Ruptures of Delight? A New Mouse Model of Plaque Rupture

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There is a strange discrepancy in the world of vascular biology. It is clear from many investigations that the rupture of an atherosclerotic plaque is the most common triggering event for occlusive thrombus formation in a coronary artery, leading to myocardial infarction. However, many large vascular biology meetings do not include specific sessions on this topic. Indeed, even flagship journals such as *Arteriosclerosis, Thrombosis, and Vascular Biology* do not list “plaque rupture” among the standard keywords to be used during manuscript submission. Why does an issue of such clinical importance have such a low profile?

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The probable cause is the difficulty inherent in studying the phenomenon of plaque rupture, so that there are actually relatively few manuscripts and communications that address it directly (a quick interrogation of the PubMed database suggests that only about 1.5% of research articles published during the last 5 years in the atherosclerosis/coronary heart disease field deal specifically with plaque rupture). Although ruptured plaques can be identified and excised at post mortem, determining how recently the rupture has occurred is an imprecise matter. Intact plaques to be used as comparators may be in danger of impending rupture—but their proximity to the clinical horizon may again be difficult to assess accurately.

The usual recourse in such circumstances is to an animal model, but experimental models of plaque rupture have come into our hands only recently. Following the pioneering work of Dr Rosenfeld’s group in Seattle, first published in 2000,1 his group, ours, and others have refined the system2–10 so that now it is possible to study spontaneous plaque ruptures in the brachiocephalic artery (also called the innominate artery) of his group, ours, and others have high levels of plasma cholesterol that membrane function may be altered; animals triggered with animals have such high levels of plasma cholesterol that membrane function may be altered; animals triggered with p53 and phenylephrine may be unusually sensitive to smooth muscle relaxants or agents that influence cell survival. Where does the new model proposed by Sasaki et al14 stand in this regard?

It has been previously shown by Dr Galis’s group that ligation of the carotid artery in cholesterol-fed apoE knockout mice produces lesions that are rich in foamy macrophages.15 The lesions in Dr Sasaki’s chow-fed apoE knockout are much less foamy. They still contain appreciable amounts of insudated lipid, but they resemble more closely the lesions produced by direct arterial injury in apoE knockout16 and are therefore not closely representative of human vulnerable lesions. Is this a problem?

During the development of mouse models of plaque rupture there has been much discussion of the phenotype of the unstable lesions, and reviewers are often insistent that dissimilarities from human vulnerable plaques are a major disadvantage or even a fatal weakness in a mouse model. This is presumably based on the philosophy that similar ends betoken similar means: that if mouse and human unstable

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plaques look very similar then their underlying biology must be correspondingly similar, and conversely that if there are significant differences of phenotype then the plaque life histories must also be divergent. But human ruptured plaques are heterogeneous17–20 and by this reckoning must develop in a range of different ways. If so, exactly which part of the spectrum of human lesions should the animal model reflect? And if on the other hand the hypothesis of similar means, similar ends is incorrect, then the phenotype of the lesions in the model is not a major issue. It is time to make a stand for pragmatism: because our goal must be to generate an animal model that can be used to understand the pathophysiology of plaque rupture and to identify clinically effective interventions, we need to avoid rejecting animal models simply because they do not generate human-like lesions. The model of Sasaki et al14 should be investigated further despite the phenotype of the lesions.

Apart from lesion phenotype, there are two other major criteria that can be used to assess an animal model of plaque rupture. The first of these is the pathophysiological development of the plaques, which should be analogous to that in human vulnerable lesions. However, until we have worked out the sequence of processes that leads to the formation of vulnerable plaques in humans—or more accurately, because of the diversity of human lesions, the set of all such sequences—we will be unable to fully assess an animal model such as this in terms of its pathophysiological congruence to man. Clearly much progress has been made toward understanding how vulnerable plaques develop, but even simple questions such as “which proteinases degrade the fibrous cap?” cannot yet be answered with certainty and we are some way short of being able to use a pathophysiological sieve to select among prospective models of plaque rupture.

The second criterion is pharmacodynamic in nature: interventions that inhibit plaque rupture in humans should also show effect in the animal model. Unfortunately we have few tools at our disposal. The best candidates, 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A (CoA) reductase inhibitors, can reasonably be hypothesized to stabilize human plaques through a mechanism independent of plasma lipid-lowering21 but this is not universally accepted. Nevertheless, for the time being it is a fair test of an animal model of plaque rupture to ask whether its lesions are stabilized by statin treatment, and this should be an important future step in the development of the new model proposed by Dr Sasaki et al.14

In summary, a simple and quick method of inducing fibrous cap defects in carotid artery lesions in apoE knockout mice has been identified. It will be important now to delineate the processes that cause the caps to break and to ask whether the same processes happen in human vulnerable plaques.

References


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