Beyond immunohaematology: the role of the ABO blood group in human diseases

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Introduction

The antigens of the ABO blood group system (A, B and H determinants, respectively) are complex carbohydrate molecules on the extracellular surface of red blood cell membranes[1]. However, along with their expression on red blood cells, ABO antigens are also highly expressed on the surface of a variety of human cells and tissues, including the epithelium, sensory neurons, platelets, and the vascular endothelium[2]. Thus, the clinical significance of the ABO blood group system extends beyond transfusion medicine and several reports have suggested an important involvement in the development of cardiovascular, oncological and other diseases[3,4].

Current knowledge on the association between the ABO blood group system and various human diseases are summarised in this narrative review.

ABO blood group and cardiovascular disorders

It has long been known that the ABO blood type has a profound influence on haemostasis, being a major determinant of the von Willebrand factor (VWF) and, consequently, of factor VIII (FVIII) plasma levels[5-7]. In detail, VWF levels are approximately 25% higher in individuals who have a blood group other than O[8]. The presence of ABH structures in VWF N-linked oligosaccharides provides the molecular basis for the ABO regulation of VWF levels[9]. The active ABO A and B glycosyltransferase enzymes, found in the Golgi system of endothelial cells, generate terminal carbohydrate modifications, i.e. A and B antigens, on the existing VWF "H" oligosaccharides, whereas the enzymatically inactive ABO O protein cannot modify these VWF H antigens[10]. The addition of A or B terminal carbohydrate antigens to VWF in endothelial cells might influence circulating VWF levels and function through several mechanisms, including the alteration of the rate of VWF synthesis and/or secretion, the regulation of VWF proteolysis by ADAMTS13, the modulation of VWF clearance, the modification of VWF biological activity or perhaps a combination of these events[11]. A number of clinical and experimental studies have assessed whether the ABO blood group could influence the traditional risk factors for arterial or venous thrombotic events[4].

Coronary heart disease

As regards coronary heart disease (CHD), its association with the ABO blood group is supported by evidence indicating that elevated VWF-FVIII levels are a risk factor for CHD[12,13] and by genome-wide association studies (GWAS) documenting that variants at ABO loci are associated with increased levels of plasma lipid and inflammatory markers (i.e., soluble intercellular adhesion molecule 1, E-selectin, P-selectin and tumour necrosis factor-a)[13-17], which are well known risk factors for CHD. In 2008, Wu and colleagues performed a systematic review and meta-analysis of studies reporting the association of non-O blood groups with a variety of vascular disorders[18]. The authors observed a consistent relation between non-O blood group and an increased CHD risk [odds *ratio* (OR): 1.25; 95% confidence interval (CI): 1.14-1.36)]; however, the restriction of the analysis to prospective studies only did not confirm the association (OR: 1.01; 95% CI: 0.84-1.23), probably because of the small sample size of these cohort studies[18]. Recently, He and colleagues[19] conducted a meta-analysis of data from the Health Professionals Follow-up Study, Nurses' Health Study and five other prospective cohort studies in which several thousands of participants were enrolled and they concluded that individuals with non-O blood group had an 11% [relative risk (RR): 1.11; 95% CI: 1.05-1.18; p=0.001] increased risk of developing CHD compared to that in O blood group individuals. These results were replicated by another recent study conducted retrospectively by our group in which we observed a statistically significant difference of prevalence of O blood group in CHD patients *vs* healthy controls (40.9% *vs* 44.5%; p=0.01)[20]. Notably, the protective effect of O blood group was maintained in a logistic regression model including possible confounding factors. However, the contrasting results of the study conducted by Jukic and colleagues[21], who performed ABO genotyping in patients with acute myocardial infarction and controls and did not find a statistically significant difference in the OO/non-OO genotype distribution (OR: 1.41; 95% CI: 0.94-2.11), show that the issue of the association between ABO blood group and CHD is still unclear and deserves further investigations.

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Venous thromboembolism

More consistent data are available in the literature regarding the ABO blood group-related risk of venous thromboembolism (VTE)[22,23]. For instance, Wauthrecht and colleagues[24] found a significantly higher frequency of non-O blood group in 369 patients with a diagnosis of deep vein thrombosis as compared with the frequency in 49,373 healthy blood donors (70.6% *vs* 53.9%, p<0.001). To further clarify the interplay of ABO blood group, VWF, and FVIII in the pathogenesis of VTE, Koster and colleagues[25] performed a case-control study of 301 consecutive patients with a first, objectively diagnosed episode of VTE and 301 healthy, matched controls. Blood group O was confirmed to be less represented among VTE patients than among controls (25% *vs* 43%), and group O subjects had lower concentrations of both FVIII and VWF as compared to those of non-O individuals. Overall, the matched, unadjusted odds *ratio* for VTE in individuals with non-O blood group *vs* O blood group individuals was 2.0 (95% CI: 1.4-2.9). After adjustment for FVIII and VWF levels, the risk of VTE among non-O blood group subjects remained significantly higher than that among individuals with O blood group (OR: 1.5; 95% CI: 1.0-2.2). In the Longitudinal Investigation of Thromboembolism Etiology (LITE) study[26], which analysed the ABO genotype in 492 participants who subsequently developed VTE and 1,008 participants who remained free of VTE, the risk of VTE among non-O blood type carriers was significantly higher than that among those with O-blood type (age-adjusted OR: 1.64; 95% CI: 1.32-2.05). This risk decreased but remained statistically significant after further adjustment for sex, race, body mass index, diabetes mellitus and FVIII levels (OR: 1.31; 95% CI: 1.02-1.68). Similar results were observed in a retrospective case-control study of a large number of Italian patients with deep vein thrombosis and controls (712 cases and 712 controls), in which it was found that having a non-O blood group increased the risk of deep vein thrombosis by 2.2 times over that of individuals with group O[27]. In the meta-analysis by Wu and colleagues[18], the 21 studies included in the VTE analysis gave a pooled odds *ratio* of 1.79 (95% CI: 1.56-2.05) for non-O compared to group O individuals and this odds *ratio* was even higher when the analysis was restricted to subjects who also carried factor V Leiden (pooled OR: 3.88; 95% CI: 2.51-6.00). In a more recent meta-analysis performed by our group on a larger number of studies and VTE cases (38 studies with 10,305 VTE cases) the findings were comparable[22]. Indeed, we found a significantly higher prevalence of non-O blood group in VTE patients than in controls with a resulting pooled odds *ratio* of 2.08 (95% CI: 1.83, 2.37; p<0.00001).

A summary of the largest studies on the association between ABO blood group and thrombosis is reported in Table I[25-33].

ABO blood group and cancer

Plenty of publications in medical-scientific literature deal with the association of a certain ABO blood type with a certain malignancy. Many of the studies before 1950 are not very reliable because of the lack of appreciation of the large numbers needed for a study to be really informative, the inadequate controls used, and the lack of awareness of the wide variations of ABO frequencies occurring over relatively limited areas even in populations considered ethnically homogeneous[34].

Gastric cancer

In 2008, about one million new cases of stomach cancer were estimated to have occurred (989,000 cases, 7.8% of the total), making it currently the fourth most common malignancy in the world (behind cancers of the lung, breast and colo-rectum) and the second leading cause of cancer death in both sexes worldwide (738,000 deaths, 9.7% of the total)[35].

The first convincing study relating ABO blood group and gastric cancer can be traced back to 1953[36]. The ABO blood-group distributions of 3,632 patients with cancer of the stomach in a number of hospitals in England and Scotland were compared with those of control groups of people in the same hospitals or localities. The relationship between blood groups and cancer of the stomach was shown by the statistics of Aird and colleagues who highlighted a 20% increase of carcinoma of the stomach in group A as compared to group O individuals and led these authors to conclude that it was "no longer possible to regard blood groups A and O (in adults) as entirely devoid of selective value". In 1961, a combined analysis on gastric cancer cases in 15 study locations in the USA, Europe and Australia, reported a significant positive association between non-O blood group and the risk of gastric cancer with an odds *ratio* of 1.24 (95% CI: 1.18-1-30) for patients with blood group A compared to those with blood group O[37]. However, in the 40 years following the early observation of Aird, there were over 150 separate sets of patients studied (more than 50,000 subjects) and almost all the reports agreed that in gastric cancer the A/O relative incidence is about 1.2[38].

More recently, in 2010, a large prospective population-based study carried out within a well-defined cohort of Swedish and Danish blood donors included in the Scandinavian Donations and Transfusions database (known as the "SCANDAT" database) involved more than one million donors who were followed for up to 35 years[39]. This study confirmed that blood group A is

Table I - Summary of the largest studies on the association between ABO blood group and thrombosis.

First author, year[ref.]	Study design	End point	Patients/controls	Main results
Arterial thrombosis				
Whincup, 1990[28]	Prospective	MI	7,662/ -	The incidence of MI was higher in group A subjects than in those with other blood groups (RR 1.21; 95% CI: 1.01-1.46)
Wiggins, 2009[29]	Case-control	MI	1,063/3,452	The A(11) allele was associated with an increased risk of MI (OR 1.23; 95% CI: 1.05-1.44)
		IS	469/3,452	The B allele was associated with an increased risk of IS (OR 1.59; 95% CI: 1.17-2.17)
Carpeggiani, 2010[30]	Case-control	MI	4,901/ND	Non-O blood group was associated with an increased risk of cardiac mortality (HR 1.53, 95% CI: 1.06-2.21)
Reilly, 2011[31]	Case-control	MI	470/463	Non-O blood group was associated with an increased risk of MI compared with that in the O blood group (OR 1.62; 95% CI: 1.23-2.13)
Venous thrombosis				
Koster, 1995[25]	Case-control	VTE	301/301	Non-O blood group was associated with an increased risk of VTE compared with that in the O blood group (adjusted OR 1.5; 95% CI: 1.0-2.2)
Morelli, 2005[32]	Case-control	VTE	301/299	Non-O blood group was associated with an increased risk of VTE compared with that in the O blood group (adjusted OR 1.4; 95% CI: 1.0-2.1)
Tirado, 2005[33]	Case-control	VTE	250/250	Non-O blood group was associated with an increased risk of VTE compared with that in the O blood group (adjusted OR 1.7; 95% CI: 1.1-2.6)
Ohira, 2007[26]	Case-control	VTE	492/1,008	Non-O blood group was associated with an increased risk of VTE compared with that in the O blood group (adjusted OR 1.31; 95% CI: 1.01-1.68)
Wiggins, 2009[29]	Case-control	VTE	504/2,172	Non-O blood group was associated with an increased VTE risk (HR 1.77, 95% CI: 1.43-2.18)
Spiezia, 2013[27]	Case-control	VTE	712/712	Having a non-O blood group increased the risk of VTE by 2.2 times (OR 2.21; 95% CI: 1.78-2.75)

Legend MI: myocardial infarction; IS: ischaemic stroke; RR: relative risk; CI: confidence interval; ND: national distribution; HR: hazard *ratio*; OR: odds *ratio*; VTE: venous thromboembolism.

indeed associated with a higher risk of gastric cancer compared to blood group O; the extent of the association was similar to those previously reported as Poisson regression analyses showed an adjusted incidence rate *ratio* of 1.20 (95% CI: 1.02-1.42).

In 2012, Wang and co-workers published a case-control study, which showed that the risk of gastric cancer in individuals with blood group A was significantly higher than that in subjects with non-A groups (A, B, and AB) (OR: 1.34; 95% CI: 1.25-1.44)[40]. On the other hand, subjects with blood group O had a reduced risk of gastric cancer (OR: 0.80; 95% CI: 0.72-0.88). In addition, the authors combined their data with those from the PubMed database from 1953 to the end of 2010 and carried out a meta-analysis (15,843 gastric cancer cases and 1,421,740 controls) that resulted in similar findings: (i) the odds *ratio* of gastric cancer in group A individuals was 1.11 (95% CI: 1.07-1.15); and (ii) the odds *ratio* of group O individuals was 0.91 (95% CI: 0.89-0.94). Interestingly, the authors also found that the *ratio* of *Helicobacter pylori* infection in blood group A patients was significantly higher than in non-A blood group subjects (OR: 1.42; 95% CI: 0.12-1.38). The link between blood type allele, *H. pylori* infection status, and the risk of advanced gastric precancerous lesions was recently investigated by Rizzato and co-workers[41]. The results of this study suggest that ABO blood group can be considered a risk factor for progression towards gastric cancer in patients with *H. pylori* infection but the association is highly dependent on *H. pylori* cytotoxin-associated gene A (*CagA*) status, which is responsible for the secretion of the CagA virulence protein that is injected in the cytosol of host cells and can play a relevant role in the development of precancerous lesions.

The statistical data supporting a relationship between ABO blood group and carcinoma of the stomach does, therefore, seem indisputable, although Iodice *et al*., in a recent case-control analysis of data from the European Institute of Oncology (Milan, Italy), failed to confirm the aforementioned relationship, possibly due to the limited statistical power of their study[42].

Pancreatic cancer

A definite correlation has also been established between ABO blood group and pancreatic cancer, which is among the most aggressive types of cancer. In fact, it has mortality rates approaching incidence rates, is the seventh most frequent cause of cancer death worldwide and led to an estimated 265,000 deaths out of 280,000 new cases in 2008[43].

The association between ABO blood group and risk of pancreatic cancer has been known for more than 40 years but received little attention. In 1960, Aird *et al*. carried out a study in the United Kingdom in a combined series of 620 patients with carcinoma of the pancreas and detected "evidence of some strength that cancer of the pancreas is commoner in persons of group A than in persons of groups O or B"[44]. Four years later, Macafee analysed the ABO blood group distribution in 119 patients with carcinoma of the pancreas and did not support the aforementioned association but "showed a deficiency of blood group A and an excess of blood group B when compared with the controls"[45].

Thirty years after the early data by Aird, a study in Italy confirmed an increased risk of pancreatic cancer among blood group B individuals (OR: 1.60; 95% CI: 1.25 to 2.04; p<0.001)[46]. Differently and almost contemporarily, a six-country hospital-based case-control study observed a modest excess risk for pancreatic cancer in blood group A individuals (OR: 1.52; 95% CI: 0.87-2.67)[47].

After the conflicting results of the aforementioned studies, several recent reports establishing an association between ABO blood group and pancreatic cancer have reignited the interest in this relation[42,48-52].

A recent cohort study in the USA found that, compared to individuals with blood group O, patients with non-O blood group had an adjusted hazard *ratio* for pancreatic cancer of 1.44 (95% CI: 1.14-1.82) and were more likely to develop this cancer[48]. The adjusted hazard *ratios* were 1.32 (95% CI: 1.02-1.72), 1.51 (95% CI: 1.02-2.23), and 1.72 (95% CI: 1.25-2.38), for blood group A, B, or AB, respectively. The age-adjusted incidence rates for pancreatic cancer per 100,000 person-years were 27 for participants with blood type O, 36 for those with blood type A, 41 for those with blood type AB, and 46 for those with blood type B.

Simultaneously, the multinational Pancreatic Cancer Cohort Consortium (PanScan) I GWAS identified pancreatic cancer susceptibility loci in the *ABO* gene[49]. In this study, 1,896 individuals with pancreatic cancer and 1,939 controls were genotyped and a significant association was reported for rs505922, a single-nucleotide polymorphism, which maps to the first intron of the *ABO* gene. This association was also replicated in an independent sample of 2,457 affected individuals and 2,654 controls from the PanScan II study. A combined analysis of these groups yielded a multiplicative per-allele odds *ratio* of 1.20 (95% CI: 1.12-1.28), thus supporting earlier epidemiological evidence that people with blood group O may have a lower risk of pancreatic cancer than those with groups A, B or AB.

In 2010, the influence of specific ABO genotypes on pancreatic cancer risk was assessed by Wolpin *et al*. in 1,534 cases and 1,583 controls from 12 prospective cohorts in PanScan by grouping participants by genotype-derived serological blood type (O, A, AB, and B)[50]. An increase in risk was noted with the addition of each non-O allele. In fact, compared with the OO genotype, subjects with AO and AA genotype had odds *ratios* of developing pancreatic cancer of 1.33 (95% CI: 1.13-1.58) and 1.61 (95% CI: 1.22-2.18), whereas the odds *ratios* in subjects with BO and BB genotypes were 1.45 (95% CI: 1.14-1.85) and 2.42 (95% CI: 1.28-4.57). The authors suggested a role of ABO glycosyltransferase specificity in pancreatic tumorigenesis. The hypothesis that ABO glycosyltransferase activity influences pancreatic cancer risk was simultaneously confirmed by the same author who showed that A^1 allele (corresponding to increased glycosyltransferase activity) confers greater pancreatic cancer risk than A^2 allele[51]. The glycosyltransferases encoded by the *ABO* gene transfer specific sugar residues to a precursor substance (the H antigen) to produce A and B antigens. However, glycans (sugars) have key biological functions in protein maturation and turnover, cell adhesion and trafficking and receptor binding and activation[53].

Contemporarily, Iodice *et al.*, through a case-control analysis, also supported a significant reduction of the risk of (exocrine) pancreatic cancer in patients with O blood group (47%). The protective effect of O group was confirmed by a meta-analysis of seven prior studies carried out by the same authors (summary RR: 0.79; 95% CI: 0.70-0.90)[42].

The hypothesis advanced by Wolpin *et al*. in 2010[51], namely that the association of pancreatic cancer with the *A* allele is predominantly due to A1 glycosyltransferase, which has greater activity than A2 glycosyltransferase[53], was recently confirmed by a large multicentre study in the context of the PANcreatic Disease ReseArch (PANDoRA) consortium[52]. Interestingly, this study showed that only carriers of the *A* allele had increased risk of the disease, while carriers of the *B* allele did not have. The discrepancy in the results could be explained by the fact that PANDoRA subjects were collected from case-control studies, while individuals included in the aforementioned studies by Wolpin *et al*. and Amundadottir *et al.* were drawn from prospective cohort studies[48-51].

Therefore, the results of the study by Wolpin *et al.* in 2010[51] and those of the study by Rizzato *et al.*[52] agree that the association of the A blood group with increased risk of pancreatic cancer is mainly due to the *A1* allele, thus establishing a direct connection between ABO glycosyltransferase activity and the increased risk of this disease.

The relevance of the interaction between the ABO blood group and *H. pylori* infection for the development of pancreatic cancer was recently analysed by Risch and colleagues in a case-control study involving 373 case patients and 690 gender- and age-matched control subjects[54]. Interestingly, these authors reported that the increased risk of pancreatic cancer among the individuals with non-O blood group was even higher if they were also seropositive for CagA-negative *H. pylori* (OR: 2.78; 95% CI: 1.49-5.20).

A summary of the largest recent studies on the association between ABO blood group and gastric and pancreatic cancers is reported in Table II[39,40,42,48-50,54].

Other types of cancer

Differently from gastric and pancreatic cancer, the correlation between ABO blood group and nasopharyngeal carcinoma remains controversial. An early study published in 1964 by Seow and co-workers did not find an association[55]. In 2011, Turkoz and collaborators carried out a multicentre, retrospective, case-control epidemiological study and observed an increased susceptibility to nasopharyngeal carcinoma in patients with blood type A (OR: 2.03, p=0.002) as compared to those with blood type O (OR: 0.53, p=0.009), thus showing a link between nasopharyngeal carcinoma and the ABO blood group as well as the protective effect of the O group[56]. After these two studies of small numbers of subjects, a very recent case-control study was conducted with 1,538 patients affected by nasopharyngeal carcinoma and 1,260 controls[57]. A relatively higher risk was observed among cases with blood types A or AB, with odds ratios of 1.287 (95% CI 1.072-1.545; p=0.007) and 1.390 (95% CI: 1.007-1.919; p=0.045), respectively, after adjusting for gender, age, smoking status, and family history of cancer. These results suggest that blood types A and AB are associated with an increased risk of nasopharyngeal carcinoma as compared with blood type O. Obviously, further studies are needed to confirm this association and to explore the mechanisms involved.

Finally, data from large prospective cohort studies indicate that the ABO blood group is associated with the risk of developing skin, ovarian and lung cancers[58-60], while no association was found with colo-rectum and breast cancers[61,62].

Table II - Summary of the largest recent studies on the association between ABO blood group and gastric and pancreatic cancers.

First author, year[ref.]	Study design	Patients/controls	Main results
		Gastric cancer	
Edgren, 2010[39]	Prospective cohort	1,089,022/NA	Blood group A was associated with a higher risk of GC compared to blood group O [AIRR: 1.20 (95% CI: 1.02 - 1.42)]
Wang, 2012[40]	Case-control	1,045/53,026	The risk of GC in subjects with blood group A was significantly higher than in those with non-A groups (OR: 1.34; 95% CI: 1.25-1.44). Blood group O subjects had a reduced risk of GC (OR: 0.80; 95% CI: 0.72-0.88)
	Meta-analysis	15,843/1,421,740	OR for GC of group A individuals: 1.11; 95% CI: 1.07-1.15; OR of group O individuals: 0.91; 95% CI: 0.89-0.94.
		Pancreatic cancer	
Wolpin, 2009[48]	Prospective cohort	107,503/NA	Non-O blood group was associated with an increased risk of PC (adjusted HR 1.44; 95% CI: 1.14-1.82)
Amundadottir, 2009[49]	Case-control (GWAS)	1,896/1,939 2,457/2,654	A significant association was reported for rs505922, a single-nucleotide polymorphism, which maps to the first intron of the ABO gene. A multiplicative per-allele OR of 1.20 (95% CI: 1.12-1.28) supported earlier evidence that people with blood group O may have a lower risk of PC than those with groups A, B or AB
Wolpin, 2010[50]	Case-control	1,534/1,583	An increased risk of PC was noted with the addition of each non-O allele. Compared with the OO genotype, subjects with AO and AA genotypes had OR of 1.33 (95% CI: 1.13-1.58) and 1.61 (95% CI: 1.22-2.18), whereas subjects with BO and BB genotypes had OR of 1.45 (95% CI: 1.14-1.85) and 2.42 (95% CI: 1.28-4.57)
Iodice, 2010[42]	Meta-analysis	5,403/125,893	The risk of PC was significantly decreased in O blood group (summary RR, 0.79; 95% CI, 0.70-0.90)
Risch, 2010[54]	Case-control	373/690	The increased risk of PC among the individuals with non-O blood group was even higher if they were also seropositive for CagA-negative *H. pylori* (OR: 2.78; 95% CI: 1.49-5.20)

Legend NA: not applicable; GC: gastric cancer; CI: confidence interval; OR: odds *ratio*; PC: pancreatic cancer; HR: hazard *ratio*; GWAS: genome-wide association study; RR: relative risk; CagA: cytotoxin-associated gene A.

In addition, very recently a higher risk for renal cell cancer was found in non-O blood group women, but not in men[63]. However, also for this type of cancer, additional studies are needed to confirm the association detected and to explore the mechanisms through which ABO blood group may influence it.

ABO blood group and other diseases: from the historical background to today

Historical background

There are proven relationships between ABO blood group and diseases for haemolytic transfusion reactions due to the transfusion of ABO-incompatible blood, transplantation of ABO-incompatible cells/tissues/organs that may, without immunosuppression, result in acute rejection, and haemolytic disease of the foetus and newborn resulting from ABO incompatibility between mother and baby, which is a relatively common event but is nearly always mild and only rarely causes severe anaemia.

In addition to the aforementioned undeniable associations of ABO blood group with diseases, medical literature, especially prior to 1990, is replete with unusual examples of diseases or other conditions that were thought to be associated with, or caused by, blood group antigen-antibody reactions. However, many of the aforementioned correlations were pure statistical associations of ABO blood group with certain diseases and some of them had already been discarded by several mid-twentieth-century papers that labelled them part of the mythology of blood transfusion[64-66]. In addition, some of the main flaws of these studies such as "the failure to take into account the *a priori* probabilities and the number of comparisons being made, the use as controls of a series of individuals of different ethnic origin than the patients (i.e., stratification), pooling heterogeneous data, errors in blood grouping, and bias in the selection or classification of cases" were clearly pointed out in 1970 by Wiener who, judging almost all these associations fallacious, concluded with an old proverb that "the proof of the pudding is in the eating"[66].

Some of the stranger and more ridiculous associations, including a more pronounced hangover in group A individuals, better teeth in group O persons, personality traits, the intelligence quotient, the socioeconomic profile of the population, and digestion were all reviewed by George Garratty[34] and were also published in highly respected journals, such as Nature in 1973 and 1984, or in several books, the last of which in 1999[67].

From infectious diseases to neuroscience

The early statistical associations with disease that are still of interest include the relationship between infectious diseases and ABO blood type. In 1917, the first publication on blood group and disease connected ABO blood type with tuberculosis[34]. Later, Mourant suggested that the major differences in the geographical distribution of ABO blood groups may be the consequence of epidemics that occurred in the past[68,69]. The concept of evolutionary selection based on pathogen-driven blood group changes is currently supported by studies on the genetic characterisation of the ABO blood group in Neanderthals[70] and ancient Egyptian mummies[71]. These studies suggest a potential selective advantage of the O allele influencing the susceptibility to several different pathogens responsible for diseases such as severe malaria[72], *H. pylori* infections[73] and severe forms of cholera[74]. The positive selective pressure could have been caused by the absence of the A and B antigens (that can be used as receptors by infectious agents) and by the presence of anti-A and anti-B antibodies. In addition, certain microbial parasites share blood group antigens with their hosts (molecular mimicry)[75]. Study of the evolution of the ABO blood group could, therefore, contribute to determining when during human history the different alleles emerged and help to identify the selective forces that might have acted on the different alleles.

Evidence supporting the view that blood group O provides a selective advantage against severe malaria has been recently reviewed and is persuasive[76-79]. The ABO system is important because the original allele, encoding glycosylation with the A sugar, acts as an adhesion ligand with infected red blood cells thus promoting rosette formation with uninfected red blood cells and adhesion to vascular endothelium, which cause vaso-occlusion and severe disease. The least rosette formation is observed in individual with blood group O, thereby explaining the prevalence of this blood group in areas in which malaria is endemic. Interestingly, a recent case-control study carried out in a tertiary care centre in Odisha (India) revealed a significant association of blood group B, but not A and AB, with severe malaria, probably reflecting a population-specific phenomenon[80]. In fact, the same authors performed a meta-analysis including previous reports and confirmed a significant protective effect of group O against severe malaria and a significant association of blood groups A and AB with the same disease but failed to corroborate this association with blood group B. Recently, Timmann *et al.* confirmed[81], by GWAS, the association between ABO polymorphism and the incidence of severe malaria. They identified two previously unknown loci associated with severe falciparum malaria in patients and controls from Ghana, West Africa. One of the loci was identified on chromosome 1q32 within the *ATP2B4* gene, which encodes the main calcium pump of red blood cells. The second was indicated by an intergenic single nucleotide polymorphism on chromosome 16q22.2,

possibly linked to a neighbouring gene encoding the tight-junction protein MARVELD3, which is expressed on endothelial cells and might, therefore, have a role in microvascular damage caused by endothelial adherence of parasitized erythrocytes.

In 1954, Aird and colleagues identified the greater susceptibility of group O individuals to peptic ulcers[82]. The relative incidences reported were 0.73 (A/O) and 0.80 (B/O) for duodenal ulcers and 0.87 for gastric ulcers (both A/O and B/O)[75]. Actually, *H. pylori* is now known as a causative agent leading to peptic ulceration and gastric cancer. In addition, non-secretion of blood group antigens is a significant risk factor for gastro-duodenal disease and the RR for non-secretors/secretors was estimated to be 1.9[83]. The blood group antigen-binding adhesin (BabA) mediates the adherence of *H. pylori* to ABO/Lewis b (Le^b) blood group antigens in the gastric pit region of the human stomach mucosa. This interaction is important not only for the adhesion of *H. pylori* to the stomach surface but also to anchor the bacterial secretion system to the host cell surface so that bacterial virulence factors can be effectively injected into the cytosol of the host cell[84].

Susceptibility to norovirus infection, the commonest cause of acute gastroenteritis in humans, is also closely linked to the expression of ABH and Le antigens in the gastrointestinal tract. A study published by Hutson *et al.* in 2002 showed that individuals with an O phenotype were more likely to be infected with norovirus (OR: 11.8; 95% CI: 1.3-103), whereas subjects with a B histo-blood group antigen had a decreased risk of infection (OR: 0.096; 95% CI: 0.16-0.56) and symptomatic disease (OR: 0; 95% CI: 0-0.999)[85]. Recently, Tan *et al.* proposed that the association of ABO blood group antigens with susceptibility to norovirus infection may be strain-specific rather than genogroup-dependent[86].

Other studies have focused on the inhibition of retrovirus infections by natural anti-A/anti-B antibodies but this hypothesis is supported only by experimental results and *in vitro* observations[75]. Furthermore, in addition to the natural antibodies that have been shown to kill *Escherichia coli in vitro*[34], two innate immune lectins, galectins-4 and -8, which are expressed in the intestinal tract, recognise and kill human blood group antigen expressing *E. coli*[87]. According to the authors, those lectins might provide immunity against pathogens that express blood group-like antigens on their surface.

One of the latest examples of diseases "statistically" linked to ABO blood group is Chikungunya virus infection[88,89]; the putative association, like that of other associations of various infections with a particular ABO group contained in several early reports[34,38,90,91], needs to be thoroughly re-evaluated and confirmed by large (genome-wide association) studies.

Recent research has also carved out a role for ABO blood group antigens in neuroscience. In fact, these antigens have been implicated in the development of olfactory nerve connectivity. In 1985, Mollicone and co-workers described the expression of B and H antigens on primary sensory cells of the rat olfactory apparatus and inner ear[92]. Five years after this early report, Villaroya and colleagues suggested a possible role of the *A* gene or a gene closely linked to the *ABO* locus in the differential susceptibility to experimental allergic encephalomyelitis in rabbits[93]. After these two reports, a further study demonstrated that the histo-blood group H carbohydrate is expressed by primary sensory neurons in both the main and accessory olfactory systems while the blood group A carbohydrate is expressed by a subset of vomeronasal neurons in the developing accessory olfactory system[94]. This study showed that blood group sugars are involved in axon guidance events in the developing olfactory systems. A more recent report also provided evidence that the cell surface carbohydrate blood group A regulates the selective fasciculation of regenerating accessory olfactory axons[95].

Conclusions

Beside its role in immunohaematology, there is accumulating evidence that the ABO blood group also plays a key role in various human diseases such as cardiovascular, neoplastic and infectious disorders. In the near future, probably many of the statistical associations observed between ABO and diseases will be reassessed by GWAS. These studies have already confirmed some of the relations detected by targeted researches carried out long before the current era of genomics, such as those with VTE, CHD, and pancreatic cancer[75].

Keywords: ABO blood group, cancer, infectious disease, venous thromboembolism, coronary heart disease.

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