Neointimal Cracks (Plaque Rupture?) and Thrombosis in Wrapped Arteries Without Flow

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In Response:

Falk and colleagues raise a number of important issues regarding lesion formation and the modeling of plaque rupture in mice. The first of these concerns the question of whether the processes that lead to neointima breakdown in the model of Sasaki et al are congruent with those occurring during the breakdown of a fibrous cap overlying a lipid-rich necrotic core. Falk et al consider that there is no obvious reason to suppose that there is any such congruence. The second deals with the genesis of thrombi in the model of Sasaki et al compared with over a ruptured atherosclerotic plaque. Falk et al argue that the processes of thrombogenesis in conditions of rapid blood flow are likely to be different to those in stagnant blood in a ligated artery, a point well supported by a plethora of experimental evidence that has accrued over many years. Falk et al conclude on these bases that the relevance of the model of Sasaki et al to human plaque rupture is not clear, with the implication that it is of limited utility.

To be of utility, animal models of human disease should enable us to learn about the pathophysiology of the disease and, relatedly, provide a faithful test-bed for potential new therapies. These are essentially pragmatic issues: the quality of the data are of overriding importance and the procedures used during disease induction, and even the appearance of the signs of the disease, need not closely parallel what happens in humans. This point can be illustrated in a couple of ways. For example, it has been possible to learn much about smooth muscle cell migration and proliferation in tissue culture. Despite the obvious differences between this model system and a human fibrous cap, the data are clearly applicable and useful. Another example is the idea that precisely the same set of biochemical processes can give rise to rather different end results in a mouse and a human. Although their cells are the same size, human coronary arteries are about 30 times greater in diameter than those in mice. A rate of cell proliferation that would occlude a mouse coronary artery by 50% after 6 months would take 60 years to produce a 5% occlusion in a human coronary artery, even if the stimuli and pathways are identical. An important corollary point is that just because an experimental lesion looks like a human ruptured plaque it does not necessarily mean that it has an identical etiology and biochemistry. Faithful mimicking of human ruptured plaques gives us confidence that the model may be useful, but is no guarantee that it will be so.

By this analysis, it is too early to reach a judgment about the relevance of the Sasaki model to human ruptured plaques. The sets of processes that give rise on the one hand to neointimal breakdown and on the other to fibrous cap breakdown may have significant overlap even though the lesions look very different. A critical test of the Sasaki model will be to determine some of the pathways by which the neointimas of the mice break down and then to compare those pathways with events occurring in human fibrous caps. If there is reasonable congruence then the differing appearances of the two lesions are not important.

Because of such considerations, new models of human disease need to be assessed in their initial stages with some sympathy, especially when there are few existing models available, as is certainly the case with plaque rupture. In particular, insistence on close recapitulation of the histopathologic features of human ruptured plaques—and it is worth emphasizing that human ruptured plaques are structurally very heterogeneous—could lead to a situation where no model is ever accepted, and the consequent slowing of progress both in the laboratory and the clinic would be a disservice to the wider community. What is needed is an opportunity for other laboratories to investigate the model and to generate the data that will enable a judgment to be made about its pathophysiological relevance. This requires suspension of harsh judgment until the descriptive phase of model generation has passed. In my view, the only feature we should insist on in the descriptive phase is that the animal model has lesions that look like a human ruptured plaque it does not have clear breaks or defects which have arisen during life, which appears to be true of the Sasaki model. The next phase of model development does concern congruence with human pathophysiology. At present our options in this area are rather limited, and to some degree investigations in animal models are going to have to proceed and then be retrospectively validated—or invalidated—by focused investigations of human vulnerable or ruptured plaques. However, unless new models are allowed to proceed to the point where other laboratories can access them and work on them, these crucial data will be gathered slowly or not at all. The Sasaki model has now reached this threshold, and it will be interesting to see how it stands up to biochemical scrutiny.
Disclosures
None.

References
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