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Editorial

Cardiovascular disease, ABO locus, and markers of platelet functionality

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Cardiovascular disease continues to be the most important global health challenge causing one third of mortality world-wide. A great proportion of cardiovascular deaths falls in the category of coronary artery disease (CAD) and occurs mainly as a result of myocardial infarction. This catastrophic event in many cases is the first sign of cardiovascular disease when it is too late for preventive strategies to be implemented and make an impact. It is thus particularly important to be able to understand mechanisms involved in cardiovascular disease and prevent such an event.

Biological pathology underlying cardiovascular disease is atherosclerosis. In CAD, atherosclerosis occurs within coronary arteries. Endothelial surface of atherosclerotic plaque could lose integrity and rupture at any time. Consequent coagulation cascade forms thrombus inside the affected coronary artery and blocks it. At this point, myocardial infarction is inevitable. Coagulation factors and platelet functioning are pivotal in formation of thrombus (blood clot). To prevent clot formation in coronary arteries and consequent myocardial infarction, currently aspirin is used as antiplatelet therapy [1] in patients with cardiovascular disease or those carrying high risk of cardiovascular disease. Aspirin blocks transformation of arachidonic acid to molecules involved in clot formation such has prostaglandins and thromboxanes.

It is for long known that ABO blood group antigens are present at the surface of platelets [2] and for nearly half a century, a link between ABO blood group antigens and cardiovascular disease was known [3]. ABO blood group is additionally associated with many traits including platelet function parameters amongst healthy adults and patients with CAD [4,5]. Upon advent of agnostic statistical approaches such as genome-wide association studies (GWAS), new insight into mechanism of cardiovascular disease at molecular level started to emerge. In recent years, GWAS showed that ABO genetic locus that encodes for ABO blood group antigens has a highly pleiotropic nature and is strongly associated with many traits including coagulation factors, adhesion molecules and cardiovascular disease (Fig. 1). Understanding biological interaction between the ABO locus and molecules involved in coagulation and clot formation is fundamental. It provides insight that could potentially lead to production of new drugs to boost prevention of cardiovascular events.

In this issue of the journal, Christiansen and colleagues investigated the role of 45 CAD genetic variants on platelet activation and aggregation. They used a sample of 879 patients with CAD under aspirin therapy. Patients who used medication with potential effect on coagulation were excluded. However, most of the patients used aspirin and as the authors pointed out some could be under aspirin treatment long before entering the study. The results showed that except for the ABO CAD risk variants, none of the CAD variants were linked to platelet aggregation and activation. The study showed that measures of platelet aggregation (arachidonic acid, and collagen) were higher and sP-selectin levels were lower amongst carriers of ABO risk allele compared to non-carriers.

GWAS on general population indicate that the ABO locus is strongly associated with serum levels of adhesion molecules such as sP-selectin [6–10]. Additional to the findings of GWAS, Christiansen and colleagues highlight differences in arachidonic acid, collagen, and sP-selectin within categories of ABO CAD genotypes amongst CAD patients who are under aspirin treatment.

As mentioned earlier, ABO locus is associated with CAD and several cardiovascular risk factors such as lipid levels and type1 diabetes. Thus, compared with non-carriers, carriers of ABO CAD risk allele are more likely to have had CAD risk factors prior to entering the study. At the same time, prescription of aspirin to prevent clot format in CAD in many countries means that individuals at high risk of CAD (i.e. those with CAD risk factors) have a greater chance to receive aspirin. This means carriers of ABO CAD risk allele are more likely to have been under aspirin therapy well in advance of the time that measurement of platelet function was taken by Christiansen and colleagues. As a result of longer duration of aspirin therapy amongst carriers, their platelet functioning parameters change disproportional to the ones of non-carriers. Such effect might lead to underestimation of the findings by Christiansen and colleagues with a magnitude that depends on the effect of long-term aspirin use on platelet function. This could be further complicated as aspirin response is not similar in all individuals. It is important for future research to distinguish effect of ABO locus on platelet functioning parameters from aspirin response. This necessitates measurement of platelet functioning parameters before and after aspirin use.

Christiansen and colleagues present interesting results, showing yet another evidence for the impact of ABO locus on platelet functioning parameters. It is however unclear if ABO locus directly impacts on platelet functioning parameters or it exerts its effect through modulating patients' response to aspirin. It is interesting to explore how the finding would be different before and after aspirin therapy and if these findings

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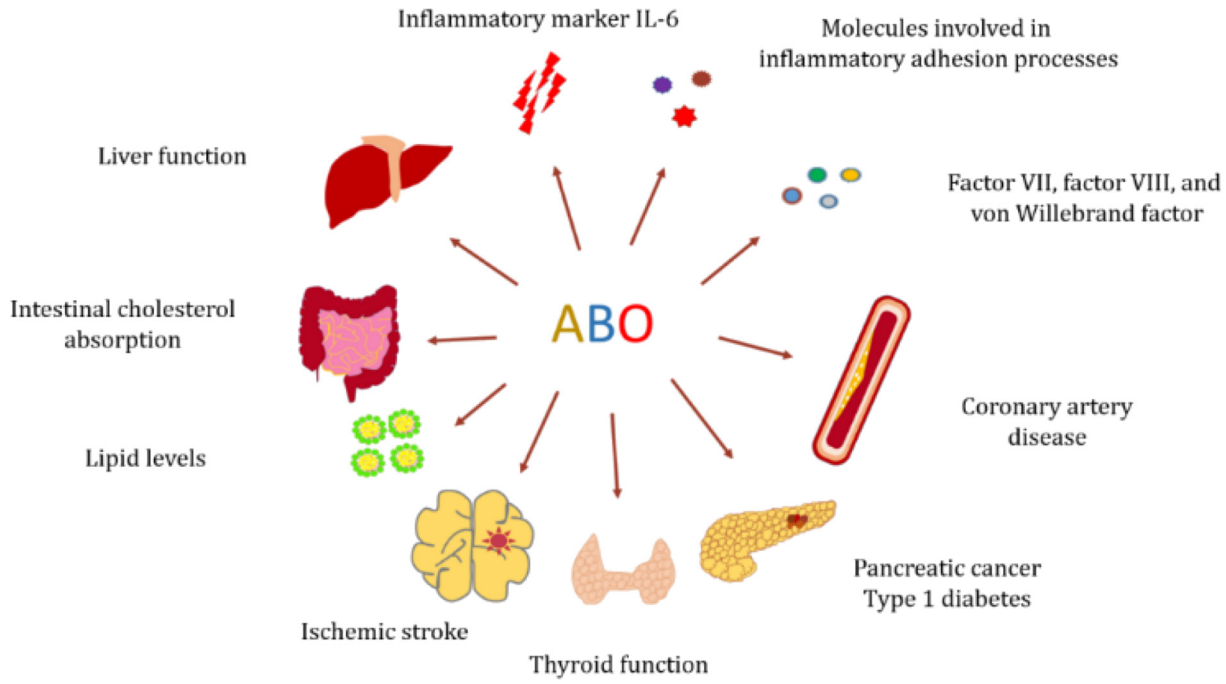

Fig. 1. Schematic illustration of pleiotropy in ABO locus.

are different amongst healthy controls who use aspirin for reasons other than CAD. Follow-up research is essential to demonstrate how the results observed here are linked to CAD and response to aspirin therapy in longitudinal studies as well as animal models.

It is yet too soon to believe that the findings of Christiansen and colleagues explain the greater chance of myocardial infarction amongst carriers of ABO CAD risk allele. Given the highly pleiotropic nature of ABO locus and presence of the ABO blood group antigens on many various cell types, it is more likely that ABO locus involves in multiple pathways leading to myocardial infarction.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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