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Review

The food glycome: A source of protection against pathogen colonization in the gastrointestinal tract

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ABSTRACT

Trillions of microbes inhabit the gastrointestinal tract of humans with significant differences in the composition and distribution of intestinal flora along its length. Normally there is a symbiotic relationship between the intestinal microflora and the host, with mutual advantages for both partners. When this relationship is altered, commensal bacteria can rapidly shift toward pathogenicity resulting in the onset and progression of gastrointestinal infection. Pathogen adhesion and colonization is often a prelude to infection, and intervention at this early stage can help prevent disease. Bacteria have evolved a multitude of adhesion mechanisms commonly targeting surface carbohydrate structures of the host. Here, we review the ability of various dietary carbohydrates to prevent adhesion of pathogens to host cells. Given their significance in disease, and their ability to cause chronic infection, we have focussed on 3 model pathogens, *Helicobacter pylori*, *Campylobacter jejuni* and *Clostridium difficile*, and dietary carbohydrates which can inhibit their adhesion. The discovery of novel anti-adhesive dietary carbohydrates, once developed as nutraceutical ingredients, may serve as a novel method for preventing infectious diseases in the human gastrointestinal tract. Anti-adhesive carbohydrates used in this context are not bactericidal. Therefore, the spread of pathogens with resistance to antibiotics is less likely to occur.

Contents

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1. Introduction

The intestinal immune system is the largest and most complex part of the immune system. Not only does it encounter a larger number of antigens than any other part of the body, but it must also distinguish between pathogenic organisms and harmless antigens, such as food components and commensal bacteria (Mowat, 2003). The intestinal epithelium is a composite of three barriers: a physical barrier, an innate immune barrier and an adaptive immune barrier. However, the barrier formed is not absolute, and crosstalk occurs between the microorganisms in the supramucosal environment and the mucosal tissues (Sansonetti, 2004). In terms of the physical barrier, the epithelium maintains its selective barrier function through the formation of complex protein–protein networks that mechanically link adjacent cells and seal the intercellular space (Groschwitz and Hogan, 2009). Two main structural components are essential: the microvilli of the brush border and the tight junctions. Microvilli are associated with a dense meshwork of actin filaments which are linked to a protein complex, known as an adherens junction, between the intestinal epithelial cells. This protein–protein network can function to regulate the permeability of the tight junctions and the barrier function of the epithelium (Sansonetti, 2004). In addition, the physical barrier is reinforced by the presence of a glycocalyx on the surface of the intestinal cells, which is comprised largely of membrane-associated glycoproteins and glycolipids. The glycocalyx is constantly renewed, maintaining a viable barrier. It is capped by, and integrated with, a secreted mucus gel: the properties of which depend on highly glycosylated secretory proteins known as mucins (Patsos and Corfield, 2009). The glycans of the glycocalyx participate in many crucial biological processes such as cell–cell and cell–matrix interactions, adhesion, signalling, differentiation and development (Gornik et al., 2006). Their location on the apical surface of the epithelial cells, permit them to serve as identification molecules for microbial recognition. Thus, the glycosylation patterns on human cells can in some cases determine whether harmless or pathogenic bacteria colonize the host. Similarly, the glycans of mucins can serve as decoys for these ligands, controlling access to those present on the glycocalyx (Carrington et al., 2009). Microbial recognition of host glycans occurs through a variety of microbial lectins. These are glycan-binding proteins with no catalytic activity that are present on the bacterial cell surface: often as submicroscopic multisubunit surface appendages known as fimbriae or pili. Such lectins can also be released by microbes in soluble forms.

Upon colonization, commensal bacterial populations make a number of key contributions to host health, including enhancing digestive efficiency, promoting immune system development, and limiting pathogen colonization. Indeed, it has been shown that biofilms consisting of mixed consortia of commensal bacteria attached to the gut epithelia form a protective barrier against food-borne pathogens (Lindsay and von Holy, 2006). In return, resident microorganisms derive benefit from association with their hosts by inhabiting a protected, nutrient-rich environment. Thus, these host-microbial associations constitute a mutually beneficial symbiosis (Duerkop et al., 2009). Conversely, enteric pathogens use virulence factors to subvert host defences and may then invade host tissues, to cause inflammatory destruction of the intestinal epithelium. The major mechanisms of innate defence against pathogens are gastric acidity, pancreatic enzymes and bile, intestinal motility and the mucin layer, the mucosal-epithelial barrier, blood group factors, competitive exclusion by microflora, pattern recognition receptors (PRRs) on the epithelial cells and secreted antimicrobial peptides such as lysozyme and defensins (Muller et al., 2005). Although innate mechanisms are adequate in protecting the gut in most cases, the memory of the adaptive immune system enables pathogens to be eradicated more specifically upon subsequent exposures. Secretory IgA functions to reduce the density of surface-associated bacteria (Suzuki et al., 2004) and restricts their transport across the gut epithelium (MacPherson et al., 2000). IgA is produced with the help of antigen presenting dendritic cells that sample bacteria at various mucosal sites, commonly Peyer's patches. By sampling the mucosal surface, the adaptive immune system can accurately control the density and perhaps the make-up of surface-associated bacterial populations (Duerkop et al., 2009). Many common virulence factors associated with intestinal pathogens have allowed the adaptation of these pathogens to the harsh environment of the GIT. Such factors allow pathogens to overcome barriers such as the acid environment of the stomach and the presence of competing microbes. The production of bacterial toxins and enzymes, which are then secreted into the extracellular environment, and the presence of lectins, are both examples of such adaptations.

It can be predicted that soluble glycans or host glycan mimics could be used to block the initial attachment of microbes and toxins to cell surfaces. Thus, preventing or suppressing infection (Gornik et al., 2006). Before the use of such anti-adhesive glycans can become a reality, a greater understanding of the pathogenic cycle of some bacterial species will be required. In particular, the identification of bacterial adhesins, colonization factors and the role played by secreted bacterial products are a priority. Indeed, the identification and characterisation of anti-adhesive food glycans may in turn facilitate the identification of previously undiscovered virulence factors. This review will focus on the role that food-based carbohydrates or glycans could have in preventing chronic colonization by pathogens and downstream pathology. Given their prevalence and ability to cause chronic infection, we have focussed on 3 model pathogens, *Helicobacter pylori*, *Campylobacter jejuni* and *Clostridium difficile*.

2. Bacterial colonization in the gastrointestinal tract

In the weeks after birth, the type of feeding is thought to be the major factor influencing the intestinal flora of the human infant (Coppa et al., 2004). Several studies suggest that bifidobacteria and lactobacilli constitute up to 90% of the microflora in breast-fed infants, while bottle-fed infants develop a more diverse microflora with a lower number of bifidobacteria (40–60%) and the presence of potential pathogens such as *Clostridium*, *Staphylococcus* and *Bacteroides* (Benno et al., 1984; Moreau et al., 1986; Balmer and Wharton, 1989; Millar et al., 1996; Harmsen et al., 2000; Favier et al., 2002). However, at any age, the resident microflora can be replaced by transient and often pathogenic microflora acquired from the external environment. The factors associated with alteration in the permanent flora include infections, local inflammation, malnutrition, immunosuppression, antibiotics, chemotherapy, radiotherapy, stress, and significant changes in dietary habits (Ogra, 2009). It is well documented that crosstalk between the mucosal surface and resident and invading bacteria occurs. Indeed, beneficial gut microflora are involved in gut development, through the formation of a submusosal microvascular networks, and nutrient sharing (Gordon et al., 2003). In addition bacterial binding is influenced by crosstalk as changing patterns in mucosal surface protein glycosylation can alter receptor sites on host tissues.

It is now accepted that mucosal surface adherence of enteric bacteria is required for colonization and subsequent development of disease. When in the adherent state, these bacteria are more likely to survive as their resistance to cleansing mechanisms, immune factors, bacteriolytic enzymes and antibiotics is higher (Ofek et al., 2003). Bacterial surface components that mediate adherence are collectively known as adhesins (Moran et al., 2009). Several bacterial species utilise specific adhesins, or proteinaceous lectins, that bind glycan structures on the surface of host tissues to facilitate attachment in the GIT tract. In general bacterial lectins have a low affinity for their carbohydrate receptor but compensate for this by using fimbriae to