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Invited critical review

Evolutionary aspects of ABO blood group in humans

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ABSTRACT

The antigens of the ABO blood group system (A, B and H determinants) are complex carbohydrate molecules expressed on red blood cells and on a variety of other cell lines and tissues. Growing evidence is accumulating that ABO antigens, beyond their key role in transfusion medicine, may interplay with the pathogenesis of many human disorders, including infectious, cardiovascular and neoplastic diseases. In this narrative review, after succinct description of the current knowledge on the association between ABO blood groups and the most severe diseases, we aim to elucidate the particularly intriguing issue of the possible role of ABO system in successful aging. In particular, focus will be placed on studies evaluating the ABO phenotype in centenarians, the best human model of longevity.

Contents

1. Introduction

The ABO blood group system, discovered in 1901 by the Austrian Nobel Prize Karl Landsteiner [1], consists of three main alleles, two co-dominant *A* and *B* and one recessive *O*, and is controlled by a single gene located on the terminal portion of the long arm of chromosome 9 (9q34.2) [2–4]. The *A* and *B* alleles encode slightly different glycosyltransferases that act by adding N-acetylgalactosamine and D-galactose to *H* substance, a joint precursor side chain which is hence ultimately transformed into *A*- or *B*-antigen. *Owing to a frameshift mutation, the O* allele does not encode a functional enzyme. Therefore, *OO* carriers who lack the active form of these transferase enzymes continue to express the basic and unmodified *H* structure, with a solitary terminal fucose moiety attached [5]. The variable combinations of the three main alleles generate four major phenotypes, A, B, AB and O, which are characterized by the presence (or absence) of A and B antigens on the surface of red blood cells (RBCs) and by the presence of natural antibodies against the antigen absent at the RBC surface in serum [1]. However, along with their expression on RBCs, ABO antigens are *also widely expressed in body fluids and tissues/cell surfaces*, including epithelial cells, sensory neurons, platelets and endothelia of blood vessels [6]. The term histo-blood group ABO is often used to reflect the wide distribution of ABO antigens. Recent evidence suggest that the ABO system could extend its clinical importance beyond immunohematology, transfusion and transplantation medicine, thus playing a role in the pathogenesis of cardiovascular, neoplastic and several other human disorders [7–10]. However, despite the fact that ABO antigens have been known for more than a century, their biological significance remains largely elusive. Therefore, the aim of this narrative review is to summarize the current knowledge on the clinical significance of the ABO

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system, providing a tentative interpretation of the available literature data according to an evolutionary perspective.

2. ABO blood group and human diseases

Although several investigators tried to authenticate the potential association between ABO blood group and a variety of diseases over the last 60 years, the results were controversial and somehow disappointing [11]. In the following paragraphs and in Table 1, the most striking associations are described.

2.1. ABO and infectious diseases

Microbial agents and humans have interacted for several thousands of years, and it is now rather clear that infectious diseases may influence population genetics as well as the evolution of human genome through selection of specific alleles able to modify the pathogenesis [12]. Since infectious agents often use cell-surface glycosylated receptors for their attachment, it can be easily appreciated how ABO determinants play a key role in determining a differential susceptibility among individuals to various infectious disorders by affecting host–pathogen interactions through their different degrees of glycosylation. In support of this close interaction, certain microbial parasites display a strong molecular mimicry and share blood group antigens with their hosts [13]. A number of examples can be found in this setting, the most interesting involving *Plasmodium falciparum* and gastro-enteric pathogens.

The association between malaria and ABO system is known since nearly 50 years [14]. It has recently been suggested that this severe infection may have played an important role in driving the current ABO distribution among populations in endemic areas [15–23]. In a recent review, Cserti and Dzik critically analyzed the literature on the association between the ABO system and *P. falciparum* malaria, showing that group O subjects tend to exhibit a favorable outcome than group A individuals [18]. In their experimental studies, Fry and colleagues [22] and Rowe and colleagues [21] provided a biological explanation for this clinical finding. Specifically, the authors found that rosettes of *P. falciparum*, which are formed between parasitized and uninfected RBCs and are responsible of vas occlusion and severe disease through adhesion to vascular endothelium, were consistently reduced in group O Malian children compared with non-O blood groups. The selective survival advantage against malaria conferred by O blood type is hence consistent with the geographic distribution of ABO antigens worldwide. Two genome wide association studies (GWAS) confirmed the suggestive association between non-O haplotypes and severe malaria [22,23].

The association between ABO and gastric ulcer was the first to be identified. In the 1954 Aird and colleagues already described the higher susceptibility of group O individuals to peptic ulcers [24]. It was later recognized that *Helicobacter pylori* is the causative agent of peptic ulcer, a disease that can be efficaciously treated by eradicating the bacterium with antibiotics and acid secretion inhibitors. In 1993, Boren and colleagues demonstrated that *H. pylori* binds to blood group O Lewis b (Le^b) but not A Le^b, thus providing a reasonable background for explaining the greater susceptibility of group O secretors to this infectious agent [25]. Although subsequent studies demonstrated that not all strains are specific for O Le^b, it can be generally assumed that *H. pylori* has an approximately 5-fold increased binding affinity for O Le^b compared with A Le^b [26]. It is now clear that the ABO/Le^b blood group antigens represent one of the major functional receptors for *H. pylori* in the gastric epithelium, and the blood group antigen-binding adhesin (BabA) has been identified as the leading mediator of this binding [27]. The interaction is important not only for *H. pylori* adhesion to the stomach surface, but also to anchor the bacterial secretion system to the host cell surface, so that bacterial virulence factors, namely the cytotoxin associated gene (CagA), can be effectively injected into the host cell cytosol [27].

Susceptibility to norovirus infection, which is responsible for the vast majority of cases of acute gastroenteritis in humans, is also closely associated with expression of ABH and Le antigens in the gastrointestinal tract [28,29]. The early study published by Hutson and colleagues in 2002 showed that individuals with an O phenotype were more likely to be infected with norovirus (odds ratio [OR]: 11.8; 95% CI: 1.3–103), whereas subjects with a B blood group antigen had a reduced risk of infection (OR: 0.096; 95% CI: 0.016–0.56) and symptomatic disease (OR: 0; 95% CI: 0–0.999) [30]. Further studies have disclosed that norovirus GI-1 (Norwalk virus) binds preferably to O secretor cells, whereas GII-3 and GII-4 strains bind preferably to A secretor cells [31,32], thus suggesting that the association of ABO blood group antigens with susceptibility to norovirus infection could be strain-dependent rather than genogroup-dependent.

Association between ABO blood group antigens and other enteric pathogens has also been described. Harris and colleagues showed that the phenotype group O confers a greater likelihood of severe infection from *Vibrio cholerae* than non-O blood group phenotypes [33]. Accordingly, Glass and colleagues suggested that the low prevalence of group O and the high prevalence of B blood group observed in the Ganges Delta in Bangladesh could be directly related to selective pressure from this infectious disease, which is reportedly endemic in that area [34]. Similarly, in an outbreak of gastrointestinal infections caused by *Escherichia coli* O157 in Scotland in 1996, 87.5% (14/16) of patients who died were from group O [35].

2.2. ABO and cancers

Another area that has been extensively studied over the last five decades is that of the association between the ABO blood group types and cancer, with and the most consistent relationship being observed for pancreatic and gastric cancers [36]. In the Nurses' Health Study and Health Professionals Follow-up Study, Wolpin and colleagues [37] found that participants with blood groups A, AB or B were more likely to develop pancreatic cancer compared to those with blood group O (adjusted hazard ratio [aHR] 1.44; 95% CI: 1.14–1.82). Further studies confirmed the protective effect of O group and showed that the A1 allele

Table 1
ABO blood groups and diseases: summary of clinical evidences on the association.

Category	Disease	ABO association	References
Infectious diseases	– *Plasmodium falciparum* malaria	O blood type protects against severe malaria	[14–23]
	– *Helicobacter pylori*-associated peptic ulcer	O Le^b is associated with *H. pylori* infection	[24–27]
	– Norovirus-associated acute gastroenteritis	O blood type is associated with norovirus infection	[28–32]
	– *Vibrio cholerae* infection	O blood type is associated with severe infection	[33,34]
	– *Escherichia coli* infection	O blood type is associated with severe infection	[35]
Cancers	– Pancreatic cancer	O blood type has a protective effect against pancreatic cancer	[37,38]
	– Gastric cancer	A blood type is associated with an increased risk of gastric cancer	[39,40]
Cardiovascular diseases	– VTE	Non-O blood type is associated with an increased VTE risk	[50,51,56,57]
	– MI, IS and PAD	O blood type has a protective effect against MI, IS, and PAD risks	[53–55]
Other diseases	– Parkinson's disease	B blood group is associated with Parkinson's disease	[65]
	– Incident cognitive impairment	AB blood group is associated with incident cognitive impairment	[67]

Abbreviations: VTE, venous thromboembolism, MI, myocardial infarction, IS, ischemic stroke, and PAD, peripheral arterial disease.