Targeting the prevention of plaque rupture as a new strategy for prevention of acute arterial cardiovascular events

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This editorial refers to 'Differential effects of PARP inhibition on vascular cell survival and ACAT-1 expression favouring atherosclerotic plaque stability' by C.P. Hans et al.,¹ pp. 429–439, this issue.

Acute arterial cardiovascular disease is usually caused by the sudden thrombotic occlusion of a vessel that is critical for maintaining adequate tissue perfusion and that contains an atherosclerotic plaque. Due to a myriad of processes within this plaque, rupture of its fibrous cap may occur, thereby exposing highly procoagulant material to the circulating blood, leading to occlusive thrombus formation and subsequent ischemia or infarction. In particular, inflammatory cells bearing tissue factor at their surface play a pivotal role in this mechanism, as tissue factor has been found to be the principal activator of the coagulation cascade, leading to the generation of thrombin and subsequent conversion of fibrinogen to fibrin. Hence, pharmacological strategies aimed at the prevention and treatment of acute cardiovascular disease thus far mainly focus on the reduction of atherosclerotic burden (e.g. by preventative strategies towards risk factors for atherosclerosis or by administration of statins) or on the inhibition of coagulation activation (e.g. by anticoagulants or anti-platelet agents). Besides these strategies, which have indeed been proven to be effective, stabilization of the atherosclerotic plaque could theoretically prevent plaque rupture and its downstream consequences and may thereby constitute another logical and novel target for the prevention of acute events.

In the present issue of Cardiovascular Research Hans et al.¹ present interesting new findings that indeed further increase the insight into the mechanisms underlying plaque rupture and novel strategies that may promote plaque stability. Focusing on poly(ADP-ribose) polymerase (PARP)-1, which is a DNA repair-associated nuclear enzyme that is activated in response to DNA damage, they have previously shown that excessive activation of this enzyme in response to local inflammation leads to cell death due to metabolic depletion. Previous studies from this group demonstrated that inhibition of PARP-1 indeed reduced cellular changes that are important for plaque dynamics and resulted in a reduction of plaque size, less collagen degradation, and increased smooth muscle cell content.² In the present manuscript Hans et al.³ extend these observations and demonstrate that in ApoE knockout mice on a high-fat diet, which is an established model for the development of atherosclerosis, inhibition of PARP decreases markers of oxidative stress and reduces apoptosis of endothelial cells and smooth muscle cells. In addition, PARP-1 inhibition through targeted deletion of the PARP-1 gene resulted in an inhibition of cellular activation and apoptosis in response to pro-inflammatory stimuli. These findings provide new insights in the role of PARP-1 in cell death in general and plaque dynamics in particular and demonstrate that PARP-1 inhibition reduces the inflammatory response, promotes foam cell death, and simultaneously protects smooth muscle cells and endothelial cells from oxidative stress and pro-inflammatory mediators. These results suggest that PARP-1 inhibition can be viewed as a new therapeutic target for prevention of atherosclerotic plaque rupture, although obviously further studies are warranted.³ It should be stressed, however, that the current observations were made in cells and models of atherosclerosis that not always accurately mimic the mechanisms of human disease and precisely predict therapeutic efficacy. Nevertheless, PARP-1 inhibition is an interesting new option for plaque stabilization, and hence prevention of acute arterial cardiovascular events, and certainly deserves further exploration.

To develop strategies that achieve plaque stabilization, more insight into the mechanisms underlying the process of plaque rupture is required. In recent years the understanding of the mechanisms causing plaque rupture has indeed considerably increased. It is clear that plaque rupture is not primarily determined by plaque size or

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structure, as has been shown in angiographic studies. Rather biologic factors within the plaque seem to play a more critical role. Among these, the balance between lipoprotein and cellular content of the plaque is an important factor. Expression of tissue matrix collagenases (such as the family of matrix metalloproteinases or MMPs) by macrophages and smooth muscle cells is pivotal for the degradation of the fibrous cap of the plaque. These cells also determine the thrombogenicity of the plaque contents due to the rate of tissue factor expression on their surface. Inflammation within the atherosclerotic plaque caused by pro-inflammatory cytokines produced by accumulated macrophages, but also by oxidative stress due to the lipoprotein content, may induce vascular endothelial cells to produce cellular adhesion factors, including monocyte chemotactic protein-1 and vascular cell adhesion molecule-1, thereby promoting further inflammatory cell involvement in the plaque. Interestingly, statins seem to affect all of these mechanisms, extending a role for this pharmacological intervention in the prevention of acute vascular events through plaque stabilization far beyond their lipid-lowering properties.

However, many of the factors involved in plaque dynamics have a dual face. For example, macrophages seem to display a series of detrimental properties towards plaque instability, but these cells simultaneously balance plaque stability through their ability to phagocytose oxidized lipoproteins and apoptotic cells. Also, vascular endothelial cells and smooth muscle cells may produce anti-inflammatory mediators, such as interleukin-10, thereby regulating excessive inflammatory activity. Hence, it seems that mechanisms involved in plaque stability and plaque rupture are rather complex and encompass a myriad of players that intensely interact with each other and may play for both teams at the same time. Further unravelling of these interactions will indeed be crucial for further development of plaque stabilizing strategies, and the effects of PARP inhibition as demonstrated here provide a good background for developing these strategies.

References