisation. In addition, terminal sialic acid residues on the capsular polysaccharides of group B streptococci (GBS) have been shown to mediate interactions with sialic acid-binding immunoglobulin-like lectins (Siglecs) on the surface of neutrophils and monocytes [7]. This interaction is dependent on the extent of O-acetylation of the sialic acid [7]. Engagement of Siglecs on the cell surface of leukocytes is believed to suppress T-cell signalling [8] and natural killer cell toxicity [9]. As such, the interaction between sialic acids on the GBS capsule and Siglecs could represent an interaction between the microbe and the host which effectively dampens down both the innate and adaptive immune responses.

Capsules have also been shown to be essential for efficient adhesion to host cells. The adhesion of group A streptococci to pharyngeal cells is mediated via the interaction between the hyaluronic acid capsule and CD44, the hyaluronic acid-binding protein [10]. This interaction between microbe and host induces a signalling pathway that promotes the efficient paracellular penetration of the mucosal epithelial layer and invasion of the underlying tissue [10]. Similarly, both the *Escherichia coli* K1 capsule and the *Neisseria meningitidis* group B capsule have been shown to be important in intracellular survival and as such may be important in traversing epithelial and endothelial barriers [11,12].

Capsules as signalling molecules

While capsules undoubtedly function in a shielding capacity to resist innate defences, there is increasing evidence that capsular polysaccharides may possess immunomodulatory activities. These properties

moderate the local inflammatory response of epithelial cells in order to maximise bacterial colonisation, as well as affecting leukocyte activation to promote the survival of bacteria within the host. This is perhaps not surprising considering the location of capsular polysaccharides on the outermost surface of the bacterial cell. There are several examples of the immunomodulatory effects of purified capsular polysaccharides from a range of pathogenic organisms. In the case of *Staphyloccocus aureus*, both capsular polysaccharide types 5 and 8 were able to bind to epithelial cells and induce interleukin (IL)-8 expression in addition to inducing IL-8, IL-6, IL-1β, and tumour necrosis factor-alpha from monocytes [13]. It was proposed that these capsular polysaccharides were acting as adhesins to promote attachment to epithelial cells whilst at the same time expressing immunomodulatory effects [13]. Likewise, the purified type 2 capsular polysaccharide of *Streptococcus suis* has been shown to induce monocyte chemoattractant protein-1 (MCP-1) production from monocytes via a TLR2/MyD88 (Toll-like receptor-2/myeloid differentiation factor-88)-independent pathway [14]. The serotype K1 capsular polysaccharide from the oral pathogen *Porphyromonas gingivalis* also elicits MCP-1 secretion, as well as MIP-2 (macrophage inflammatory protein-2) and RANTES (regulated on activation, normal T-cell expressed and secreted) from murine macrophages. It has also been shown to stimulate macrophage migration [15]. The ability of the purified K1 capsular polysaccharide to induce inflammatory chemokines would suggest that the capsular polysaccharide is involved in generating the inflammatory lesions typical of periodontal disease as a consequence of *P. gingivalis* infection [15].

In contrast, in *Salmonella enterica* serovar Typhi (*S. typhi*), the Vi capsular antigen reduces TLR-dependent IL-8 production from intestinal mucosa [16] and IL-17 secretion [17]. This indicates that in this case the Vi antigen is acting to reduce intestinal inflammation, possibly playing a role in reducing the influx of neutrophils to the site of infection and thereby promoting the increased survival of *S. typhi* [16,17]. Indeed, it has been speculated that the Vi capsule may contribute to the evasion of the adaptive immune response by disrupting TLR signalling [18]. Most strikingly, the purified polysaccharide A from the gut symbiont *Bacteroides fragilis* has been shown to have potent anti-inflammatory properties [19]. Administration of the polysaccharide was capable of preventing inflammatory disease in mice infected with *Helicobacter hepaticus* [19]. This anti-inflammatory response required IL-10-producing $CD4^+$ T-cells and demonstrates how a cell surface polysaccharide could be playing a key role in mediating microbe-host interactions and preventing the induction of an inappropriate inflammatory response as a consequence of the colonisation of a gut symbiont [19]. Therefore, it is clear that certain capsular polysaccharides may be endowed with potent immunomodulatory properties above and beyond any role they may fulfil in either shielding the bacterium or promoting adhesion.

Future directions

The role of capsular polysaccharides as signalling molecules in contributing to the interplay between microbe and the host puts a new perspective on the age-old question of capsule diversity. A big question that remains unanswered is what drives capsule diversity in an organism such as the pneumococcus. One possibility is that chemically diverse capsular polysaccharides will interact differently with the host in terms of chemokine/cytokine induction. This interaction could range from neutral (no induction) to either end of the inflammatory spectrum. As a consequence, the expression of different capsular polysaccharides may induce a different dialogue between the microbe and the host, in which case, different capsular polysaccharides may confer a selective advantage in different human hosts, depending on the local mucosal environment they encounter. It is important to remember that, with many bacterial pathogens, disease is the atypical state and is a result of an imbalance in the fine interplay with the host. Continued colonisation and the quiet life of the commensal are often the goal, and it is possible that capsular polysaccharides play important roles in maintaining the dialogue between host and microbe and in stabilising this equilibrium. When considering the interaction between capsular polysaccharides and the host, the level and regulation of *in vivo* expression of capsules will be vital, and understanding this is an exciting challenge.

Capsular polysaccharides have long been used as effective vaccine candidates. However, the observation that capsular polysaccharides have immunomodulatory properties offers the opportunity to use purified capsular polysaccharides as pharmacological agents to intervene in and manipulate the host response in a range of disease scenarios. The huge diversity of capsular polysaccharides in the microbiome offers a route to engineer polysaccharides with the desired pharmacological properties.

Abbreviations

GBS, group B streptococci; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MIP-2, macrophage inflammatory protein-2; MyD88, myeloid differentiation factor-88; RANTES, regulated on activation, normal T cell expressed and secreted; *S. typhi*; *Salmonella*

enterica serovar Typhi; Siglecs, sialic acid-binding immunoglobulin-like lectins; TLR, Toll-like receptor.

Competing interests

The authors declare that they have no competing interests.

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