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VESSEL WALL, BUT NOT PLATELET, P2Y₁₂ CONTRIBUTES TO EARLY ATHEROGENESISL West, S Francis, R Storey *University of Sheffield*

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The fundamental role of platelets in atherothrombosis is well defined but the extent of their role in early atherogenesis remains unclear. The P2Y₁₂ receptor is responsible for amplifying and sustaining the platelet activation response and P2Y₁₂ inhibition has been shown to be crucial in modulating the vessel wall response to injury. We therefore hypothesise that P2Y₁₂ activation is important in atherogenesis.

ApoE^{-/-} and ApoE^{-/-}P2Y₁₂^{-/-} mice were fed either a chow or western diet for 12 weeks and atherosclerotic burden was assessed by *en face* Oil Red O staining of whole aortae and histological analysis of the aortic sinus and brachiocephalic artery. Bone marrow transplants were performed to determine the roles of platelet versus vessel wall P2Y₁₂ in early atherogenesis following 4 weeks of western diet.

Oil Red O staining showed no difference in total lesion area between ApoE^{-/-}P2Y₁₂^{-/-} and ApoE^{-/-} mice for either diet when assessing the aorta as a whole. However, further analysis of the aortic arch alone uncovered a significant reduction in atheroma in ApoE^{-/-}P2Y₁₂^{-/-} mice fed a western diet (8.54±0.85 versus 16.67±1.25 %; P<0.0001). Similarly histological analysis revealed attenuated lesion area in the brachiocephalic artery (P<0.05) but not in the aortic sinus. Bone marrow transplants demonstrated that mice deficient in vessel wall P2Y₁₂, regardless of platelet P2Y₁₂ expression, had significantly reduced atheroma in both the aortic sinus and brachiocephalic artery (P<0.001).

This work identifies an important role for vessel wall P2Y₁₂ in promoting early atherogenesis. Despite the proven role of platelets in atherothrombosis and the profound effect of P2Y₁₂ on platelet reactivity, we found no platelet P2Y₁₂ effect on early atherogenesis. Published data has linked P2Y₁₂ expression with vascular smooth muscle cell mitogenesis, providing a potential mechanism for the effects seen in these results.