To be useful, animal models for human diseases must be well defined. Thus we are concerned that investigators will be mislead by the definitions and terminology used by Jackson et al to describe putative plaque rupture models in mice. We are especially concerned with their use of “acute plaque rupture” to describe murine lesions that do not mimic any of the key features of human plaque rupture and use of “buried fibrous caps” as questionable evidence for past ruptures.

The consensus of cardiologists and pathologists is that rupture of human atherosclerotic lesions, defined as a structural defect in the fibrous cap overlying a necrotic core, is responsible for most coronary thrombi. This defect is associated with variable amounts of luminal thrombosis and plaque hemorrhage. Although neither thrombus nor plaque hemorrhage is required by this definition of plaque rupture, detection of these vital reactions is critically important to exclude possible postmortem artifacts. Confusingly, and in contrast to their original publications that emphasized luminal thrombosis, the current review by Jackson et al no longer considers thrombosis an important component of their “acute plaque rupture” model in mice.

Interpretation of mouse models will be very confusing if terminology is used in an inconsistent fashion. Use of precise and transparent terms does not in any way limit the use of animal models to study specific processes. Death of smooth muscle cells in the fibrous cap, growth of the necrotic core, accumulation of macrophages, and proteolysis within the fibrous cap are all believed to play important pathogenic roles in weakening and final rupture of the cap. Experiments addressing each of these processes in murine models are discussed in detail in the online version of our review article in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology.

Unfortunately, the key features of human plaque rupture (necrotic core, torn fibrous cap, and cap inflammation) are not required by Jackson et al in their “acute plaque rupture” model. As illustrated, this term is used to describe a disrupted endothelium with a few displaced erythrocytes in the intima (Figure 2 in Johnson et al). The “cap” is not much more than an endothelial layer, overlying a minimal connective tissue layer, lacking smooth muscle cells, and unable to accommodate the inflammatory cells assumed to play key roles in plaque rupture in humans. While our review stresses possible artifacts when evaluating such minimal endothelial changes, we acknowledge that the changes described here may be real and suggest a comparison to the “erosion” lesions described in human disease. However, equating minor surface disruption with a torn fibrous cap, cap inflammation and exposure of a necrotic core is misleading.

The character of their “spontaneous plaque rupture” is confused further by Figure 1 in the new review. This figure is unlike their earlier published data but is surprisingly similar to the disrupted lateral xanthomata originally described by two of us in the innominate artery of older apoE knockout mice. Even here, as stressed in our review, the murine lesions fail to fulfil some of the key features of human plaque rupture. Whether similar lesions exist in humans is unknown and needs to be explored.

Aside from the contradictory comments about the importance of luminal thrombus in their acute rupture model, the claim by Jackson et al that fibrin presence is indicative of thrombus remnants is confusing because of the lack of documentation of their method. All clotting factors necessary for the generation of fibrin, including fibrinogen, are present in atherosclerotic lesions. Bini and others have tried to distinguish fibrin from fibrinogen using existing monoclonal antibodies, but only achieved success by combining biochemical and histochemical approaches. Thus, the fibrin-specificity of the polyclonal antibody used by Jackson et al is critical and needs to be appropriately validated. Taking all these considerations into account, their evidence for fibrin in “buried fibrous caps” and the specificity for these structures are not fully convincing.

We do not understand the repeated claim that “buried fibrous caps” prove the existence of previous episodes of “acute plaque rupture”. Contrary to the experience cited by Jackson et al, we and others have seen spontaneous plaque fissuring, plaque hemorrhage, and multilayered plaques in the aortic sinus in old apoE knockout mice. Our view is very well represented by an explanation offered in a recent editorial by Martin Bennett: “In particular, the presence of multiple buried fibrous cap-like structures in human and mouse arteries does not necessarily prove that such structures occur by plaque rupture and repair. Such appearances could also occur by episodes of rapid lipid deposition, macrophage efflux, and smooth muscle cell recruitment without invoking fibrous cap rupture and repair. Episodes of thrombus formation in association with previously ruptured plaques were very rare in the study by Williams...
Terminology: Terms Describing Atherosclerotic Plaque Disruption and Related Features

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque Disruption</td>
<td>We suggest use of this term as a generic term, including any lesion where continuity of the surface is lost. Previously, plaque disruption has been used as a synonym for plaque rupture, or for all lesions with missing endothelium even if there is no break in the underlying plaque.</td>
</tr>
<tr>
<td>Endothelial Denudation</td>
<td>We prefer “endothelial denudation” to the term “erosion” because “erosion” has come to be used when endothelial denudation occurs with thrombosis, even though denudation does occur both in humans and animal models without formation of a thrombus.</td>
</tr>
<tr>
<td>Erosion</td>
<td>“Erosion” has come to be used when endothelial denudation occurs with thrombosis in the absence of breaks in the fibrous cap and, therefore, without access to a necrotic core. Erosion may even occur over lesions that lack a necrotic core. The term is confusing because it conflates denudation and thrombosis, even though we do not know that the two are causally connected.</td>
</tr>
<tr>
<td>Plaque Rupture</td>
<td>Plaque rupture is a term used consistently by those studying coronary thrombosis. It implies a structural defect (a gap) in the fibrous cap that separates a necrotic core of an atherosclerotic plaque from the lumen, resulting in exposure of the necrotic core to the blood via the gap in the cap. Neither thrombus, nor plaque hemorrhage (see below), is required by this definition of plaque rupture, but these vital reactions are important to exclude artificial plaque disruption. Endothelial denudation, fissures, or microvessel-derived intraplaque hemorrhage do not expose a necrotic core and, consequently, do not meet the definition of plaque rupture.</td>
</tr>
<tr>
<td>Plaque Fissure</td>
<td>This term is best used for breaks in plaques that do not expose a necrotic core. In a fissure there is no or minimal loss of plaque material. Michael Davies reintroduced the term and used it synonymously with plaque rupture; however, it is also used to refer to limited areas of disruption that do not meet the criteria for rupture. Murine lesions arising by disruption of the lateral xanthoma may be classified as plaque fissure.</td>
</tr>
<tr>
<td>Healed Fissure/Rupture</td>
<td>Fissures and ruptures may heal forming scarred lesions that may include thrombotic debris. In mice, there is speculation that periodic ruptures could produce multilayered lesions; however, such lesions are more likely to arise simply by episodic plaque growth, with new tissue (e.g., a xanthoma) forming atop an older lesion.</td>
</tr>
<tr>
<td>Necrotic Core</td>
<td>A hypocellular plaque cavity devoid of collagen and containing necrotic debris and cholesterol clefts. It originates, at least in part, from dead lipid-laden foam cells and has been called the graveyard of dead macrophages. Synonyms: lipid core, atheromatous gruel, and pultaceous debris.</td>
</tr>
<tr>
<td>Fibrous Cap</td>
<td>The fibrocellular structure that separates the necrotic core from the blood. Thus, if a plaque does not contain a necrotic core, a fibrous cap cannot be defined. Endothelium alone does not make a fibrous cap.</td>
</tr>
<tr>
<td>Plaque/Intraplaque Hemorrhage</td>
<td>Bleeding (extravasation of erythrocytes) into or within a plaque. It may originate either from the lumen through a disrupted cap or from breakdown of defective microvessels within the plaque. When possible, we use the term “plaque hemorrhage” for the former and “intraplaque hemorrhage” for the latter. It is very important to distinguish plaque hemorrhage originating by disruption of the fibrous cap from intraplaque hemorrhage arising by breakdown of microvessels within the plaque.</td>
</tr>
<tr>
<td>Vulnerable Plaque</td>
<td>Although commonly used to mean a plaque containing a large necrotic core with an overlying thin and inflamed fibrous cap, this related term “unstable”, “vulnerable”, or “destabilized” is generally better to be used to describe lesions prone to rupture. “Unstable” plaque is a more comprehensive term that includes vulnerable plaques that rupture and even the development of platelet-rich arterial thrombosis can be studied in mice. With the recent development in molecular imaging technologies, exciting opportunities now exist for the use of mouse models not only to explore basic mechanisms of plaque development but also to explore mechanisms of plaque rupture.</td>
</tr>
<tr>
<td>Thrombus</td>
<td>A solid mass formed from fibrin and platelets in vivo and within the vascular lumen. In contrast to postmortem clots (and some red thrombus) formed in stagnant blood, thrombi formed in flowing blood during life contain clumps of platelets and/or fibrin membranes.</td>
</tr>
</tbody>
</table>

et al, emphasizing the possibility of this alternative explanation. We do agree with Jackson et al that cuff models of rapid plaque development deserve attention. However, as previously described by Biessen and Krans and coworkers, spontaneous plaque rupture occurs rarely if ever in these models. We still see no reason to accept the changes occurring after cuffing of an occluded artery as a model of plaque rupture and have recently discussed our concerns.

In summary, we agree with another statement published recently by Martin Bennett, a coauthor of the review article by Jackson et al: “The brachiocephalic artery develops advanced atherosclerosis reproducibly, including lumen narrowing and medial thinning, and shows evidence of possible plaque rupture, although the appearances that define the latter are still controversial. A more precise definition of terms might help settle this controversy. Our fundamental disagreement with Jackson et al is related to their resistance to the use of descriptive terms versus terms that imply interpretations. After reading their review article, we feel even more compelled to discourage the use of deterministic and/or conclusory terms such as “vulnerable”, “unstable”, “destabilization”, and “buried fibrous caps” when describing atherosclerotic lesions. The definition and identification of human-like plaque rupture should be clearly and cautiously separated from putative surrogate markers, including the (intra)plaque hemorrhage described in our own model. To assist in that effort, we offer terminology outlined in the Table.

This dispute must not leave the impression that no useful mouse models exist to study plaque rupture and its consequences. Although human-like plaque rupture only rarely occurs spontaneously in mice, it was recently induced by a more sophisticated approach. Very useful murine models of rupture-related features do exist, and even the development of platelet-rich arterial thrombosis can be studied in mice. With the recent development in molecular imaging technologies, exciting opportunities now exist for the use of mouse models not only to explore basic mechanisms of plaque development but also...
obtaining proof-of-principle for in vivo plaque characterization and assessment of disease activity.43–46

Disclosures

None.

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Putative Murine Models of Plaque Rupture
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