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IgA antibodies to beta2-glycoprotein I and atherosclerosis

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Beta2-glycoprotein I (β_2-GPI), a phospholipid (PL)-cofactor with natural anticoagulant properties [1], is a 50-kDa serum protein composed of five homologous domains. Domains 1–4 each consists of 60 amino acids, while the fifth domain has an extra 20 amino acid terminal segment containing the PL-binding site [2,3].

Sera from patients with the antiphospholipid syndrome (APS) are usually reactive to cardiolipin in assays which utilize β_2-GPI [4]. Antibodies directed to β_2-GPI itself can be found in patients with APS [5] or thromboembolic pulmonary hypertension [6].

The relationship of anti-β_2-GPI antibodies with atherosclerosis is intriguing, since β_2-GPI has been found in atheroma [7]. A case report has previously linked anti-β_2-GPI antibodies to cerebral infarction [8]. An association of IgG anti-β_2-GPI with coronary heart disease was found in patients with or without a history of previous myocardial infarction, which suggests that the antibodies are not induced by tissue necrosis [9]. More recently, anti-β_2-GPI antibodies, mostly of the IgA isotype, were associated with acute coronary syndromes. Such antibody response was particularly notable in young males with previous stroke [10].

For the last 5 years, our group has focused on examining this potential association in diverse groups of atherosclerotic patients. In all of these studies, a case-control design was utilized. IgG, IgM and IgA anticardiolipin (aCL) [11], as well as IgG, IgM and IgA anti-β_2-GPI antibodies [12], were detected by immunoassays.

Firstly [13], we set up to analyse the association of aCL and anti-β_2-GPI antibodies with cerebral disease. Ninety-three patients with acute ischemic stroke and 93 controls were evaluated for age, sex, race, hypertension, smoking, previous cardiopathy, diabetes mellitus (DM), hypercholesterolemia and previous history of cerebral ischemia. The adjusted OR for IgA anti-β_2-GPI antibodies was 4.6 (90% CI 1.5 to 14.3, $p=0.025$).

The next step [14] was to evaluate this association in a population diagnosed with acute myocardial infarction (AMI). Eighty-two patients with AMI and 82 controls, assessed with regards to age, sex, race, hypertension, smoking, previous heart disease, DM and hypercholesterolemia, were studied. The adjusted OR for anti-β_2-GPI IgA antibodies was 3.4 (95% CI 1.3 to 9.1, $p=0.015$).

The same evaluation was done for a population with peripheral artery disease (PAD) [15]. Seventy-seven cases and 93 controls were studied for age, sex, race, hypertension, smoking, DM and hypercholesterolemia. The adjusted OR for IgA anti-β_2-GPI antibodies was 5.4 (95% CI 1.8 to 15.8, $p=0.01$). The non-adjusted OR for IgA aCL was 11.5 in this population ($p=0.04$).

Uniformly, an independent risk association of IgA anti-β_2-GPI antibodies with atherosclerotic disease was found in these populations [13–15]. Except for the PAD group, aCL antibodies were not significantly detected as compared to controls. IgA anti-β_2-GPI and IgA aCL

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might comprise antibodies of different specificities, as suggested in patients with systemic lupus erythematosus (SLE) [16]. Moreover, IgA anti-β_2-GPI antibodies were associated with unexplained recurrent abortions even in women aCL-negative [17].

The majority of our atherosclerotic patients with IgA anti-β_2-GPI antibodies did not present features of APS [18]. In the majority of our atherosclerotic sera, IgA reactivity to β_2-GPI occurred independently of aCL. Thus, we may infer that the antibodies directed to β_2-GPI from atherosclerotic patients differ from those of aCL-positive APS patients. It has been shown, using recombinant β_2-GPI and β_2-GPI domain-deleted mutants expressed in insect cells, that the anti-β_2-GPI autoantibody from APS patients recognize domain 1 of β_2-GPI [19]. It could be that anti-β_2-GPI antibodies from atherosclerotic patients bind different epitopes in the β_2-GPI molecule.

APS classification criteria have not included anti-β_2-GPI antibodies to date [20]. If it is added in the future, then concerns about the fine antibody specificity will have to be taken into account to distinguish anti-β_2-GPI responses of autoimmune and atherosclerotic disorders.

A pathogenic role for anti-β_2-GPI antibodies in atherosclerosis is hypothetical. In vivo, the antibodies could bind available β_2-GPI on apoptotic cell surfaces. Opsonization of apoptotic cells by anti-β_2-GPI antibodies facilitates phagocytosis of these cells by macrophages [21].This could eventually be the case at atheroma plaques. Immunization of apolipoprotein E-deficient mice with β_2-GPI generates anti-β_2-GPI antibodies and atheroma formation [22]. In the same murine model, immune tolerance was obtained after oral administration of β_2-GPI [23].

The relationship of β_2-GPI with the oxidized LDL (OxLDL) molecule is of current interest. In plasma, OxLDL binds to β_2-GPI through the OxLig-1 and OxLig-2 ligands. The β_2-GPI/OxLDL complex can be found in peripheral blood of patients with autoimmune and infective disorders, but also in atheroma. There, it could behave as an atherogenic autoantigen [24].

The interaction of OxLDL with "scavenger" receptors of macrophages is prevented by binding of the lipoprotein to β_2-GPI. The complex β_2-GPI/OxLDL, targeted by IgG, could be internalized by occupation of IgG receptors at the macrophage surface. Thus, IgG antibodies directed to this complex could be intermediating the generation of "foamy" cells [25].

Anti-β_2-GPI antibodies of APS patients are not cross-reactive with antibodies to pure OxLDL in ELISA plaques [26]. Interestingly enough, anti-β_2-GPI and antiphosphatidylserine antibodies were predictors of arterial thrombosis in patients with APS [27]. Likewise, antibodies to the β_2-GPI /OxLig1 lipid complex were strongly related to arterial thrombosis in patients with SLE and APS [28,29]. The definite association of these antibodies with arterial disease is noteworthy in autoimmune diseases, since they might be promoting atheromatosis.

Our data in atherosclerotic patients showed a strong, reproducible predominance of IgA antibodies to β_2-GPI. The pathogenetic significance of this finding is unknown. It is possible that these antibodies are directed to the β_2-GPI/lipid complex and not solely to β_2-GPI.

From such findings, a hypothesis can be pursued. IgA receptors have been found in the macrophage cell membrane. They are highly glycosylated 60-kDa molecules. Occupation of these receptors is associated with a variety of biological actions by macrophages, including phagocytosis [30]. We suggest the possibility that the IgA anti-β_2-GPI autoantibodies detected in atherosclerotic patients may be atherogenic by occupying IgA receptors of macrophages. The internalization of the OxLDL component of the complex would culminate with the formation of "foamy" cells. An important point to be investigated is the determination to which epitopes of the β_2-GPI molecule the IgA antibody binds.

Why the IgA isotype is mostly involved in this humoral response in atherosclerosis is also a matter to be resolved. While in infection the IgA response is clearly associated with the defense of mucosal sites, little is known on the role of IgA in autoimmunity. Molecular mimicry of the β_2-GPI molecule with bacterial/virus peptides has been reported [31]. It could be postulated that the IgA anti-β_2-GPI response of atherosclerotic patients is indirectly related to occult infection.

In summary, a pathogenic role for IgA anti-β_2-GPI antibodies in atherosclerosis is yet to be confirmed. Whether this autoantibody binds to the β_2-GPI/lipid complex, to β_2-GPI on apoptotic cells, or is an epiphenomenon is open to discussion. We emphasize that this response looks distinct from the anti-β_2-GPI reactivities seen in SLE/APS [5,32]. The IgA anti-β_2-GPI response seen in patients with acute cerebral and myocardial syndromes, as well as in PAD, independently of other risk factors for atherosclerotic disease, may represent one of the links between autoimmunity and atheromatosis. The clinical and laboratory implications of such findings should be soon clarified.

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