The anti-phospholipid syndrome (APS) is defined by recurrent thrombosis and miscarriage in the presence of anti-phospholipid antibodies (aPLs). APS causes an inflammatory vasculopathy and promotes thrombosis and atherosclerosis in the setting of "oxidative stress" [1]. Anti-oxidant systems are depleted, and critical disease-related proteins, such as β2-glycoprotein I become oxidised. Unfortunately, trials of non-selective anti-oxidants for treatment or prevention of vascular disease have generally proved disappointing. More refined manipulation of not only global redox state, but of oxidation-dependent signalling may be required.

Reactive oxygen species (ROS) are important biochemical intermediates in cytokine signalling. The NADPH oxidase (Nox) enzymes localise superoxide production within endosomes [2]. This architecture may protect the cytoplasm from oxidation during routine signalling by TNFα and IL-1β. Ironically, downstream steps in these pathways are also linked to ROS production and over-activation of these receptors can promote global cytoplasmic oxidation. Nox-dependent signalling plays a critical role in vascular inflammation associated with hypertension, diabetes and atherosclerosis [3].

In this issue of Thrombosis and Haemostasis, Mueller-Calleja et al. (4) provide important new insight into the mechanism by which human monoclonal aPLs activate mononuclear cells. Uptake of these antibodies by endocytosis triggers superoxide production by endosomal Nox2. This is required for induction of caspase-1 and NOD-like receptor 3 (NLRP3) transcription and assembly of the NLRP3 inflammasome. Parallel activation of TLR7/8 or TLR2 induces pre-IL-1β expression which is then readily converted to active IL-1β by the assembled inflammasome. The authors propose that endosomal Nox coordinates pro-inflammatory and pro-coagulant signalling in innate immunity.

The mechanism by which aPLs activate endosomal Nox2, and how this process is regulated remain to be determined. However, the current work provides exciting new targets for therapeutic intervention in APS. Nox enzymes are already the focus of drug development in a variety of inflammatory conditions, and redox-active endosomes provide a unique biochemical environment for selective drug delivery.

Conflicts of interest
None declared.

References