This editorial refers to 'Vessel wall, not platelet, P2Y12 potentiates early atherogenesis' by L.E. West et al., pp. 429–433, this issue.

Platelets play a key role in primary haemostasis and also represent an important interface between thrombosis, immunity, and atherogenesis. Platelet-triggered inflammatory pathways contribute to the formation of atherosclerotic lesions and athrombosis. Platelets express receptors for a variety of agonists that initiate platelet activation, which is then amplified and sustained by activation of the G-protein-coupled purinergic receptor P2Y12. P2Y12 mediates platelet aggregation and secretion of platelet granule contents in response to ADP. P2Y12 is also a well-established target for anti-thrombotic drugs, such as the thienopyridine compounds ticlopidine, clopidogrel, and prasugrel or the direct, reversible antagonists ticagrelor, cangrelor, and elinogrel. Clinical studies have shown that in addition to preventing arterial thrombus formation in patients with coronary artery syndromes or after stent implantation, anti-thrombotic/anti-platelet therapy is also associated with systemic anti-inflammatory effects. While these findings imply an important role for vessel wall P2Y12 expression would likely be higher in vessel wall cells of atherosclerotic than in naive animals. In human vascular smooth muscle cells, P2Y12 expression is transcriptionally regulated via NK-kB, a key regulator of pro-inflammatory signalling pathways. Activation of the NF-kB signalling pathway in atherosclerosis-prone areas has been well documented.

Another recent study also evaluated the role of P2Y12 in lesion progression in ApoE mice following 20 weeks of high-fat diet. Consistent with the findings of West et al., P2Y12 deficiency was also found to attenuate late lesion progression. However, under this condition, both platelet and vessel wall P2Y12 appeared to contribute to lesion progression. This would point to an increasing contribution of platelet P2Y12 to atherogenesis with a particularly pronounced role in the advanced lesion. This notion is in agreement with clinical observations of enhanced platelet reactivity in patients with advanced stages of atherothrombotic diseases.

Over the past years, it became evident that haematoopoietic as well as non-haematoopoietic cells, including cells present in the vessel wall, express P2Y12. Possible candidate cell types in the vessel wall, in which P2Y12 expression may have relevance to atherogenesis include endothelial cells, smooth muscle cells, and immune cells such as monocytes and macrophages. P2Y12 expression has been reported in endothelial cells, where its expression may be transcriptionally regulated by certain toxins, such as nicotine. Human vascular smooth muscle cells also express P2Y12. In these cells, ligation of P2Y12 has been implicated in the regulation of calcium signalling and vasoconstriction. In addition, thrombin, the central regulator of coagulation, has been shown to enhance P2Y12 transcription through activation of the NF-kB signalling pathway in human vascular smooth muscle cells in vitro. Possible actions of smooth muscle P2Y12 may include induction of pro-inflammatory cytokine production and Gxi-mediated signalling.
An obvious limitation of the study of West et al. is that it provides no information on the cell types expressing P2Y12 in the vessel wall. The signalling pathways downstream of platelet P2Y12 have extensively been studied. Activation of P2Y12 inhibits adenylate cyclase activity and subsequently reduces cAMP-mediated signalling such as granule secretion and regulates PI3 kinase and Akt signalling. Whether ligation of P2Y12 triggers similar pathways in vessel wall cells, i.e. in smooth muscle or endothelial cells, remains speculative. Potential pro-inflammatory and atherogenic effects of P2Y12 may involve signalling pathways known to be present in both platelets and smooth muscle cells; for example, coupling to surface toll-like receptors or secretion of growth factors. Figure 1 summarizes the possible actions and transcriptional regulation of P2Y12 in cells of the vessel wall.

An unexpected observation in this study was the failure of the P2Y12 inhibitors ticagrelor and clopidogrel to reduce lesion size at the early disease stage. Earlier studies have reported an effective inhibition of ADP-induced vasoconstriction by ticagrelor and clopidogrel in isolated arteries. Whether the unresponsiveness to these anti-platelet compounds was due to their limited bioavailability within the vessel wall and/or differences in platelet and vessel wall P2Y12 sensitivity to inhibitors remains to be investigated. However, indirect evidence suggests systemic anti-inflammatory effects of P2Y12 inhibitors, which may extend beyond inhibition of platelet functions. Clearly, additional studies are needed to address the impact of P2Y12 antagonists on the progression of atherosclerotic lesions and possibly plaque rupture. One perspective for the clinical use of P2Y12 inhibitors is to define the role of vessel wall P2Y12 for vascular lesion progression. The study of West et al. provides a solid starting point for such future studies. Considering the complexity of platelet and vessel wall P2Y12-mediated actions, it remains a future challenge to investigate whether therapeutic interventions aimed to targeting vessel wall P2Y12 could have clinical benefits for patients with atherosclerosis.

Conflict of interest: none declared.

Funding
This work was supported by grants from the Deutsche Forschungsgemeinschaft (SFB612, TPB11 to B.H.R.) and the Canadian Institutes of health research (MOP-97742 to J.G.F.).

References


