The Intima
A New Soil

Stephen M. Schwartz

Weninger and colleagues,1 in this issue of Circulation Research, have simply and elegantly reported on a piece of fundamental arterial biology totally unexplored before: the developmental origins of the intima in the siphon of the internal carotid artery. This site was chosen for study because the parasellar internal carotid artery in adults has the unwelcome fate of being highly prone to atherosclerosis at a site where the outcome is stroke. Moreover, this site, like the origin of the left anterior descending coronary artery, develops a focal intimal thickening long before the usual changes of lipid accumulation, characterized as “atherosclerosis,” occur. It is very reasonable, therefore, to consider the developmental biology of such sites as very early events that set the scene for localization of atherosclerosis in adults. Particularly intriguing is their evidence that the shape of the vessel, rather than the flow patterns, may determine the degree of intimal hyperplasia and ultimately constitute a risk factor for development of clinically important lesions at this critical site.

The surprise is that this is only the second atherosclerosis-prone site to be studied at such an early stage. There are very few studies of developmental intimal formation at any site, despite our knowledge that this tissue, the arterial intima, is the normal tissue, the “soil,” in which atherosclerotic lesions develop.2 The only extensive studies of intimal formation are in the ductus arteriosus.3–5 Of course, the ductus is not a site that develops atherosclerosis. The only atherosclerosis-prone intima reported on before the present study is the left anterior descending carotid artery.6

Our lack of knowledge of the role of the intima in atherosclerosis may be an inadvertent result of the recent success of studies of atherosclerosis in fat-fed or genetically hyperlipemic animal models.7–9 Such studies equate macrophage accumulations in the early lesions of atherosclerosis. In severe cases, such accumulations of lipid can even occlude coronary arteries.10 This identification of foam cell lesions, also called “fatty streaks,” with the precursors of the human atherosclerotic lesion is not fully consistent with the classification scheme of the American Heart Association Committee on Lesions. The consensus committee did report on fatty streaks in humans; however, the scheme identified the early lesions at sites prone to show atherosclerosis in adults as deposits of lipid deep within intimal masses.11 This consensus view is also supported by studies of human coronary arteries by the Velicans12,13 and of swine vessels by Thomas et al.14 Indeed, Thomas and colleagues used detailed cell kinetic studies to show that lesions in this animal model arose by relatively few cell doublings of the preexisting intimal cells. The concept of lesions arising in preexisting intimal masses was later supported by studies from this laboratory showing that the clonal properties of plaque smooth muscle cells may be best explained by expansion of preexisting clonal masses, found even in nonatherosclerotic intima.15 We simply do not know whether similar clonality can eventually occur in the lesions induced by hyperlipemia in animal models at sites that do not have a preexisting intima.

The mechanism(s) underlying intimal formation are almost completely unknown, except in the special cases of neointimal formation after balloon angioplasty.2 In this special case, a cascade of growth functions accounts for proliferation of medial cells and their migration across the intimal elastica. There is no reason to believe, or not to believe, that similar mechanisms underlie the spontaneous formation of intima during development.

Among the few studies of spontaneous intimal formation, the most elegant studies are those of Rabinovitch et al,2 who have investigated the formation of the intima in the ductus arteriosus. These studies blocked intima formation by gene therapy with a decoy RNA designed to block fibronectin transcription. A second piece of the puzzle may have emerged from Keating’s use of knockout mice to model supravalvular aortic stenosis. This human genetic disorder is accounted for by massive deletions in the elastin gene. Intriguingly, normal mice do not spontaneously form an arterial intima. However, deletion of elastin by homologous recombination in mice results in formation of an exuberant intima whereas hemizygous deletion results in a formation of excess numbers of elastic lamellae.16 These studies suggest that intimal formation may be a developmental anomaly, dependent on completion of the internal elastica at an appropriate time to prevent trapping of some smooth muscle cells between the endothelium and the internal elastica.

Given the evidence for a concordance of the distribution of neonatal intimal masses with the distribution of lesions in adult humans, it seems likely that some property of the intimal cells accounts for localization of lesions. Perhaps the simplest hypothesis, as put forward by Williams and Tabas,17 is that the cells making up these intimal masses have special properties that contribute to lipid accumulation at focal sites.

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There is some evidence that intimal cells do have a very different phenotype than medial smooth muscle. More than 80 genes have been identified as showing differential expression between intimal smooth muscle compared with normal medial cells. However, a large part of these differences represents differential expression by cells in a healing wound, in the case of angioplasty, or at an inflamed site, in the case of atherosclerosis. The relevance of such responses to injury to properties of spontaneously formed intima is not known.

A large number of studies compare such adaptive changes of intimal cells to the changes seen when smooth muscle cells dedifferentiate in vitro. These studies purport to distinguish smooth muscle cells in a “synthetic” versus a “contractile” phenotype. This distinction arises because cultured smooth muscle cells are dedifferentiated, highly replicative, and synthetic. It is true that in vivo intimal cells, including smooth muscle cells, in the atherosclerotic plaque lack the contractile proteins that characterize smooth muscle cells in the media. However, dedifferentiated, smooth muscle cells in the intima have never been shown to be replicative, their contribution to contractile properties of vessels has not been studied, and there is little evidence that these smooth muscle cells are any more active than medial smooth muscle cells in protein synthesis. In short, the terms “synthetic” and “contractile” are poorly defined, and we do not know the relevance of these in vitro to the phenotype of intimal cells.

One important issue is a dearth of literature on the in vitro properties of cells cultured from the intima. Although cells from the spontaneously formed intima have not been studied in vitro, there is some evidence that the most important intimal cells, that is, the plaque smooth muscle cells, are genetically distinct from medial smooth muscle. There are several reports of chromosomal changes or loss of heterozygosity in cells obtained from the plaque (reviewed in Schwartz et al ). The most impressive of such data comes from recent studies by McCaffrey et al , suggesting that plaque cells have a distinctive mutation in the transforming growth factor- receptor. If this report holds up, then we need to consider the possibility that lesions arise in a subset of smooth muscle cells with a somatic cell mutation.

Such a genetic change implies that cultured intimal cells, or at least plaque cells, should have very distinctive properties. The only relevant literature on properties of intimal cells may be a report showing that rat smooth muscle cells cultured from the neointima formed after balloon injury have growth properties quite distinctive from the properties of cultured medial cells. These properties include a very distinct morphology and expression of platelet-derived growth factor-B, phenomena also seen in the rat neointima in vivo. A few studies have also appeared reporting special properties of cells grown from advanced human plaques including loss of replicative life span and acquisition of a high apoptotic rate. We do not know, however, whether these changes are acquired over the decades of exposure to cytokines and cytotoxic oxidation products. Again, the observations by McCaffrey et al suggest that cultured plaque cells have distinctive properties and that these properties might reflect selection of a subset of cells with a somatic mutation. Unfortunately, to my knowledge, there are no studies of the properties of human intimal cells cultured from nonatherosclerotic sites.

Finally, it is essential to realize that we do not know the origin of all intimal cells. Bobryshev and Lord have noted that some human intimal cells express markers for dendritic cells, suggesting a shared origin with immunocompetent cells located throughout the body. Recent publications even raise the disturbing possibility that intimal cells may arise by delamination of endothelial cells or even from circulating precursors.

In summary, Weninger et al have written a potentially seminal article. In their discussion, they raise very intriguing questions about the relevance of their developmental data to the later development of atherosclerotic lesions in these sites. Access to this site in surgical specimens, but even more importantly by noninvasive imaging, suggests that we will learn a great deal more in the studies to come.

References


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