Research Article

ABO, H, Lewis and Secretor histo-blood group-like carbohydrates in pathogenic and non-pathogenic invertebrates

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ABSTRACT

ABO, H, Lewis, and Secretor histo-blood group systems express a repertoire of carbohydrate antigens in human hematopoietic and non-hematopoietic tissues. The oligosaccharide components of these systems are widely distributed in nature, including animal and plants. A set of reports demonstrated that pathogenic and non-pathogenic invertebrates are able to synthesize and/or acquire histo-blood group-like carbohydrates from hosts. These abilities seem to be related to strategies for cell invasion as well as escape from host’s innate and adaptive immune responses. This text revised the literature and offers a tentative explanation for the presence of histo-blood group-like carbohydrates in pathogenic and non-pathogenic invertebrates and its importance in terms of evolution.

Background

ABO, H, Lewis, and Secretor are histo-blood group systems characterized by the expression of carbohydrate antigens in human hematopoietic and non-hematopoietic tissues [1]. Their antigens are recognized by specific polyclonal and monoclonal antibodies and, by some lectins which allow the identification of the classical ABO, H and Lewis red blood cell phenotypes as well as the salivary Secretor and non-Secretor phenotypes [2]. The correct identification of the four main ABO phenotypes is required to match recipients and blood donors for transfusion purposes and recipients and organ donors for transplantation purposes [3].

The frequencies of ABO, H, Lewis, and Secretor phenotypes in humans are well established in all populations worldwide [4]. The potential applications of these histo-blood group systems in different areas are under investigation and offer new opportunities for the development of new technologies and personalized medicine [5, 6, 7].

The structure of the ABO, H, Lewis and Secretor histo-blood group carbohydrate antigens is built by the addition of specific monosaccharides onto different precursor oligosaccharides. Since these monosaccharides and their precursor oligosaccharides are conserved in living beings and are involved in glycosylation processes in eukaryotic cells, the presence of histo-blood group-like carbohydrates in species other than humans is expected [8].

Studies carried out in the past determined the ABO, H, Lewis, and Secretor phenotypes in some vertebrates such as monkeys from the old and the new world [9]. However, demonstrations of histo-blood group-like carbohydrates in tissues and secretions of invertebrates are scarce. This text compiled the past publications and offers a tentative explanation for the presence of histo-blood group-like carbohydrates in pathogenic and non-pathogenic invertebrates and its importance in terms of evolution.

I Biosynthetic pathways of ABO, H, Lewis and Secretor histo-blood group carbohydrates in humans

The histo-blood carbohydrates from ABO, H, Lewis, and Secretor systems are not primary gene products. Their syntheses are controlled by specific enzymes encoded by ABO, FUT1, FUT2 and FUT3 genes.

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These enzymes, named glycosyltransferases, add in a predefined sequence, monosaccharide units to precursor oligosaccharide chains to build new antigenic specificities [10].

The structure of ABO, H, Lewis, and Secretor histo-blood group carbohydrates contain six types of monosaccharides: β-D-Glucose (Glc), β-D-N-Acetylglucosamine (GlcNAc), β-D-Galactose (Gal), β-D-N-Acetylgalactosamine (GalNAc), α-Fucose (Fuc) and D-Mannose (Man) [11]. Six types of precursor oligosaccharides (type 1: Galβ1→3GlcNAcβ1-R; type 2: Galβ1→4GlcNAcβ1-R; type 3: Galβ1→3GalNAc1-R; type 4: Galβ1→3GalNAcβ1-R; type 5: Galβ1→3Galβ1-R; type 6: Galβ1→4Glcβ1-R) serve as substrate for the glycosyltransferases encoded by ABO, FUT1, FUT2 and FUT3 genes to build the histo-blood group carbohydrates [10]. (Table 1) shows data on the ABO, H, Lewis, and Secretor histo-blood group systems, gene location, glycosyltransferases, the immunodominant monosaccharides and synthesized carbohydrate structures from type 1 and type 2 precursor oligosaccharides. (Figure 1) represents the biosynthesis of histo-blood group carbohydrates from the precursor oligosaccharide type 1, as known in humans.

Figure 1: Schematic representation of the biosynthesis of histo-blood group carbohydrates from the precursor oligosaccharide type 1 as stated for humans. Modified from De Mattos (2)

Table 1: Data on the ABO, H, Lewis and Secretor histo-blood group systems, gene location, glycosyltransferases, the immunodominant monosaccharides and synthesized carbohydrate antigens from type 1 and type 2 precursor oligosaccharides. Modified from De Mattos (2)

<table>
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<tr>
<th>Systems</th>
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<td>Fuc, GalNAc, Gal</td>
<td>Le^a, Le^b, ALe^b, BLe^a</td>
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<tr>
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<td>ABO</td>
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<td></td>
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<td>a1,3-N-Galactosyltransferase</td>
<td>GTB</td>
<td>Gal</td>
<td>B type 1, B type 2</td>
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*As stated by Human Genome Committee
II Histo-blood group-like carbohydrates in invertebrates

The majority of biological activities related to histo-blood group carbohydrates in invertebrates refer to the presence of lectins which act agglutinating human red blood cells from some ABO phenotypes [12, 13]. However, studies focusing expression of histo-blood group-like carbohydrates in the secretions and tissues from invertebrates are scarce. Even so, some studies explored this matter in pathogenic invertebrates of interest for human medicine. Other ones evaluated non-pathogenic invertebrates with different purposes.

The first reports showing the presence of ABO, Lewis and Secretor histo-blood group-like carbohydrates in invertebrates were published around the 40’s. The authors concluded that some invertebrates were able to express histo-blood-like carbohydrates taking into account that their crude extracts as well hemolymph neutralize anti-A and anti-B human agglutinins. Table 2 shows the results of some studies suggesting the expression of histo-blood group carbohydrates in human pathogenic and non-pathogenic invertebrates.

III Histo-blood group-like carbohydrates in pathogenic invertebrates

Human blood group-like substances resembling A and B antigens were demonstrated in helminths in the past [14-17]. These old studies isolated fractions of polysaccharides carrying ABO blood group specificities in helminths such as Ascaris lumbricoides, Trichinella spiralis, Fasciola hepatica, Schistosoma mansoni, Necator americanus and the adult and larval stages of Taenia saginata. They concluded that those helminths express histo-blood group-like carbohydrates since their fractions of polysaccharides were able to neutralize anti-A and anti-B agglutinins of human serum.

The presence of A blood group substances was also demonstrated in extracts from Ascaris suum by Soulsby & Coombs [18]. Metabolic products of this parasite were able to neutralize anti-A antibodies and elevated the titers of anti-A agglutinins in infected pigs. Subsequent investigations also demonstrated elevated agglutinin titers in patients infected by Toxocara spp. larvae [19-21].

Besides the demonstrations of ABO, H, Lewis, and Secretor histo-blood group-like carbohydrates synthesized by parasites, evidence that some helminths acquire these antigens from the host was reported. Using indirect immunofluorescence assays Goldring and colleagues verified that juvenile forms of Schistosoma mansoni (schistosomula) when cultured in human blood from various blood types can adsorb the histo-blood group carbohydrates such as A, B, H and Leb to their surface [22]. These authors also observed that non-carbohydrate antigens like the red blood cell glycoproteins M, N, S, RHD and Duffy do not adsorb the schistosomula surface. They proposed that this ability could be used by the parasite to mask the surface antigens from the host allowing schistosomula to evade of specific humoral or cellular immune responses.

Studies carried out in the next decades reported the presence of histo-blood group-like polysaccharides with A and B specificities other invertebrates. Worms as adult nematode and the microfilariae of Loa loa contain in their integument these histo-blood group-like carbohydrates [23]. The authors concluded that these parasites incorporate host’s A and B histo-blood group carbohydrates in their surface.

Evaluation by hemagglutination inhibition tests demonstrated the presence of ABO and Lewis blood group-like carbohydrates in extracts of Fasciola hepatica. Specific substances such as A, B, H, Lea, and Leb were found on cell membranes of the tegumental syncytium and epithelium cells, by indirect immunofluorescence [24]. Using the same methods applied to assay human histo-blood group glycosyltransferases, Ben-Ismail and colleagues [25] were able to demonstrate that F. hepatica express 3-alpha-N-acetyl-D-galactosaminytransferase (GTA), and 2 and 4 alpha-D-fucosyltransferases (FUTIII). The presence of these enzymes is coincident with the previous demonstrations by the same group that F. hepatica is able to express ABO and Lewis histo-blood

| Table 2: Studies suggesting the expression of ABO and Lewis histo-blood groups carbohydrates by human pathogenic and non-pathogenic invertebrates. |
|-----------------|----------|----------------|-----------------|-----------------|
| **Invertebrates** | **Sources** | **Carbohydrates** | **Potential biological effects** | **References** |
| **Pathogenic** | | | | |
| Schistosoma mansoni (schistosomula) | Outer surface | A | Mimicry host’s tissue | 43 |
| Loa loa (adult) | Integument | A, B | Mimicry host’s tissue | 23 |
| Schistosoma mansoni (schistosomula) | Outer surface | A, B, H, Leb | Mimicry host’s tissue | 22 |
| Fasciola hepatica | Epithelium cells | A, B, Lea, Leb | Escape of immune response | 24, 25 |
| Toxocara canis (second stage larvae) | Outer surface | A, B | Cross-reaction in serodiagnosis | 26 |
| Toxocara canis (second stage larvae) | Outer surface | A, B | Cross-reaction in serodiagnosis | 44 |
| Schistosoma mansoni (cercariae) | Gut, tegument, oral sucker | Leb | Modulation of immune response | 27 |
| Ascaris Lumbricoides (adult) | Tissue extracts | H | Escape of immune response | 29 |
| Ascaris Lumbricoides (adult) | Tissue extracts | A, B | Escape of immune response | 30 |
| **Non-Pathogenic** | | | | |
| Amphioxus lanceolatus | Crude extracts | A | ? | 45 |
| Phallusia mammilata | Serum | A | ? | 45 |
| Loligo vulgaris | Gonads | A | ? | 31 |
| Octopus vulgaris | Hemolymph | A | ? | 31 |
| Crassostrea virginica (eastern oyster) | Hemocytes, plasma | A | Host-parasite interactions | 33, 39 |
group carbohydrates. However, the origin and the biological significance of the presence of histo-blood group-like carbohydrates in this parasite remain unclear. The simultaneous presence of histo-blood group-like carbohydrates as well some enzymes involved in their synthesis, suggest that these antigens can take an important role in the host-parasite interactions.

A and B histo-blood group-like carbohydrates were also detected in mucins from Toxocara canis larvae, by indirect immunofluorescence. Excretions and secretions from this parasite were able to neutralize anti-A and anti-B antibodies in vitro experiments [26]. These authors argue that the presence of A and B epitopes in this larva might cross-react with human ABO antibodies and can interfere with serological diagnostic procedures when larvae or their products are used for.

Fucosylated epitopes such as Lewis X (Le^x), a stereoisomer of Lewis A (Le^a) histo-blood group carbohydrate, is expressed by schistosomes [27]. Based on the analysis by indirect immunofluorescence, these authors demonstrated that Lewis X (Le^x) carbohydrate is expressed mainly in the gut and on the tegument of adult worms, on eggshells, and on the oral sucker of cercariae. The presence of Le^x in worms suggests that histo-blood group-like carbohydrates might be immunogenic during infection and may lead to a better understanding of the function of glycans in the immune response against schistosomiasis stages.

Another studied invertebrate in respect to the presence of ABO histo-blood group carbohydrates is the worm Ascaris lumbricoides. Extracts of this worm were able to neutralize anti-A, anti-B and anti-H monoclonal antibodies by inhibition agglutination tests [28-30]. These studies pointed out that the expression of H, A, and B histo-blood carbohydrates could be a strategy to mimicry host’s tissue by modification of its cuticular surface as well as facilitate the escape of the host’s immune response. However, there are no demonstrations if this worm expresses histo-blood-group carbohydrates or if it acquires them from the host’s tissue.

**IV Histo-blood group-like carbohydrates in non-pathogenic invertebrates**

Uhlenbruck and colleagues reported that some marine invertebrates express different forms of histo-blood group-like carbohydrate such as glycoproteins and polysaccharides [31]. Using anti-A lectin extracted from Helix pomatia, these authors were able to detect A histo-blood group carbohydrates in gonads, and hemolymph from Loligo vulgaris, and Octopus vulgaris, respectively. In another study, Ogamo and colleagues isolated, purified and characterized the chemical and serological properties of A histo-blood group-like glycoprotein isolated from oyster viscera [32].

Hemocytes and plasma of the Crassostrea virginica (eastern oyster) express a larger range of glycans, including structures carrying sulfated and methylated variants of the histo-blood group-like A epitope [33]. Other report demonstrated that Perkinsus marinus, a pathogen of oysters, uses A histo-blood-group-like carbohydrates expressed on its surface to bind the galectin CvGal1 present in the surface of hemocytes from C. virginica [34].

**V Evolutionary importance of histo-blood-like carbohydrates in invertebrates**

The studies above mentioned demonstrated that the expression of ABO, Lewis and Secretor histo-blood group-like carbohydrates represent a biological event conserved along the evolution of pathogenic and non-pathogenic invertebrates. A variety of explanations has been proposed to justify the wide distribution of these glycosylated structures in these living beings. One of them is related to the glycosylation due the fact that this process is crucial to the functions of structural proteins, enzymes, and receptors [8]. Another one refers to the cells host invasion by pathogens. Some histo-blood group carbohydrates act as receptors for bacteria and virus and its presence of absence affect the resistance or susceptibility to diseases. This phenomenon has been reported for human and non-human pathogenic virus and bacteria as well as by oyster’s pathogens [34-36]. Therefore, histo-blood group-like carbohydrates represent a useful model for studying host-parasite interactions dependent of glycans.

To escapes from host’s immune response seem to be a vital strategy, especially for pathogenic invertebrates such as helminths and nematodes. Evidence that host’s histo-blood carbohydrates are used to mimicry host’s tissue was reported [22, 30]. This strategy of evasion from innate and humoral and cellular immune responses might represent and advantage for parasite surveillance in the host cavities as well as in other tissues.

The demonstration of glycosyltransferases similar to those observed in humans (GTA and FUTIII) in F. hepatica, represents a strong evidence that the genes controlling the expression of these enzymes appeared early in invertebrates and were conserved along of the divergent evolution [24, 25]. This event is coincident with the presence of histo-blood group-like carbohydrates in the gut and on the tegument of adult worms such as Schistosoma mansoni [27].

Despite the demonstrations of histo-blood group carbohydrates in non-pathogenic invertebrates such as marine oyster, there are no convincing propositions that these oligosaccharide structures exert the same biological role as proposed for human pathogenic invertebrates. Anyway, one cannot be ruled out that hist-bloosd group-like carbohydrates act in the same way as they work for pathogenic invertebrates. Interactions between histo-blood group-like carbohydrates and galectins in hemocytes from C. virginica is a good evidence that some biological role of histo-blood group carbohydrates was conserved along the evolution of invertebrates [34, 37].

The presence of histo-blood group-like carbohydrates in oysters seems to have medical importance, especially in relation to food. The consumption of oysters contaminated with norovirus has been often associated with gastroenteritis outbreaks [38]. In the past it was demonstrated that recombinant norovirus can bind histo-blood group-like carbohydrates expressed by C. virginica, C. gigas, and by C. sikamea oysters [39]. This observation reinforces the importance of histo-blood group-like carbohydrates in invertebrates as facilitators for dissemination of a human pathogen.

Taking into account that the diversity of ABO, H, Lewis, and Secretor
hists-blood group carbohydrates in mammals evolved as a selective pressure imposed by pathogens, it seems reasonable to point out that similar pressure was imposed by nature against invertebrates [40].

Concluding remarks

As invertebrates do not display the classical humoral and cellular adaptive immune responses as vertebrates, the expression of a repertoire of carbohydrates, including those belonging to ABO, H, Lewis, and Secretor histo-blood group carbohydrates could represent and additional strategy for defense against microbial infection and innate immunity [41]. The attachment of mucins carrying histo-blood group-like carbohydrates to the T. canis epicuticle seems to permit a rapid escape from host antibodies [42].

Would be desirable the characterization of the chemical structure of the histo-blood group-like carbohydrate from invertebrates, especially among those pathogenic activities, in order to understand not only the chemical nature but also the serological properties and the evolution importance. The resulting knowledge could have potential applications. Additionally, we could clarify the biological importance of histo-blood group-like carbohydrates in cell-to-cell connections as well as understand their role in secretions and in the hemolymph of invertebrates.

Knowing the phylogenic expression of ABO, H, Lewis and Secretor histo-blood group carbohydrates in invertebrates might help to understand how these carbohydrate antigen systems evolved, their importance in terms host-parasite interactions, the role of glycosylation as well as pathogenic invertebrates modulates the immune response of the host.

Authors’ Contribution

All authors equally contributed to the concept and preparation of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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