The Arterial Medial Cell, Smooth Muscle, or Multifunctional Mesenchyme?

Understanding of the pathogenesis of atherosclerosis in man is still incomplete. This is largely due to the dearth of data regarding the artery wall and its metabolism.

In this editorial emphasis will be placed on two basic assumptions regarding the artery wall and atherogenesis.

1. The medial cells of the artery are of prime importance in the pathogenesis of atherosclerosis.

2. They represent a single cell type in the arterial media, a cell which is probably responsible for the production of collagen, elastin, smooth muscle fibers, and basement membrane (acid mucopolysaccharides), and furthermore, they are the chief cell in which one can identify serum lipoproteins in human and animal atherosclerosis.

Many histology textbooks still state that two separate cell types exist in the arterial media, smooth muscle cells and fibroblasts. I have yet to find an electron microscopist who has seen cells resembling the usual fibroblasts in the normal arterial media.

Wolinsky and Glagov have recently proposed that the structural and functional unit of the aortic media consists of circumferential “smooth muscle” cells attached to coarse, elastin lamellae with collagen fibers and a fine elastin net in a matrix of acid mucopolysaccharide. They have called this the “lamellar” unit.

Buck stated 3 years ago that “with the exception of capillary endothelial cells in the outer third of the media of the aorta in man and several other species, smooth muscle is virtually the only cell type in the arterial media.” He gave prime credit to Pease and Paule who in 1960 were among the first to provide electron microscopic evidence for this unicellular concept.

The corollaries of this concept are (1) that these cells must fabricate several components of connective tissue regularly found in the media and (2) that these components may vary in relative proportion and arrangement with disease states.

What are the flaws in assuming that this “multifunctional” cell type is the exclusive medial cell, and therefore, responsible for each of the substances and each of the functions as diagramed in figure 1? First, we must admit...
that much of the evidence is only circum-
stantial and also we have to admit that an
occasional widely dispersed fibroblast might
produce the collagen.

No other cell has been seriously proposed
as the cell which produces elastin in the
arterial media. The only problem that one has
to cope with is that many elastic tissue fibers
are produced elsewhere in the body where
there are apparently no smooth muscle cells.
This paradox does not weaken the case for elas-
tin being formed by the multipotential medial
cell any more than the formation of keratin
by cells of two different germ layers weakens
the case for its being formed by the ectoderm
as well as the entoderm. Then there is the inti-
mate relationship of this single arterial medial
cell type to both the basement membrane and
arterial acid mucopolysaccharides. Perhaps
most histologists would not necessarily think
of the smooth muscle cell as a probable cell
of origin of arterial basement membrane and
other arterial acid mucopolysaccharides. Al-
though basement membranes are associated
with many kinds of cells of all germ layers,
they are almost invariably associated with
smooth muscle, and acid mucopolysaccharide
exists in many other tissues which are rich
in smooth muscle.

Let us assume then that there is a single
cell type in the media of arteries which con-
tains myosin, which also has the capacity to
form both collagen and elastin and which
probably is associated with the formation of a
basement membrane and of the acid mucopoly-
saccharides. Assuming this is fact, what is the
role of this cell in atherogenesis?

Many investigators have called attention in
recent years to the presence of cells with the
characteristics of smooth muscle cells in the
thickened intima. Furthermore, there are now
at least nine separate reports by different in-
vestigators which indicate that the most fre-
quent location of intracellular lipid in ather-
sclerotic lesions is in the cytoplasm of these
cells. Implicit in these observations has been
the assumption that migration into or prolifera-
tion of these cells (or both) represents the
major part of the increased cell population
observed in the thickened intima. There are
two other implications of the "smooth muscle
cell" in the pathogenesis of atherosclerosis
in animals. A part of the purpose of this edi-
torial is to propose and to document partially
the importance of this medial cell in human
atherogenesis in these two other ways:

1. We have observed frequently and yet
have rarely seen it reported by others that the
atherosclerotic lesion, at almost all stages, is
characterized by lipid accumulation in pre-
existing medial cells as well as in the intima.
In man the "pure" fatty streaks frequently show
lipid in medial cells at the same time as one
sees lipid in the intimal cells. These lipid-
laden cells consistently react with specific anti-
body to low-density lipoprotein. In the rat,
when we first reported lipid-filled plaques
in the coronary arteries, we also demonstrated
the accumulation of lipid in the aortic endothelium and in the superficial medial cells.5 In the Cebus monkey, we noted intracellular medial lipid as characteristic of the developing atheromatous lesion whether it followed feeding of hydrogenated fat or feeding of other food fats. In a later study reported in 1961, we suggested that some types of food fat stimulate the proliferation which takes place in the intima, possibly as a response to lipid in the Cebus monkey's medial cells.6

2. This leads us to the second major proposal, namely that much of the intimal "fibrous" thickening and collagen formation may be derived from division and migration of these multifunctional medial mesenchymal cells rather than from preexisting fibroblasts or from the maturation of immigrating mononuclear inflammatory cells or from endothelial cell proliferation. Abundant lipid in preexisting medial cells accompanied by thickening of the intima has been observed in recent Rhesus monkey experiments in our laboratory in which the atherogenic procedure of Taylor and his co-workers has been augmented and accelerated by using a mixture of butter oil and coconut oil with cholesterol.7 This produces severe aortic and coronary disease in 9 months or less.8 Both the thickened intimal cells and the underlying medial cells have myriads of small droplets of fat in their cytoplasm. From these and other experiments we believe that there is a definite trapping of serum lipoprotein in these cells.

From recent studies in rabbits, it appears that many of the cells previously called "foam cells" may be modified medial cells, at least in the more advanced and chronic lesion. Imai and associates9 and Constantidines10 have demonstrated that many, if not most, of the cells in the thickened intima of the truly arteriosclerotic arterial plaque in the rabbit are probably smooth muscle cells or, if you will, modified medial cells.

Knieriem and Kao in this laboratory have developed a specific antibody against human striated muscle myosin and against bovine aortic myosin.11 These antibodies cross-react sufficiently to make it possible to obtain convincing pictures of arterial cells stained with these antibodies after they are labeled with fluorescein. These workers have demonstrated that the intracellular lipid droplets, the low density lipoprotein, and the fluorescence from the antmyosin are all intimately associated in the same cells of the thickened intima.

In summary, then, these considerations strongly suggest that there is really only one cell type in the arterial media and that it is a multifunctional cell in the sense that it fabricates or takes part in the fabrication of elastin fibers, mucopolysaccharides, and myosin.

In the atherosclerotic arteries of man and experimental animals, this cell, in situ, frequently is found to contain lipid which, on fluorescence microscopy, has the antigenic specificity of low-density lipoproteins. During the development of fatty plaques, this cell type probably both proliferates and migrates to contribute in a major way to the thickened intima. It seems possible that much of the fibroplasia in the thickened intima may be the result of the increased collagen formation by these multifunctional cells at the expense of elastin formation or myosin formation. Similar diversion of synthetic processes may account for the increased acid mucopolysaccharides seen in some atheromatous lesions.

It is possible that this cell also sometimes circulates and colonizes in order to produce the atheromas which have been observed on some prosthetic implants in arterial lumina. In future studies, more attention should be given to the cytological and metabolic characteristics of this multifunctional medial mesenchymal cell in the arterial media and in the diseased intima.

ROBERT W. WISSLER

References
3. PEASE, D. C., AND PAULE, W. J.: Electron

On the Motivation to a Scientific Career

Since no trait peculiar to scientists has yet been recognized, it seems best to assume that at all times and in all places approximately the same percentage of men has been endowed with the qualities which make for effective scientific performance, but that conditions for the emergence of scientific vocations have not always been equally favorable. It would seem, in other words, that the accidents of individual life and, even more, the demands of the environment, as well as the facilities that it offers, are the most important factors in determining whether certain innate endowments lead a given individual to become the abbot of a new monastic order or the director of a research team—whether medieval mysticism, concern with universal laws of nature, or the urge to develop powerful engines has the most appeal to the gifted mind. . . . Whatever the independence of their behavior, all men are to some extent social parasites who derive their thoughts and preoccupations from their social environment.—RéNÉ Dubos: The Dreams of Reason: Science and Utopias. New York, Columbia University Press, 1961, p. 134.
The Arterial Medial Cell, Smooth Muscle, or Multifunctional Mesenchyme?

ROBERT W. WISSLER

Circulation. 1967;36:1-4
doi: 10.1161/01.CIR.36.1.1

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1967 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/36/1/1.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/