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Initial host-pathogen interactions explained by the Organism Prearranged Recognition Theory: fundamental role of saccharides

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Luz P Blanco contributed to this work in her personal capacity. The views expressed are her own and do not necessarily represent the view of the National Institutes of Health or the US Government.

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Abbreviations

OPRT, organism prearranged recognition theory; LPS, lipopolysaccharide.

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Abstract

Herein based on literature available a hypothesis is provided about molecular basis for initial events in establishment interactions. This hypothesis asserts that: "recognition and interaction that occur between organisms is prearranged. There are membrane receptors with or without soluble components derived from the respective organisms that bridge specific interactions". Organisms' prearranged recognition theory (OPRT) can be specifically applied to host-microbe interactions where most microbes are coated (opsonised) by soluble components (opsonins) from the host, but there are also some microbes that can bypass host opsonization expressing receptors for the host cells or secreting host's opsonin-like molecules. The receptors involved in organism's interactions, their specificity and repertoire depend on saccharides from glycoproteins, glycolipids, and polysaccharides (glycans) which are abundant extracellular components. Based in OPRT is possible to explain species-specific interactions and several other phenomena, such as hyper-infectivity, tissue tropism, differential sensitivity to disease depending on type O-blood, and tumoral cell promiscuity. The lipid raft domain in cellular membrane is proposed as the main location where interactions will trigger cellular responses. Possible scientific and biotechnology applications and alternative routes to modify organism's interactions and consequences are discussed. It is a novel hypothesis regarding the degree to which an organism's interactions are prearranged and the role of saccharides epitopes.

Keywords: Species-specificity; saccharides; extracellular-matrix; host-pathogen; antibodies

Main

Here it is presented a hypothesis regarding the degree to which an organism's interactions are prearranged. I have deduced initially OPRT from my studies with *Vibrio cholerae*, which is a human species-specific pathogen [1]. The main virulence factor of this pathogen is cholera toxin, the host receptor of which is the ubiquitous glycosphingolipid ganglioside GM1. The ganglioside GM1 has the same structure in different species, but only humans are sensitive to *V. cholerae* infection and especially O-blood type subjects [2]. Therefore, I proposed that a *Vibrio cholerae* toxin/microbe-GM1 bridging molecule exists in the human intestine that is missing in other species but is present more abundantly in the more sensitive blood type O individuals, allowing *V. cholerae* to colonize and to produce the cholera disease. The O-blood group people do have antibodies against A and B blood group antigens (which are saccharides). These antibodies could serve as bridging or special opsonins for *Vibrio cholerae* microbe/toxin interaction with GM1, making O-blood subjects more sensitive to cholera disease than other blood groups.

Previously it has been demonstrated that type O-blood group antigen in host cells is unable to directly interact with cholera toxin better than A or B blood group antigens can [3]. However, nonimmune human antibodies (sIgA or IgG), which are glycoproteins from healthy non-immunized people, recognize *V. cholerae* and the cholera toxin and also interact with GM1 as I have formerly described [1]. It is possible therefore, to envision these antibodies act as host opsonins that bridge the microbe/toxin interaction with the host cells.

Besides cholera disease, infections with Norwalk virus [4], *Escherichia coli* O157 [5], and *Helicobacter pylori* [6] are found more frequently in type O-blood group subjects (for in depth review in this matter see Cooling, 2015 [7]). Type O blood group people have antibodies against the A and B saccharide antigens that cross-react with microbial and viral envelope saccharide epitopes [8], giving type O-blood group antigen individuals more opportunities to interact with different organisms or to enhance interactions with those that are prearranged or express the right receptors. Other examples of antibody- enhancing interactions involve IgG and IgE, which can have a role in antigen-sampling through the epithelial barriers; particularly critical is the role of lumenal IgE in people with food hypersensitivity [9] and in pregnancies where non-immune IgG enhances infection of placental erythrocytes with *Plasmodium falciparum* [10].

Most humans at 6 months of age have cross-reactive anti-GM1 antibodies in their serum. The generation of these antibodies coincides with the appearance of anti-blood group antigen and anti-Forssman antibodies; this has been related to immune response development against microbes or, applying the OPRT, probably the development of the primordial organism's interactions [11]. Additionally, there are anti-saccharide antibodies (opsonins) present in the gut environment proposed to have "a protective role against pathogens" [12], but in my view they are likely allowing the colonization or interaction with the highly abundant, normal mucosal microbiota.

In fact, sIgA is important for microorganism's colonization of oral, airway, and gut environments together with mucus. The amount of sIgA in the gut's lumen is determined by the type and presence of bacteria [13]. Secretory IgA and mucins form high-molecular- weight aggregates or networks that allow microorganism colonization in the form of biofilms. The presence of sIgA in gut biofilms has been characterized in different species [14], but the repertoire of sIgA is limited [15]; however, glycans in the sIgA structure allow the innate recognition of microbe surface saccharides, broadening the range of interactions sIgA is able to establish [16]. Also, gut sIgA has two different origins; one is dependent on (75%) and the other is independent (25%) of T lymphocytes [17]. This dichotomy may help in understanding conflicting data about the protective versus gut colonization enhancing role of sIgA. However, supporting a role of sIgA in establishment of organism interactions, sIgA has been proposed as an endogenous adjuvant (a promoter of element interactions) because antigenic epitopes expressed in the secretory component of the IgA can induce antigen- specific systemic and mucosal immune responses [18], sIgA has immune modulatory effects similar to a common adjuvant [19], and sIgA can enhance *Vibrio cholerae* transcytosis through mucosal antigen-sampling, M-like cells as I formerly described [1].

OPRT Hypothesis

Broadening my original studies with *V. cholerae* to explain widely the prearrangement rule in interactions, I have deduced the following novel hypothesis: The Organisms' Prearranged Recognition theory (OPRT) that asserts that: "The recognition and interaction that occur between organisms is prearranged. There are membrane receptors with or without soluble components derived from the respective organisms that bridge specific interactions.

Based on this hypothesis, there are two types of organisms or microbes for a specific opsonizing host-organism: those for which interactions could not be established (type I) and those for which interactions could be productively established (type II). Type I organism which is unable to establish interaction, will thus go unnoticed because it is without host-specific opsonin receptors and is unable to directly express host specific receptors. Type I organisms for a human host-organism are those multiple microbes that fail to establish interaction, but they will interact (invade, infect, colonize, adhere, etc.) with other species. Type II organisms, which will productively establish interactions with a given host-organism are either opsonized by the host opsonins or are able to directly express receptors for the specific host cells receptors or secrete host's opsonin-like molecules (Figure 1). Depending on their ability to disseminate and overgrow inside the host, type II organisms can either be beneficial (for example normal colonizing microbiota) or deleterious (invasive pathogenic organisms). The latter affects the energy homeostasis of host cells and tissues and produces damage and eventually lead to disease. Factors such as the nutritional or the immune state of the host will determine if a beneficial organism can be transformed into a deleterious organism. The damage-response framework theory explains the possible outcomes, once the initial interactions are established [20]. Antibodies -and in particular, natural antibodies- play an instrumental role as main opsonins or bridging molecules in the organisms' interactions, but so also do other abundant and ubiquitous glycoproteins and glycolipids. The interactions that happen between organisms and the immune system follow this hypothesis; however, the type of receptors and antigens involved in these types of interactions are mainly -but not exclusively- proteins and peptides. In cell membranes, probably the lipid raft platforms are the location where the first events involved in recognition and interactions are initiated including the vigilance that triggers defensive signalling cascades to prevent invasion and pathogen's proliferation. In the following sections of this work, I will discuss data that supports OPRT, propose additional molecular signatures that broaden the application of OPRT and the implications of saccharides manipulations in interactions.

Molecular basis for the repertoire and diversity of receptors

The diversity and repertoire specificity of opsonin substances, as well as organisms' receptors, are based mainly on saccharide epitopes present in glycans, glycoproteins, glycolipids, sugar coats, capsules, cell walls, etc. All these receptors are either in the cellular membrane, extracellular matrix, or secreted. The importance of saccharides in the interaction between different organisms and elements can be deduced from the mortality rates and high severity of diseases related to genetic disorders in the saccharides' biosynthetic pathways [21]. In the mucosal system, glycoproteins, such as antibodies and mucins, are the main prearranged recognition opsonins. In serum, lymphatic fluid, and tissues, the opsonins can be antibodies, as well other glycoproteins, and glycolipids. Envelope antigens containing saccharide epitopes that are the receptor targets for opsonization in organisms such as bacteria, fungi, parasites, and viruses are commonly used in serology to classify their serotype group. The serology of organisms is related to the surface antigens (usually saccharides) expressed, such as the lipopolyssacharide's (LPS) O antigen in

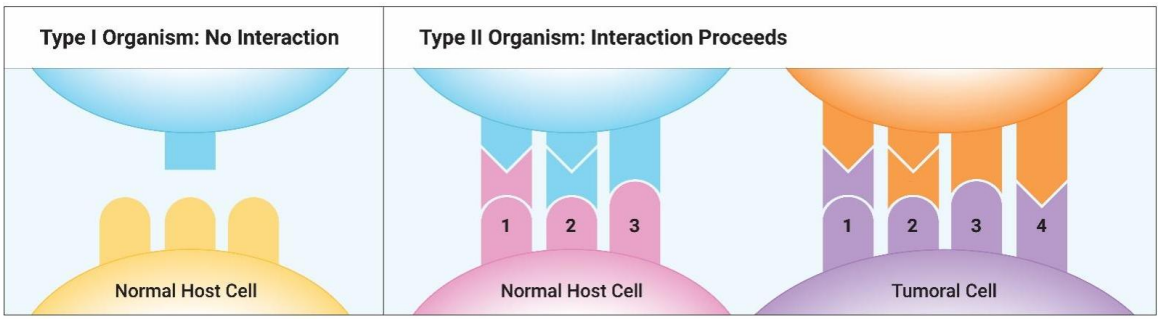

Figure 1 Diagram depicting the organisms' prearranged recognition theory (OPRT) in an oversimplified view. Type I organisms are not opsonized nor are they able to express a host-specific receptor; thus, type I organisms are not able to interact with that specific host-organism and they will go unnoticed. Examples of type I organisms for the human host-organism are the microbes that affect other species different than humans. Type II organism's interactions are mediated by (1) host or/and (2) microbe -specific derived opsonins that recognize type II organisms. Additionally, some type II organisms directly express host-specific like receptors (3). These type II organisms' characteristics allow interaction with that specific host. Tumoral host cells express additional envelope receptors (4) mimicking the opsonins and host-specific receptors, explaining their higher promiscuity and enhanced ability to interact with each other and normal cells better than normal cells.

Gram-negative bacteria. This characteristic also determines their ability to productively interact with a specific host [22]. These receptors are what host opsonins can detect or recognize to allow interactions with a foreign organism. In fact, applying the OPRT, we can understand why serotypes are useful in classifying the host's susceptibility range or the organism's species-specificity. Antibodies (which are glycoproteins) could basically be considered as the main bridges for an organism's interaction because they allow the interaction of foreign antigens and microorganisms with cells. Supporting the central role of glycoconjugates in human gut interactions, saccharides resemble microbial receptors, bacterial LPS, and the structure of tumoral antigens [23], thus ensuring that these structures are familiar to the host. Human gut mucins, which are components of the mucus and glycoproteins, are highly diverse, and provide a broad repertoire of host receptors [24]. The mucus layer also has been characterized as instrumental to the structure, nutrient source, and stability of the normal gut microbiota [25].

Carbohydrates and microbial extracellular proteins but not host genomic DNA provide the molecular basis for specific cell-cell recognition

Clearly and unexpectedly, species-specificity phenomenon is not necessarily determined in the DNA because the gene expression of human chromosome 21 in murine aneuploid hepatocytes mirrored the gene expression of this chromosome in the normal human cell environment [26]. Moreover, human immunoglobulins are produced normally in transgenic mice with an immunoglobulin-knockout and genomic fragments codifying for human immunoglobulins [27]. And furthermore, a trans-chromosomic rat model with human chromosome 21 trisomy also develops Dawn-like syndrome [28]. However, DNA epigenetic changes could potentially modulate carbohydrate biosynthesis genes' expression changing the course of host pathogen interactions [29].

Indeed, the role of carbohydrate interaction (glycan-glycan) which is as strong as protein-protein interaction, has been clearly established in the model of species-specific cell-cell recognition of the marine sponge [30]. The glycans allow species-specific reconstitution of sponge structure from individual disaggregated cells and also has been implicated in mechanisms determining the multicellularity evolution [31]. Carbohydrates have a self-recognition capability, and the specificity of these interactions has been demonstrated using glycans derived from marine sponges, surface plasmon resonance detection system, and atomic force microscopy [31]. In a multicellular organism and a membrane bilayer environment, protein-glycolipid interactions require a lipid bilayer environment for proper presentation of the saccharide epitopes with higher affinity and specificity to proteins [32]. Carbohydrates located in the surface of cells, such as glycoproteins, glycolipids, gangliosides and others, are already known to participate in cell-cell adhesion and cell response in highly diverse events [33]. Indeed, supporting OPRT, are the host's recurrent receptor's positive selection for glycans [34] together with involvement of specific microbe glycan substructures and human lectins in diverse facets of the bacteria-host interactions [35, 36].

Additionally, several glycoproteins participate in interactions required for a proper immune system response [37] and in processes associated with viral infectivity such as autophagy and endocytosis [38]. Furthermore, glycosylation in diverse viruses plays a role in processes such as attachment, infectivity, entry, and replication, which also require host glycoproteins, including SARS-COV-2 [39, 40]. Some selected examples of microbe- or toxin-host interactions where saccharides play a role in attachment or infection are depicted in Table 1.

In humans and mice, muscle integrity depends on glycosylation because mutations in glycosyltransferases have been associated with some muscular dystrophy cases [41]. Also, endocrine system alterations are due to congenital glycosylation defects [42]. Overall, there is strong support for the role of saccharides as the host's receptors for the interactions to proceed and for the specificity of interactions even within the tissues and organs of the host itself. The molecular mechanism involved in particular in host-pathogen interactions described here probably has long been hindered because 2-3% of the total genome is involved in saccharide biosynthesis pathways that are not well characterized and the high complexity of glycans associated to glycoproteins [43]. Moreover, genetic manifestations of saccharide disorders that affect specific host-pathogen interactions probably require multiple simultaneous gene changes that are not necessarily linked.

As I have already described, microbial extracellular expressed proteins also play a role in the species-specificity phenomenon [44]. Indeed, the content of primitive amino acids and intrinsically disordered regions in microbial secreted protein is positively correlated with the pathogen's host range. Primitive amino acids and intrinsic disordered regions feature in proteins give more flexibility and interactivity. Indeed, more promiscuous generalists secrete proteins containing more primitive amino acids and intrinsic disordered regions compared to the specialist or species specific pathogens that are restricted to one host [44].

Molecular basis for species-specificity, tropism, and hyper-infectivity phenomenon

The organism prearranged recognition theory gives the molecular basis for species-specificity of colonization, infection phenomenon, and for *in vivo* cell tropism of some infectious or deleterious organisms. Species-specificity is given by an organism's ability to express appropriate receptors for the host's opsonins or host's opsonins-like molecules, and this allows the host to interact specifically with only those organisms. Also, the cell tropism of certain

Table 1 Selected examples of saccharides involved in microbe- or toxin-host interactions

Microbe or toxin/ tissue/ cell interaction	Process or molecules involved	Reference
Acanthamoeba keratitis/ corneal epithelial cells	A mannose-binding lectin from the parasite is involved in interaction with host cells	[107–109]
Actinomyces naeslundii/ colonizing oral epithelium	Saccharides in gangliosides are recognized by the pathogen	[110, 111]
Arcanobacterium pyogenes/ adhesion to host cells	Bacterial neuraminidase involved in host cell adhesion	[112]
Bacteria (*Yersinia and Mycobacterium*)/ infection of nematodes	SFR-3 expressed in nematodes' secretory cells, plays a role in surface glycoconjugates composition	[113, 114]
Burkholderia cepacia/ human airway explants	Dextran and xylitol inhibit adherence to human airway explants	[115]
Candida albicans/ host buccal epithelial and Caco-2 cell line	Putative beta-glucanase mannoprotein MP65 involved in adherence	[116]
Candida albicans/ model of haematogenously disseminated candidiasis in mice	Fungal glucanase adhesin has a role in hyphal morphogenesis, adherence to plastic, and pathogenesis	[117]
Candida albicans/ host epithelial and innate immune cells	Fungal O- and N-glycosylation required for interactions with mannose-binding receptor and TLR	[118–120]
Candida glabrata/ human epithelial cells	Fungal lectin involved in adherence	[121]
Cry toxin from *Bacillus thuringiensis*/ intoxication of target nematode cells	Saccharide biosynthesis of pathways related with gangliosides in nematodes are required for toxin sensitivity	[122–124]
Escherichia coli/ genomic characterization of ability to interact with humans versus other species	Genomic locus containing 9 genes important for interaction with human cells involved in metabolism of sialic acid	[125]
Escherichia coli/ human bladder cells	Adherence to human bladder cells is prevented by D-mannose rich extracts	[126]
Escherichia coli/ invasion of dying intestinal epithelial cells	FimH adhesin binds oligomannose glycans on early apoptotic cells	[127]
Filovirus/ entry into human macrophages	Entry into human macrophages is promoted by C-type lectin specific for galactose and N-acetylgalactosamine	[128]
Helicobacter pylori/ colonization of transgenic mice	Saccharides expressed in porcine milk proteins inhibit mice colonization	[129]
Helminth parasites and tumoral antigens/ human dendritic cells	C-type lectin MGL recognizes parasite and tumoral antigen carbohydrates	[130]
Pseudomonas aeruginosa/ model epithelial cells	MDCK mutants in saccharide biosynthesis are protected from bacteria toxicity	[131]
Pseudomonas aeruginosa/ colonization of the respiratory tract	Neuraminidase has a role in mucosal infection enhancing biofilm formation	[132]
Pseudomonas aeruginosa/ recognition of various type of glycans	Using glycan microarrays	[133]

Table 1 Selected examples of saccharides involved in microbe- or toxin-host interactions (*Continued*)

Microbe or toxin/ tissue/ cell interaction	Process or molecules involved	Reference
Plasmodium berghei/ invasion of murine erythrocytes	Parasite express a membrane receptor for heparan sulfate-like receptor in erythrocytes	[134]
Rotavirus/ interaction with blood group and glycans	Recombinant VP8 analysis of glycan binding and blood antigen specificity	[135]
Ruminococcus gnavus/ human gut symbiont	Glycoside hydrolase specific for A-blood group antigen from mucin for nutrient acquisition	[136]
Streptococcus pneumoniae/ colonization of nasopharyngeal and lung tissues	Bacteria express a surface lectin to recognize flamingo cadherin receptor	[137]
Streptococcus pneumoniae/ human airway epithelial cells	Host species specificity probably related with deglycosylation of glycoconjugates by bacterial exoglycosidases	[138]
Streptococcus pneumoniae/ chinchilla tracheal epithelium	Lacto-N-neotetraose, asialoganglioside-GM1 inhibit adherence but neuraminidase enhances adherence	[139]
Type I reovirus/ M cells interaction	Virus recognizes glycoconjugates containing sialic acid in the apical membrane of M cells	[140]
Yersinia pestis/ human respiratory epithelial cell lines	Modified disaccharides affect bacterial adhesion	[141]

organisms is determined by recognition of opsonins, for which there are host tissues or cell-specific receptor(s) that allow interaction to proceed only with those tissues. Applying the OPRT to understand the hyper-infection phenomenon is straightforward, where pathogens that have been inside a host acquire a more virulent phenotype and already carry the host's opsonins that optimizes them for interaction with any subsequently appropriate hosts. The enteropathogens *Vibrio cholerae* [45] and *Citrobacter rodentium* [46] display hyper-infection, or host-adapted phenotypes. The hyper infectious phenotype is acquired after host passage and is temporarily acquired because it is gradually lost once the pathogen is outside the host. The host's shield of opsonins probably aids the organism in resisting stressing conditions inside and outside the host, such as the acid pH, temperature, osmolarity, and proteases. Opsonins also may help organisms to build biofilms, where they are in a more protected state, compared with their planktonic, free-living state [47]. In support of this hypothesis, it has been recently shown that aggregates or biofilm arrangements of *Vibrio cholerae* contribute both to increased infectious capability and greater environmental persistence, when compared to free-swimming planktonic cells [48, 49].

The OPRT explains why it is usually difficult to reproduce the species- specificity property of interactions *in vitro*, probably because species-specific opsonins are not present (fetal serum used in culture is from a different species, frequently of bovine origin), changing the organism's coat of opsonins and rendering them unable to interact optimally or-the opposite-making them artificially able to interact with a non-host organism. Supporting this statement recently an adhesin from *S. pneumoniae,* that might be involved in species specificity phenomenon of pneumococcal infection, show preferential recognition of human derived albumin but not to homologous albumin from other species [50]. Also, the *in vitro* ability of different *Salmonella* serotypes to resist macrophages does not correlate with their *in vivo* virulence [51]. Indeed, it has been very difficult to reproduce *in vivo* conditions of infections for *in vitro* settings using cell lines like tumoral cells [52].

Molecular basis for promiscuity of tumoral cells

The more promiscuous an organism is (in other words, the more interactions it can establish), the higher chances to develop a deleterious interaction or to acquire pathogenic organisms compared to non-promiscuous organisms. The promiscuity is a function of the repertoire or diversity of opsonins and receptors each organism expresses and carries. Diversity of opsonins can probably be induced, and it is different between even individuals of the same species. Tumoral cells are one of the most promiscuous of cell types because they change their "coat" or outer shell, unlike normal, non-transformed cells; thus, tumoral cells express a variety of saccharides on their surfaces, presenting a broader repertoire of receptors and opsonins, such as novel membrane-associated mucins [53]. These novel envelope glycoproteins allow tumoral cells to be colonized by different types of bacteria and viruses, and to interact with each other and with other normal cells both *in vivo* and *in vitro* with high avidity and efficiency (Figure 1). Tumoral cells express organisms' interaction molecules in their membranes, so they are prompted to adhere and to interact, and they express mucin and mucin-like glycoproteins containing N- and O-glycans that play a role in cell transformation, cell adhesion, invasion, immune escape, and metastasis [54]. Understanding the chemistry of carbohydrate biosynthesis in cancer cells should help in defining innovative therapies against them [55]. Other glycoproteins, particularly, those with a high sialic acid content, are also associated with the inherent properties of cancerous cells [56], and these properties have been used to target cationic polymers against certain mucosal tumoral cells [57] and by pathogens to interact proficiently with non-tumoral host cells [58].

Vigilance toward and detection of type II organisms

The vigilance toward and detection of type II organisms by the host are mediated through receptors able to recognize saccharide epitopes-for example, gangliosides and cell differentiation molecules or lectin-like molecules in the cellular membrane of innate immune cells. Also, toll-like receptors that recognize microbe-derived and tissue damage generated molecules play a role in host vigilance, as is

discussed below.

The glycosynapse concept developed by Hakomori supports the proposal that gangliosides play a functional role in organisms' interactions [59]. In the review cited, Hakomori shows how gangliosides in clusters or microdomains, together with functional membrane proteins, play a significant role in processes such as cell-adhesion, development, and differentiation and in tumor progression; and more recently gangliosides also have been associated with myeloid cells ability to infiltrate tumors and generate tumor-associated immunosuppression [60]. The role of gangliosides in pathogen detection and host-pathogen interactions is suggested by the long list of pathogens that are able to recognize the carbohydrate portion of the glycosphingolipids [61]. Importantly, some viruses, several toxins, and abundant bacteria use gangliosides as receptors to infect cells [62]. Moreover, ganglioside GM1 is able to present antigens [63] and to activate secretion of neurotrophins [64]. In general gangliosides can insert into membranes [65], and they also stabilize lipid domains in cellular membranes [66]. Remarkable, some tumoral cells secrete gangliosides; this ability probably allows them to modify and to improve their interactions with other cells as well as to regulate the immune responses [67]. Strikingly, *Vibrio cholerae* secretes a neuroaminidase that transforms more complex gangliosides into GM1 incrementing the number of cholera toxin receptors [68]. And the bacterial toxin allows the pathogen to acquire nutrients form host's cells and thrive in the gut environment [69].

A corollary of OPRT is the following: If there is the ability to sense or to be recognized, then there is the ability to interact and to produce cellular responses. This property of the interactions facilitates vigilance against any organism that can trespass, overgrow, or invade deeper portions of the body that might remain sterile. The sensing is accomplished through detection of the microbe's derived molecules or the host damage signals by toll-like receptors, gangliosides, or CD receptors, and cellular responses or signalling events are originated in lipid raft platforms in the membranes. These kinds of receptors are expressed by innate immune cells that, when they sense any potential deleterious organism or damage signal, trigger an alarm response, especially when the detection or interaction is happening in tissues that must remain sterile and is disrupting the energy homeostasis balance. For example, in dendritic cells the CD209 (DC-SIGN) receptor recognizes the N-acetylglucosamine sugar residues within the core LPS of diverse bacteria [70] and meningococcus pilus beta-arrestin adhesin interaction with beta-2-adrenergic receptor activates signalling via hemodynamic traction of the human specific saccharides residues on the endothelial cells [71].

The alarm response is based on cytokines type, location, and amount; heat shock proteins (HSP) produced or expressed by cells can also trigger a specific defensive immune response, for example cellular- and humoral-specific immune responses. Strikingly, the specific immune responses also require prearrangement to take place. Accordingly, antigens interact with MHC molecule receptors to be presented to lymphocytes that might have the precise prearranged receptor, and antibodies that are already present recognize specific antigens. Clearly, prearrangement in a broad variety of interactions is pervasive.

The interaction of immune-specific cells and antibodies with the triggering target antigens or the recognized microbe produces a defensive response towards elimination or restriction of the organism because it allows interaction of the invading organism or antigen with specific immune effector cells; however, low-affinity and high-multiplicity interactions through saccharide moieties in antibodies (erroneously considered "non-specific" types of interactions) allow the prearranged interaction to proceed without an aggressive component. This proposition is clearer to visualize by analysing sIgA interaction with normal colonizing microbiota in the gut. High-affinity specific sIgA is probably involved in the immune exclusion phenomena of pathogens, but normal microbiota -which exist as a highly stable ecosystem-are coated with sIgA [72]. They are not excluded from the intestinal lumen and neither do they induce a specific immune effector response [73], despite the fact that they are processed by mucosal dendritic cells [74]. In fact, more recently, sIgA has been characterize as important molecules to maintain the gut homeostasis and prevent disease [75]. Moreover, in a murine model of *Streptococcus pneumoniae* colonization where the bacteria interact with the host, antibodies do not participate in bacterial clearance [76], natural secretory immunoglobulins enhance viral enteric infections produced by norovirus and reovirus [77] and gut microbiota is opsonized with natural innate polyreactive IgA [78].

Glycoproteins that play a role in organisms' interactions

The role of glycans in mucins for colonization, biofilm formation, and cell-cell interaction phenomena is well-documented. Mucins are important for interaction phenomena such as colonization and adhesion of a variety of microorganisms, not only in the gut but also in the airway apparatus, in the oral microbiota and even between tumoral cells [79]. A septic shock in mice infected with the human species-specific pathogen *Salmonella typhi* can be induced only when the bacteria are pre-opsonized with mucin [80]. Mucin gives a new coating to the bacterium that bridges the interaction of *S. typhi* with murine cells. Importantly, the expression of certain envelope-mucin molecules has been associated with the malignancy of tumoral cells and metastasis. In fact, inhibition of MUC-4 (a surface associated mucin) expression in a highly aggressive pancreatic tumoral cell line suppresses metastasis in mice [81].

There are so many examples of host glycoproteins that are important for the adhesion or attachment processes of viruses, bacteria, fungi, and parasites that they are difficult to fully enumerate in this work. For example, fibronectin (glycoprotein) and other extracellular matrix components have been described as important host elements in pathogen-host interactions, and fibronectin is also able to interact with ganglioside GM1 [82], so fibronectin is a perfect host opsonin or adjuvant molecule because it bridges the organism's interactions [83]. Some gut bacteria can interact with mucins and even express mucin-like proteins in their surface. Also, epithelial cells express receptors for mucin-like proteins which are important for the promotion of interactions [84]. More selected examples of host glycoproteins involved in host-pathogen interactions are depicted in Table 2.

Outlook

The prediction is that most of the species-specificity interactions are probably ruled by the OPRT. One important application of the OPRT is that interactions between organisms can be modulated, changing the saccharides exposed on surfaces or expressed by opsonin molecules in the host. This could be exploited to develop more efficient antibiotics and anti-tumoral drugs with a broader spectrum by creating saccharide synthesis inhibitors and using enzymes involved in polysaccharide synthesis, or free saccharides as competitors. Conditions that affect saccharide interactions, such as changing the pH or the ionic strength environment, should also block the attachment between tumoral cells or pathogens and the host cells. Indeed, applying OPRT it is possible to envision multiple scientific and biotechnology smart applications to solve a variety of issues as summarized in Figure 2.

Most organism-host interactions are developed in a lipid raft environment where clusters of receptors and sugar epitopes are produced. This is why, for the development of preventive or therapeutic saccharide therapies, the "multivalent saccharides" approach should be applied [61]. Non-toxic carriers of multivalent saccharides, such as dendrimers, can be used; however, they should be designed specifically to each pathogen and their pathogen-neutralizing ability needs to be tested [85]. Other recent carriers used in biotechnology are chitosan in the form of coated hydrogels, carbon dots, carbon nanotubes, nanoparticles and nanofibers with applications such as: antimicrobial treatments, disruptors of biofilms, wound healing and decontamination, reduction of bacterial adherence and microbial sensors [86–90]. Glycan

Table 2 Selected examples of host glycoproteins involved in organisms' interactions

Glycoprotein and microbe	Process or molecules involved	Reference
Collagen		
Haemophilus ducreyi	Collagen-binding NcaA outer membrane protein has a role in infections that lead to chancroid (genital ulcer disease)	[142]
Staphylococcus epidermidis	Adhesin with a role in establishment of biofilms in implant devices infections	[143]
Complement C3 factor		
HIV	Virus opsonization enhances infection of dendritic cells and T cells via CR3 and DC-SIGN receptors	[144]
Klebsiella pneumoniae	Adherence and internalization of bacteria into airway epithelial cells is enhanced by opsonization	[145]
Defensin		
Haemophilus influenzae and Neisseria meningitides	Interaction with epithelial cells is enhanced by opsonization	[146]
Extracellular matrix		
Paracoccidioides brasiliensis	Interaction with cells through a surface-associated glyceraldehyde-3-phosphate dehydrogenase	[147]
Factor H		
Streptococcus pneumoniae	Invasion of mouse lungs in vivo is promoted by host factor H that recognizes surface bacterium PspP receptor	[148]
Fibronectin		
Bartonella henselae and Pasteurella multocida	Pathogen recognition of fibronectin plays a role for interaction with host	[149, 150]
Clostridium difficile	Adherence to epithelial cells	[151]
Salmonella typhimurium	Adenosine induces polarized fibronectin secretion by epithelial cells and both adenosine and fibronectin enhance bacterial attachment and invasion	[152]
Scedosporium apiospermum	Filamentous fungus adherence to lung epithelial or fibroblasts	[153]
Staphylococcus aureus	Truncation of fibronectin binding protein inhibits bacterium interaction with host cells	[154]
Streptococcus	A surface collagen-like protein Scl1 has a role in integrins recognition in host cells	[155]
Streptococcus agalactiae	FbsA (fibronectin receptor) enhances adherence to human epithelial cells and to human brain microvascular endothelial cells	[156, 157]
Streptococcus group A	Fibronectin binding gene prtF2 is associated with enhanced bacterial internalization	[158]
Streptococcus group A	Collagen-like protein 1 interacts with fibronectin in wounds	[159]
Vibrio vulnificus	Outer membrane OmpU has a role in microbe pathogenesis	[160]
Yersinia pseudotuberculosis	YadA recognition of fibronectin is determinant of their ability to infect human cells	[161]
Glycosaminoglycans		
Streptococcus pneumoniae	Attachment to nasopharyngeal epithelial cells mediated by glycosaminoglycans	[162]
Streptococcus uberis	The adherence and internalization of the bovine mastitis-associated bacteria is enhanced by host glycosaminoglicans	[163]
Keratin		
Staphylococcus epidermidis	Bacterial adhesin SdrF recognize keratin to allow their colonization of the skin	[164]
Lactoferrin		
HIV-1	Together with natural antibodies enhances adsorption on epithelial cells and dendritic cells	[165]
Streptococcus uberis	Serves as a “bridge” for internalization into bovine mammary epithelial cells	[166]
Mucin		
Clostridium difficile	Flagellar proteins FliC and FliD play a role in adherence and gut colonization in mice	[167]
Streptococcus group A	Mucin and human pharyngeal cells are recognized through receptors containing sialic acid	[168]
Helicobacter pylori	Co-localizes with MUC5AC in human stomach	[169]

Table 2 Selected examples of host glycoproteins involved in organisms' interactions (*Continued*)

Glycoprotein and microbe	Process or molecules involved	Reference
Lactobacillus johnsonii	Bacterial surface-associated elongation factor Tu mediates attachment to human intestinal cells and mucins	[170]
Lactobacillus reuteri	A prevalent gut microbe, expresses a surface protein MapA with a role in mucus and human epithelial Caco-2 cells recognition	[171]
Pseudomonas aeruginosa	Mucin is recognized by adhesin-flagellar system	[172]
Staphylococcus aureus	Bacterial surface proteins recognize saccharide moieties in mucin, possible role in nasal colonization	[173]
Vibrio cholerae	Adherence to mucus and villus surface in human small intestine	[174]
Salivary CD14		
Actinobacillus actinomycetemcomitans	Invasion of human oral epithelial cells and interleukin-8 production is enhanced	[175, 176]
sIgA		
Colitogenic bacteria	Highly coated with sIgA associated with inflammatory bowel disease	[177]
Lactobacillus rhamnosus	sIgA coated bacteria enhance in interaction with dendritic cells and Treg differentiation	[178]
Surfactant protein D		
Cryptococcus neoformans	Infection of mouse is facilitated and resistance against macrophage is enhanced	[179]
Tamm-Horsfall		
Pseudomonas aeruginosa	Urine glycoprotein enhances in vivo urinary infections produced in mice	[176]
Thrombospondin-1		
Gram-positive pathogens	Adherence to host cells is promoted through recognition of peptidoglycan	[180]
Vitronectin		
Pseudomonas aeruginosa	Enhances infection via αvβ5 integrins in airway epithelial cells	[181]
Low-molecular-weight human salivary mucin		
Some oral bacteria	Bridges interaction of bacteria and neutrophiles	[182]
Streptococcus	Surface glycoproteins GspB and Hsa recognize mucin and sIgA	[183]

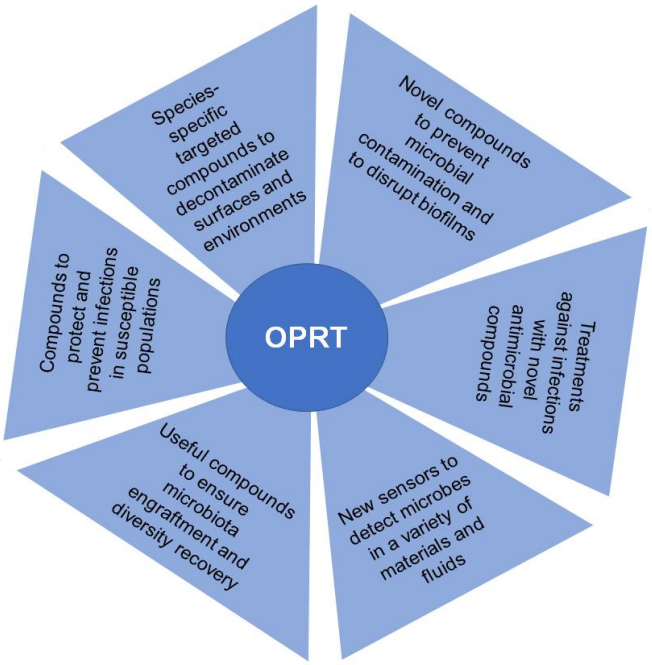

Figure 2 Possible scientific and biotechnology applications of OPRT

microarray techniques may be useful in characterizing the organisms' glycomes [91] and lectins per se might be useful in preventing microbial adherence [92]. Lipid raft domains are important not only for cell activation but also for cell-cell interaction and the organisms' interactions. In this GM1 ganglioside-enriched environment, signalling proteins are organized, and many microbes use lipid rafts as gateways for invasion or interaction with eukaryotic cells [62]. Even immune cell interaction happens through the immunological synapses that are in lipid raft domains [93].

An interesting and encouraging finding is that enteropathogenic bacteria *in vitro* adherence to epithelial cells is abrogated by prebiotic galactooligosaccharides [94], and peptides that recognize hyaluronic acid prevent wound infections by staphylococcal bacteria in a mouse model of infection [95]. Using a sialyltransferase inhibitor in a mouse model, pulmonary metastasis of a mouse colon adenocarcinoma was blocked, probably through inhibition of the tumour cells- platelets interaction because of a reduction in tumour sialic acid residues [96]. And heptyl alpha-D-mannose high affinity ligand of the FimH type 1 pili from uropathogenic *Escherichia coli*- has been shown to inhibit biofilm formation, bacterial adhesion and invasion of host cells [97]. These data encourage the field of prophylactic and therapeutic drug development based on saccharide moieties modification or recognition. Importantly, suitable techniques to better characterize saccharide structure and interactions are already available. Hence, I envision using arrays of glycans or glycoproteins (either directly or *in situ*: cellular membranes, whole cells, or tissues) and pathogens either coated or naked of host opsonins to characterize the key molecules involved in the initial interactions and then engineer possible intervention strategies.

However, a warning: we must be very careful manipulating saccharide interactions and always keep in mind that they will determine the ability of organisms and cells to interact, so, in changing saccharides, we can create new repertoires of possible interactions and change species-specificities, create organisms that can be highly deleterious for different hosts, or interfere with host immune cell-cell interactions. In fact, the glycosylation levels in the organism, per se, are critical for interactions to proceed and for certain receptors proper functioning [98] and glycans play an essential role in the immune system to fight disease and in preventing autoimmunity [99]. For example, in elderly humans augmented glycosylation of critical proteins may cause poor activation of their immune cells. T cells from aging mice also show defects in activation correlated with hyper glycosylation patterns; once the modified glycoproteins are enzymatically corrected, T cell activation is restored [100]. Also, the humoral immune response is impaired in transgenic mice that overexpress O-linked glycans on T cell membranes because the T-B cell interaction is affected [101]. Even at the level of transcription regulation in the T and B lymphocyte activation, the O-glycosylation of NFAT and NFKB is required for transcription factor translocation into the nuclei and for the induction of IL-2 cytokine production, as was described [102]. On the other hand, excessive de-glycosylation can also be deleterious-in fact, de-glycosylation of serum IgA seems to be related to IgA nephropathy, the enhanced attachment of IgA to mesangial cells, and the induction of apoptosis and proliferation reduction in these cells [103]. So, the state of glycosylation is delicately balanced in nature and currently is not straightforward to manipulate.

Therapies with saccharides also may have a detrimental effect, interfering with required immune system interactions of innate or adaptive mechanisms, such as the undesired effect that is produced by glucuronoxylomannan-derived saccharide from *Cryptococcus neoformans* fungus capsule. This saccharide is produced during *C. neoformans* infections and interferes with surfactant protein D recognition and agglutination of acapsular opportunistic pathogens, enhancing the fungus virulence potential and probably of other pathogens *in vivo* [104]. Another example: *in vitro* studies have demonstrated that saccharide residues in the C1 inhibitor that recognize LPS can prevent septic shock. This interaction inhibits up-regulation of TNF-alpha production [105], so exogenously added saccharides in this particular case can interfere with a host's innate protective pathway, and that could lead to septic shock. Nonetheless, certain polysaccharides have robust immune-modulator properties and can be used as therapeutic agents [106]. The overall conclusion is that glycosylation is a clue to interactions between organisms, and great caution is advisable in its manipulation; however, in order improve treatments against infection diseases and fundamental health issues, indeed an urgent need is to better investigate saccharides participation in interactions broadly.

Overall, in this work, a novel hypothesis is presented regarding both the degree to which organisms' interactions are prearranged and the importance of saccharide epitopes in the molecular mechanism of these prearrangements.

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