Unraveling the Mechanisms of Plaque Rupture in Murine Models

To the Editor:

Mice are rapidly becoming a model of choice for atherothrombosis and coagulation-related studies, but the suitability of murine models with extensive atherosclerosis for the interphase of these two processes, ie, plaque rupture and intramural thrombosis, remains controversial.1 Plaque ruptures and spontaneous erosions reaching the core of atheromas occur spontaneously, but rather infrequently, in a variety of murine arteries.2,3 In their recent article, von der Thüsen and colleagues4 utilized a combination of a perivascular collar, transfection with the proapoptotic factor p53, and acute phenylephrine-induced stress to achieve a high frequency of rupture in the carotid artery. However, the accompanying editorial from Dr Majesky emphasizes the absence of fibrin-rich clots and questions whether this is a valid model of human plaque rupture. We believe that the requirement of a murine model to faithfully reflect human plaque rupture is counterproductive. Although fibrin-rich thrombi do occur in mice,3 fundamental differences between mice and humans exist in hemodynamic conditions, anatomy of normal arteries, composition of atherosclerotic lesions, mechanical properties, and degrees of stenosis. In humans, approximately 2/3 of acute coronary syndromes evolve from plaques that are mildly obstructive before the acute event. In contrast, even early stages of murine lesions are associated with substantial stenosis and hemodynamic alterations that may influence rupture and thrombus formation. Two pathomechanistic differences appear particularly important: (1) murine atherosclerosis has a far greater propensity to invade the media; and (2) murine atheromas frequently show multiple superimposed smooth muscle caps3 that may be particularly prone to—or be the result of—deep erosion or rupture. A report of frequent spontaneous rupture of such plaques in the brachiocephalic artery also highlights important regional differences.5 Despite these differences, substantial similarities exist between murine models and humans and valuable insights may be gained by modulating specific factors influencing inflammation and plaque stability, as von der Thüsen et al demonstrated.

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Response

We wish to thank Drs Napoli and Palinski for their appraisal of our recent study and for their qualification of some of the criticisms put forward in the editorial of Dr Majesky.1 We fully concur with their opinion that progress in the design of new murine substrates for therapeutic and mechanistic studies on plaque rupture will not be aided by demanding that human thrombotic rupture be accurately reproduced. In view of its high clinical relevance, there is an urgent need for adequate animal models for thrombotic rupture. As also pointed out by Dr Bennett in a recent editorial in Arteriosclerosis, Thrombosis, and Vascular Biology,2 this new testing ground for therapeutics that intervene in plaque rupture should ideally be “a model of acute synchronous and reproducible rupture in a large portion of treated animals.” Although we do realize that several specific phenomena associated with thrombotic plaque rupture in humans are absent in the p53 model (eg, lack of fibrin-rich lesions), grosso modo it meets these criteria.3 Moreover, thrombotic rupture is widely considered a 3-step process involving plaque destabilization, a biomechanical trigger to incite cap rupture, and an intramural procoagulant milieu. Also in this respect, the p53 model essentially mirrors the current paradigm. We agree with Dr Majesky that the potential of the p53 model for high throughput screening will indeed be limited, but this was not the major motivation for its development. Although far from optimal, we consider the present model with its rapid development time, accessibility of lesions, high incidence of events, and temporal/spatial control already useful for mechanistic and therapeutic studies. In addition, new studies are underway to further enhance the physiological relevance of the individual steps required to achieve plaque rupture in this model. For instance, the use of strong triggers with prolonged vasopressor activity may require further improvement and we consider more physiological stressors, like hypoxic or mental stress,4 intracranial ACTH injection, or IV epinephrine injection as possible options in this regard. Apart from validating the pros and cons of the p53 model, the mere finding that p53 overexpression destabilizes plaques may hold the key to delineating one of the pathways in the plaque destabilization process in humans and thus possibly to paving the way for new therapeutic entries to prevent this process.

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