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Association of the ABO blood group with certain human diseases

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ABSTRACT

Following the discovery of ABO blood group over 100 years ago, a variety of studies sought to determine whether different disease states are influenced by ABO inheritance. As oligosaccharide antigens, ABO blood group antigens are widely expressed on the membrane of red blood cells and tissue cells, as well as in the saliva and body fluid. It is by far the most important blood group system in human immunohematology and transfusion medicine. While, other than determining blood group phenotype, accumulating evidence indicates that ABO blood group is implicated in the development of a number of human diseases. This review mainly focuses on the association between ABO blood group and cardiovascular system risk, corona virus disease 2019 (COVID-19), affective disorders, allergic diseases, as well as cancers.

Keywords: ABO blood group, cancer, cardiovascular disease, COVID-19, affective disorder, allergic disease

INTRODUCTION

The ABO blood group system was first described in 1900 by K Landsteiner, based on the observation of red blood cell agglutination patterns when blood types from different donors were mixed[1]. This discovery represents the basic underlying concept for blood transfusion. Based on RBC agglutination patterns, individuals can be divided into four major groups: A, B, AB, and O. ABO is located on chromosome 9q34.2, which is comprised of seven exons with DNA variants altering the gene´s enzymatic activity[2]. In the A and B phenotypes, the H antigen is modified by the addition of N-acetylgalactosamine (A) or galactose (B) that are each transferred by the action of GTA or GTB, respectively. Both GTA and GTB are highly homologous and differ only in four amino acids, however, they exhibit distinct specificities[3]. In recent years, certain blood groups have been linked to an increased risk of certain diseases[4]. And scientists believe that the correlation may be due to the fact that ABO blood group antigens are expressed not only on the membrane of red blood cells, but also on platelets, vascular endothelial cells, mucus secretions and epithelial tissues[5]. The mechanism basis for their specificity in relation to certain human diseases is still being studied intensively[6].

ABO BLOOD GROUP AND CARDIOVASCULAR DISEASES

Cardiovascular disease (CVD) continues to be the most important global health challenge worldwide. The first time ABO blood groups were shown to be associated with CVD was in 1962 when A and B blood groups were linked to ischemic heart disease (IHD)[7]. The majority of previous studies have indicated that individuals with non-O blood groups demonstrate an increased risk for several thromboembolic diseases, including ischemic heart disease,

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pulmonary thromboembolism (PE), and deep vein thrombosis[8–9], as well as familial hypercholesterolemia[10]. Recently, a trial aimed to investigate the relationship between blood group type and coronary collateral circulation also demonstrated that O blood group predicts good coronary collateral development among patients with coronary artery disease[11]. Similarly, patients with non-O blood group types have a higher risk for development of high-grade atrioventricular block (HAVB) compared with O blood group patients[12], and blood group A is associated with the risk of myocardial infarction (MI)[13]. Data extracted from the study revealed that harboring a non-O blood group poses an additive effect with other thrombophilia markers in the causation of TE and that the inclusion of ABO group testing in the management of those patients can help to identify patients at high risk, suitable for counseling, further testing or closer monitoring[14].

The reason why the ABO blood group is a risk factor of CVD is still under investigation. The main biological pathology underlying cardiovascular disease is atherosclerosis. As mentioned earlier, ABO antigens are not only expressed on the surface of red blood cells but also on epithelial and endothelial cells, T-cells, B-cells and platelets[15]. ABO blood type is additionally associated with many traits including platelet function parameters amongst healthy adults and patients with CAD[15]. These antigens might also be found in the circulation and body secretions, if the individual has the *FUT2* gene secretor phenotype[16]. Different levels of the vWF have also been suggested to explain the relationship between ABO blood groups and CVD risk due to its level and biological activity being reduced in O-group individuals[17–20]. Besides, the expression of blood group antigens on vWF also plays a role in platelet aggregation. Finally, type O individuals, who have 25% lower levels of von Willebrand factor, are at risk for increased bleeding, but decreased thrombosis[21].

Furthermore, upon the advent of agnostic statistical approaches such as genome-wide association studies (GWAS), new insights into the mechanism of cardiovascular disease at a molecular level have started to emerge. In recent years, GWAS showed that the genetic ABO locus that encodes for ABO blood group antigens has been associated with many traits including coagulation factors, adhesion molecules and cardiovascular disease due to its a highly pleiotropic nature[15,22]. Understanding biological interactions between the ABO locus and molecules involved in coagulation and clot formation could potentially lead to the production of new drugs to boost the prevention of cardiovascular events.

ABO BLOOD GROUP AND CORONA VIRUS DISEASE 2019 (COVID-19)

At present COVID-19 is spreading rapidly worldwide, however, even yet there are no biomarkers that can predict COVID-19 susceptibility. By investigating the relationship between ABO blood group and COVID-19 susceptibility, an independent study found that the risk of COVID-19 in type A blood was significantly higher than that in non-A blood. Also, when comparing with non-O blood, the risk of type O blood was found significantly lower. The distribution pattern of type A and type O blood in deceased patients was similar[23]. Given the accumulating evidence that COVID-19 is associated with significant coagulopathy[24–25], and that micro-thrombi disseminated through the lung vasculature contribute to acute respiratory distress syndrome (ARDS)[26–27], the association between ABO blood group and COVID-19 susceptibility is of particular interest. Beside platelets, covalently-linked ABO (H) determinants are present on a number of plasma glycoproteins, including the von Willebrand factor (vWF), and factor Ⅷ (F Ⅷ), which play a major role in determining the reduced risk of thrombosis observed in group O subjects[17]. It is important to note that markedly elevated plasma vWF:Ag and F Ⅷ:C levels have been reported in patients with severe COVID-19 pneumonia[28]. These novel findings provide interesting insights into the biological mechanisms that result in ABO blood classification, which may contribute to inter-individual differences in COVID-19 susceptibility.

ABO BLOOD GROUP AND AFFECTIVE DISORDERS

As ABO blood types represent part of the genetic phenotype, the gene-environment interaction takes a predominant role in affective disorders including depression and anxiety. This topic received attention by the medical community as early as the 1960s of last century[29]. Recently, a clinical-cross sectional study evaluating the correlation between ABO blood types and preoperative anxiety was carried out[30]. It enrolled 352 patients with different ABO blood types scheduled for elective surgery and found the AB group displayed a high preoperative anxiety level. Another study in China demonstrated that blood group B was associated with reduced odds of postpartum depressive symptoms (PPDS) in pregnant Chinese women. So non-blood group B may be a useful risk factor for PPDS in Chinese pregnant women[31]. Hence, scientists have found some clues that ABO may play an essential role in affective disorders.

ABO BLOOD GROUP AND ALLERGIC DISEASES

Allergic diseases develop from abnormal reactivity of the immune system, whereby the immune system becomes hyper-responsive to allergens that are not harmful to the body[32]. Allergic diseases include anaphylaxis, food allergies, asthma, rhinitis, conjunctivitis, angioedema, urticaria, eczema, eosinophilic disorders (including eosinophilic oesophagitis) and drug and insect allergies[33]. The ABO blood group system is a complex carbohydrate molecule that acts as a surface marker and may behave as potential receptors for microorganisms or substances such as toxins or allergens that could influence the susceptibility of individuals to diseases[34].

One common manifestation of allergic diseases is allergic rhinitis (AR). It is a global health problem and its epidemiology has been the subject of numerous studies worldwide. According to one study, O blood group phenotype is associated with allergic rhinitis[35]. However, a case-control study in Croatia, using PCR-SSP to determine ABO genotyping on five main alleles, found no correlation between certain ABO blood group genotypes and parameters/biomarkers of ventilatory dysfunction in patients with allergic and nonallergic asthma[36]. Currently, there is no unanimity on the specific histo-blood groups linked to respiratory atopy risk, although asthma phenotypes are associated with specific blood groups. This discordance in results may be because some studies evaluated only patients with a diagnosis of allergic rhinitis, whereas the majority of patients enrolled in previous studies were carriers of atopic diseases other than allergic rhinitis.

Even if the correlation between ABO blood group and allergic diseases requires more research and data to confirm its nature conclusively, existing data still contribute to a better understanding of the pathophysi-ology and clinical variability of these diseases and may help to improve prevention and diagnosis strategies.

ABO BLOOD GROUP AND CANCERS

Associations have also been made between ABO blood group and cancer. The first report describing a link between A antigen and increased stomach cancer risk was published in 1953[37]. Investigations taken over the last decades involving a large body of work has linked blood subgroups, in particular non-O phenotypes, to the incidence of various cancer types and their progression, although no underlying biological mechanism has yet been established[38]. Researchers speculate that differences in ABO blood group antigen may affect the occurrence and development of cancer including cell movement, signal transduction and escape from immune killing from the host body. Meanwhile, cancer cells can also evade the surveillance of the immune system by expressing antigens similar to ABO blood group antigens[39–40]. Here, we list several common tumors found on clinic to discuss the role of ABO blood type in them.

Gastric cancer

In China, gastric cancer is the second most common type of cancer. A large genetic study to evaluate associations between ABO blood groups and genotypes with increased risks of gastric cancer in Chinese populations reported that blood group A and AB were associated with elevated gastric cancer risk[41]. Furthermore, associations between genotypes AO and AB and a higher risk of gastric cancer were revealed compared with the OO genotype. Nevertheless, even partial results supported the above research, for example, the frequency distribution of gastric cancer patients with the A blood group was significantly increased (χ^2=4.708, P=0.000). However, Yu *et al.*[42] also clarified the risk of gastric cancer in people with AB blood to be lower, and the frequency distribution of gastric cancer patients with the AB blood group significantly decreased (χ^2=9.630, P=0.002). This is the same as the results that the median overall survival (OS) of patients with positive preoperative serum CEA and blood type AB was significantly higher than that with blood type non-AB[43]. These results suggest that AB blood is a controversial factor in the development of gastric cancer and further prospective studies are warranted to confirm their relationship.

Lung cancer

Lung cancer is the leading cause of cancer death worldwide, and many cases present at an advanced stage at diagnosis, a major obstacle to improving outcomes. According to initial researches, no relationships were obtained between ABO blood group and the malignant pulmonary cancer[44–45]. This was until recently, when research involving 1 601 patients with lung cancer treated in China, reported that blood group O or B had significantly prolonged OS, DFS, and LRFS compared with those with the blood group A or AB[46], which was in agreement with a study conducted by Fukumoto K *et al.*[47], who demonstrated that ABO blood group can be an independent prognostic factor in patients with non-small-cell lung carcinoma (NSCLC).

Antigens A and B are expressed on the surface of red blood cells as well as numerous other tissues through-

out the body[48], including lung cancer tissues[49]. Greater loss of antigens within the tumor cells has been associated with less favorable prognosis, and in non-small-cell lung carcinoma, the loss of antigen A was associated with shortened progression and decreased survival[50].

The inconsistent findings from these studies could possibly be attributed to small sample size, which resulted in inadequate statistical power, poor study design that included inappropriate controls, and residual confounding from population heterogeneity. Fundamentally, studies of other larger cohorts are needed to confirm the relationship between the ABO blood group and prognosis among patients with lung cancer.

Breast cancer

Breast cancer is the most common type of malignancy and the main cause of mortality in women globally. Its occurrence rates are increasing in China[51]. In current biomedical literature, a number of studies have investigated the role of the ABO blood group in breast cancer risk and pathology. However, it remains controversial whether ABO blood groups have any association with malignant cancer. On the one hand, several studies found that there is no association between ABO blood group and breast cancer risk in either English or American patient populations[52–53], as with two reports from Turkey[54–55]. On the other hand, two control studies demonstrated a significant correlation between breast cancer and blood group A[56–57]. They also provided some suggestions to reduce breast cancer incidence and its burden including preventive and screening programs for breast cancer, especially in young women.

Pancreatic and liver cancers

Pancreatic cancer (PC) has the worst prognosis of all cancers. ABO gene variants have been identified as susceptibility factors for PC[58]. Serological evidence of non-type O carriers and meta-analyses of blood types also confirm an association between non-O blood types and increased risk of PC[39,59–60]. Individuals with phenotype B have a 1.5-fold higher incidence rate than individuals of phenotype O[61–62]. Recently, a study focused on the influence of ABO blood type in the clinical course of PC in Japanese patients[63], found that the median survival time (MST) of patients with A alleles was shorter than that of patients with non-A alleles (P=0.048), and tumor invasive behavior may be more frequent in those with A alleles than in those with non-A alleles. The results were presumably due to the impact of blood type on disease onset and tumor behavior. Understanding the mechanisms underlying differences in the clinical course of PC according to ABO blood type may lead to the discovery of new drugs and improve the long-term outcomes.

Hepatocellular carcinoma (HCC) is an aggressive tumor with a poor prognosis and is the third most common cause of cancer-related deaths worldwide[64]. Studies reporting whether there is a relationship between the characteristics and prevalence of ABO blood type in patients with HCC are few, and the data are still controversial. However, some studies reported that blood group A was found to be a risk factor for HCC[65]. One study found individuals with phenotype B had a median overall survival of only 34 months compared with 55 months for individuals with phenotype O[66], which may have been due to B blood group having a higher vascular tumor invasion rate[67]. In addition, the tumor was less multicentric in the AB blood group, while, AB and non-O blood group were shown to have poor OS[68].

There is still an absence of sufficient data on the relationship between HCC and blood groups. However vascular invasion and multicentric localization of tumors have been found to be significantly related with blood group and can be used to predict the prognosis of HCC.

CONCLUDING REMARKS AND FUTURE PERSPECTIVE

Following the first clinical observation made over 60 years ago, the role of antigens in the ABO blood group system in relation to human disease biology has been intensely studied by countless investigators and is now widely recognized to be associated with a number of diseases or hemostatic complications. Evolutionary adaptation of ABO blood group has been identified as able to extend individuals´ life by eluding most serious diseases, including subarachnoid hemorrhage[69], ischemic stroke, coronary artery disease (CAD), peripheral arterial disease, pregnancy complications[70], acute lymphoblastic leukemia[71], first and recurrent venous thromboembolic events (VTEs)[72], and residual vein obstruction after deep vein thrombosis[73]. All above diseases are closely related to a particular ABO blood group or groups and cardiovascular thrombus formation.

Trends in the relationship between blood group and incidence of various types of cancers have also been noted. One hypothesis about the mechanisms by which the ABO blood group influences the prognosis of cancer patients, is that ABO antigens in tumor cells play an important role in intercellular adhesion and

membrane signaling, both of which are critical to the progression and spread of malignant cells[5,15].

In summary, inconsistencies still exist in the association between blood group and the risk of certain diseases. The regulatory mechanisms between ABO blood group and human health need to be clarified. Furthermore, deeper and more extensive research on how to modulate the expression of blood group genes is also needed to help the diagnosis and treatment of human diseases[74].

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