Editorial Commentary

Monocyte-platelet cross-talk in peripheral artery disease—how much does the pathogenesis of atherosclerosis depend on anatomical location?

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Atherosclerosis results from a complex interaction between leucocytes (primarily monocytes), endothelial cells, endothelial shear stress and platelets. Vascular remodelling is influenced by traditional risk factors and also mediated by cytokines (1). Monocytes are mononuclear cells of myeloid origin and represent about six percent of the total leukocyte population (2). Current nomenclature divides them into three (functionally diverse) subsets; Mon1 (CD14++CD16, formerly known as classical) represent about 85% of monocyte population, Mon2 (CD14++CD16+, formerly intermediate), about 5% and Mon3 (CD14+CD16++, previously non-classical), about 10% (3). Monocytes play a significant role in the pathogenesis of atherogenesis.

Platelets are recognised as important contributors to innate and adaptive immunity. Leucocyte interaction with activated platelets leads to up-regulation of pro-inflammatory cytokines, endothelial adhesion and production of reactive oxygen species. This is mediated through intracellular compartments containing α-granules, lysosomes and dense core granules as well as a complex membranous system allowing storage and release of the various factors (4). MPAs (monocyte-platelet aggregates—formed during the cross-talk between activated platelets and monocytes) are early markers of diabetes, endothelial dysfunction and subclinical atherosclerosis (5-7) and are a useful indication of platelet activation (8)—increased levels are present in ACS and post coronary angioplasty (9,10). Experiments in healthy people have shown that expression of CD16 on the surface of Mon1 incubated with autologous platelets increased compared to Mon1 monocytes in the medium without added platelet cells—an effect which correlated strongly with the degree of MPA formation ($r=0.88$, $P<0.0001$) and was associated with increased monocyte adhesion to endothelial cells (11). More recently MPAs from Mon2 monocyte subpopulation have been associated with diffuse coronary artery disease (CAD) (12), acute heart failure (13) and post ST-elevation myocardial infarction (9).

Despite the systemic nature of atherosclerosis, differences in disease topography, morphology and severity exist. For example, South Asians have the highest rate of CAD amongst all populations. Epidemiological studies suggest that they are twice as likely as Europeans and five times as likely as Chinese people to develop premature CAD (14) with three vessel disease found in 50% men and up to 33% of pre-menopausal women (15). Yet, South Asians have less peripheral artery disease (PAD) than other ethnicities despite a higher prevalence of severe diffuse CAD (16). This would suggest the presence of pathways, in the development of atherosclerosis, that are more prominent in PAD.

In their paper "Platelet-Derived MRP-14 Induces Monocyte Activation in Patients With Symptomatic Peripheral Artery Disease" (17), Dann *et al.* eloquently delineate the role of myeloid-related protein (MRP)-14 in promoting MPA formation, upregulating the

inflammatory profile [interleukin (IL) 1β, tumour necrosis factor (TNF)-α and monocyte chemo-attractant protein (MCP)-1 a.k.a. CCL2] of monocytes and driving their migration. Furthermore, they demonstrate a degree of specificity of MRP-14 to lower limb PAD patients and an association with cardiovascular and limb-related adverse outcomes (17). Crucially, MRP-14 produces a proatherogenic immunophenotypic profile on monocytes in PAD patients that is similar to the types of receptor seen most commonly on Mon2 (3).

The authors' main objective was to profile platelet activity, mRNA and effector roles in symptomatic PAD patients. Of course, it is likely that many of the cohort will have bystander CAD (or CAD that is less symptomatic than the claudication distance). Indeed, the authors acknowledge previous profiling of MRP-14 on the platelets of patients with acute STEMI and stable CAD (18). The absence of a healthy control group in Healy's paper makes referencing the MRP-14 found in stable CAD patients problematic and therefore could be a significant confounder regards its precise origin. Nevertheless, the effector data are robust and provide a novel insight regards platelets as drivers of inflammation in PAD patients.

Whilst platelets are key mediators in atherosclerosis, their inhibition does not necessarily halt its progression and despite widespread acceptance of the inflammatory response to injury theory, effective anti-inflammatory drugs in vascular disease have not been forthcoming until very recently (19). With attention now focused on monoclonal antibodies, the priority is to tease out pertinent pathways of the vascular inflammatory process. Several lines of inquiry implicate Mon2 subset as the dominant monocyte population and the most frequently aggregated to platelets in severe forms of coronary and peripheral vascular disease (9,12,20,21). For example, a cohort of patients with critical limb ischaemia—a risk factor for long term restenosis after femoropopliteal angioplasty with drug coated balloons (22)—were found to have significantly higher Mon2 counts than controls (20). It would be interesting to note whether the mechanisms underlying monocyte migration described by Dann *et al.* were accompanied by upregulation of CD16 and CCR2 on the monocyte surface.

The importance of immune specificity was highlighted in the recent CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) trial which randomised over 10,000 patients to 50, 150 or 300 mg of Canakinumab respectively against placebo and found a statistically significant reduction in the primary endpoint (non-fatal myocardial infarction, any non-fatal stroke, or cardiovascular death) with the 150 mg dose compared to placebo (19). Canakinumab, a monoclonal IL1ß inhibitor, effectively reduced high sensitivity C reactive protein and whilst it may benefit stable CAD who have ongoing inflammatory risk after appropriate lipid-lowering therapy, it did so at the expense of increased risk of fatal infection.

Herein lies the real challenge of the future—targeting the immune system with enough specificity to slow, or even halt the progression of CAD whilst maintaining adequate host defences.

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Footnote

Conflicts of Interest: GY Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo and has been on the speakers' bureau for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. RA Brown has no conflicts of interest to declare.

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