Commentary

Atheroma: links with antiphospholipid antibodies, Hughes syndrome and lupus

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Summary

Antiphospholipid antibodies (aPL) are found in a variety of autoimmune diseases, and are thought to predispose to arterial and venous thrombosis. These antibodies, when investigated in different assays in vitro, activate endothelial cells and promote uptake of modified LDL to macrophages. These observations suggest that aPL can contribute to atheroma development by targeting some of the sequential steps that constitute early atherogenesis. If substantiated by large-scale clinical trials, the pro-atherogenic properties of aPL may merit screening and intervention programs in selected populations.

In 1993, the Lancet carried an article by Vaarala and colleagues which suggested that some antiphospholipid antibodies were capable of cross-reacting with oxidized low-density lipoprotein (oxLDL). This finding focused attention on the reports of accelerated arterial disease seen in individuals with the antiphospholipid (Hughes) syndrome, and has provided a new line of atheroma research. Since the description of the syndrome in 1983, it has been clear that its many features include venous and arterial thrombosis. This propensity, both to arterial thrombosis and accelerated arterial disease, had of course, long been recognized in lupus, and a variety of hypotheses had been put forward—notably as an effect of long-term steroid therapy. It now seems likely that the strongest arterial risk factor, both in SLE and in Hughes syndrome (antiphospholipid syndrome) is the presence of antiphospholipid antibodies (aPL). Further, it is clear that there are ‘subjects’ of aPL with different specificities—some (predominantly those requiring the co-factor β2GPI for binding) being more strongly associated with thrombosis. A more recent clinical observation was that aPL cross-reacted with oxLDL were more closely associated with arterial than with venous thrombosis. If proved correct, this observation has implications, not only for therapy in lupus and in Hughes syndrome, where arterial disease (especially stroke), is currently treated with warfarin to a high INR, but also more broadly in terms of the pathogenesis and prophylaxis of atheroma.

The formation of atheroma is increasingly recognized as an inflammatory process in the arterial wall, including the accumulation of macrophages and activated T-lymphocytes. A high oxidative capacity in the arterial wall leads to oxidation-mediated endothelial injury and to a vital decrease in the physiological function of the endothelium. It is an attractive working hypothesis, therefore, to assume that antibody responses to oxidized plasma

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proteins, such as oxLDL, β2GPI, prothrombin or heat-shock proteins may influence this inflammatory reaction and the associated thrombotic risk in atherosclerosis.

The association of ‘autoimmune’ aPL with thrombotic events has been documented so consistently that their causal role in establishing a prothrombotic state is highly suggested. Indeed, well-conducted clinical trials have shown that the occurrence of aPL can be considered as an independent risk factor for myocardial infarctions and cerebral strokes. These findings have prompted an elaborate effort by many investigators to determine the mechanism by which aPL induce thrombosis. Activation of endothelium cells and platelets, and induction of tissue factor have all been suggested as possible mechanisms for the prothrombotic diathesis. An interesting point which relates to these findings is the requirement of β2GPI for the mentioned functional properties, further emphasizing β2GPI targeting by aCL.

The issue of target recognition of aCL is apparently more complex than initially thought. Other than binding β2GPI, aCL were shown by several authors to cross-react with oxLDL and some have even suggested that the true target of some aCL may actually reside in neo-epitopes appearing within phospholipids upon their oxidation. These observations bear particular relevance to the study of the interrelations between aCL and atherosclerosis, since oxLDL is considered a major immunogen characterizing risk groups which may, in the future, benefit from regimens aimed at reducing antibody titers or to intervening with its atherogenic effects.

In a recent study, β2GPI-reactive aPL were shown to enhance the uptake in vitro of oxidized lipoproteins to macrophages, leading us to speculate that these antibodies may have a role in atherosclerosis. The modern view of the atherosclerotic process is based on the assumption that the early stages of fatty streak formation are the result of monocyte adherence to endothelial cells at sites of local tissue stress. Subsequently, the adherent monocytes turn to macrophages expressing the scavenger receptor which allows for an unregulated influx of oxidized LDL to these cells.

Each of the steps constituting early atherosclerosis can actually be influenced by aPL. Endothelial cell activation can be triggered by aCL in vitro. The effect is mediated by upregulation of adhesion molecules and the surface of the cultured endothelial cells. As mentioned above, aCL can also increase the uptake of oxidized LDL by monocytes. Moreover, since thrombotic events are considered as part of the atherosclerotic process, the creation of a prothrombotic ‘atmosphere’ by aCL can contribute to atherogenesis.

We have recently tested the hypothesis that aCL induced by immunization with human β2GPI affect atherosclerosis. Indeed, transgenic mice lacking the LDL receptor were found to develop accelerated atherosclerosis upon immunization with β2GPI. This animal model substantiated the link between the anti-β2GPI response and atherosclerosis. However, if aPL can be found to possess proatherogenic properties, population screening programs may characterize risk groups which may, in the future, benefit from regimens aimed at reducing antibody titers or to intervening with its atherogenic effects.

References


