In previous publications, these authors demonstrated the association of 2GPI/HLA class II complex on endothelial cells and the complex is transported to the plasma membrane to present the peptide cargo to CD4 T cells.

In antigen-presenting cells, HLA class II molecules present peptide antigens derived from extracellular proteins by the endocytic pathway to the CD4 T cells via the peptide-binding groove.2 Following their assembly in the endosomal reticulum with an invariant chain (Ii), the Ii/HLA class II complexes are transported to the late endosomal compartment called the major histocompatibility complex (MHC) class II compartment. Here, Ii is proteolytically processed and removed, allowing peptide loading to the antigen-binding groove in the HLA class II complex. The HLA class II complex is then transported to the plasma membrane to present the peptide cargo to CD4 T cells.

In previous publications, these authors have shown that the HLA class II molecules can also transport certain intact misfolded proteins such as the immunoglobulin G heavy chain from the endosomal compartment to the cell surface.3,4 Compared with HLA class I molecules, the peptide-binding groove of HLA class II molecules is open, and it can accommodate longer peptides. By using 293T cells transfected with complementary DNA for β2-GPI and HLA class II complex, the authors showed that misfolded β2-GPI was bound to HLA class II molecules inside the cell. This interaction presumably occurs in the endosomal compartment, and the complex is transported to the cell surface. The binding of the β2-GPI/HLA class II complex depends on the HLA-DR alleles. Certain APS-susceptible alleles such as HLA-DR7 and HLA-DR4 bound to β2-GPI more effectively than other alleles. Although these studies were performed in transfected 293T cells with forced expression, the authors demonstrated the association of β2-GPI/HLA class II complex on endothelial cells in the placenta of patients with APS but not in the placenta of patients without APS. HLA class II–bound misfolded β2-GPI is not only a target of antibody–induced injury but is also a potent inducer of antigen–specific B cells and may play a role in the persistence of these antibodies in APS patients.

These novel findings raise several interesting questions, which have a direct bearing on the mechanism of the procoagulant state of the placenta associated with APS. Endothelial cells, the most extensively studied target, express class II antigens only after stimulation. This raises the question of whether only inflamed endothelial cells are the targets of the antiphospholipid antibodies. However, most patients with APS do not have evidence of vasculitis or other inflammatory conditions. Macrophages, the professional antigen-presenting cells, express HLA class II molecules and internalize β2-GPI/phosphatidylserine–containing vesicles and platelet microparticles, and they can potentially express this epitope on their surface. In monocytes, antiphospholipid antibodies induce tissue factor, the major initiator of the coagulation system.4 Furthermore, the HLA class II molecules can transmit outside-in signals by triggering multiple pathways, and several signal transduction cascades have been shown in endothelial activation by β2-GPI–dependent antiphospholipid antibodies.

Despite a large number of studies on this subject, the precise mechanism of the procoagulant state in APS is still elusive.5 The Tanimura et al study provides yet another potential cell surface receptor for β2-GPI that may be involved in the induction of the procoagulant state.
HLA class II meets $\beta_2$-glycoprotein I

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