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Visions & Reflections

A bright future for anti-adhesion therapy of infectious diseases

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The alarming increase in drug-resistant bacteria makes imperative a search for novel means of fighting bacterial infections. One attractive possibility is the use of agents that interfere with the ability of bacteria to attach or adhere to the tissues of the host, adhesion being a prerequisite for infection [1, 2]. The validity of this approach has been unequivocally proven in experiments in a variety of animals, from mice to monkeys, and recently also in humans [3]. Because anti-adhesive agents are not bactericidal, the propagation and spread of resistant strains is less likely than when using bactericidal agents such as antibiotics.

Adhesion of many infectious bacteria is mediated by surface lectins in the form of submicroscopic multisubunit organelles designated as pili or fimbriae, with distinct carbohydrate specificities. For adhesion and resultant infection, the sugar(s) recognized by the lectins should be present on the target cells. This is nicely illustrated by *Escherichia coli* K99 that is specific for *N*-glycolylneuraminic acid [4]. The latter sialic acid is found on intestinal cells of newborn piglets, but is replaced by *N*-acetylneuraminic acid when the animals develop and grow. It is also not formed normally by humans, explaining why *E. coli* K99 can cause diarrhea (often lethal) in piglets, but not in adult pigs or in humans.

That sugars could block adhesion and thus prevent infection was first demonstrated by us more than two decades ago [5]. Infection of mouse bladders with a strain of *E. coli* that expresses mannose (type 1) fimbriae was markedly diminished by presuspension of the organism in a solution of methyl α-mannoside, but was not affected by glucose, a sugar to which the bacteria do not bind. These findings have provided an impetus for attempts to develop carbohydrate-based anti-adhesive drugs for the prevention and therapy of microbial infections. Saccharides are eminently suitable for this purpose. They are unlikely to be toxic or immunogenic, in particular since many of those that inhibit adhesion are normal constituents of cell surfaces or body fluids. In a variety of animals, including rats, guinea pigs, monkeys, and calves in addition to mice, experimental infection by different bacteria was prevented by specific sugars [3]. Significantly, sugars have been used in rhesus monkeys infected with *Helicobacter pylori*, the causative agent of gastric ulcer in humans. Of six *H. pylori*-infected monkeys that were treated with sialyllactose (NeuAcα2,3 Galβ4Glc), a cell surface saccharide for which certain strains of this organism have an affinity, two were cured permanently, and a third was transiently cleared, although three of the animals remained persistently colonized [6]. The limited degree of protection achieved in this study may reflect the need for additional receptor analogs to inhibit the multiple adhesins produced by *H. pylori*, preferably in combination, or presented in multivalent form on suitable carriers.

The use of single, low-power sugar inhibitors may also explain the failure of the two clinical experiments with

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such inhibitors carried out to date. In one of these, sialyllactose administered by nasal spray for 3 months failed to reduce the incidence of nasopharyngeal colonization with *Streptococcus pneumoniae* and *Haemophilus influenza* and acute otitis in children [7].

In addition to the sialic-acid-specific adhesin, these pathogens produce other adhesins with distinct receptor specificity, and preventing their ability to colonize the respiratory tract may require a cocktail of adhesion inhibitors.

Anti-adhesive sugars, in addition to blocking the attachment of the bacteria to tissues, act similarly on the binding of toxins such as those of *Shigella dysenteriae* type 1, or of the homologous verotoxins of *E. coli*, all of which are Galα4Gal specific. In this system, polyvalent inhibitory sugars, when appropriately designed, were markedly more inhibitory than monovalent ones; while the latter were active at the millimolar level only, the former were active at the nanomolar level [8].

Bacterial adhesion may be mediated by means other than lectin-carbohydrate interactions, e.g., hydrophobically [1]. It is not surprising, therefore, that non-carbohydrate compounds can also be anti-adhesive. A well-studied case is cranberry juice, from which a high-molecular-weight inhibitor of adhesion has been isolated. The material, which is tannic acid like, inhibits the adhesion of P fimbriated, galabiose-specific *E.coli*, and of sialic-acid-specific *H. pylori* to human epithelial cells, as well as the coaggregation of many oral bacteria [9, 10]. Strikingly, in two independent clinical trials, one in old volunteers [11] and the other in young women [12], consumption of the juice over a period of several months reduced by about one-half the incidence of urinary tract infection caused by *E. coli*. Furthermore, in a study we recently carried out in collaboration with Erwin Weiss and his colleagues from the School of Dentistry, daily rinses with mouth wash supplemented with the high-molecular-weight material from cranberries significantly reduced the salivary counts of *Streptococcus mutans*, the major cause of dental caries [13].

The future of anti-adhesion therapy depends on the development of a combination of powerful inhibitory carbohydrates each targeted to a distinct bacterial surface lectin, and of the finding of non-specific inhibitors, preferably of dietary origin, that target a number of adhesins at the same time. Once such compounds become available, they might become the drugs of choice for the management of infectious disease.

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