Editorial

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\(^1\) 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\(^2\) 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\(^3\) 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

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that much of the evidence is only circumstantial 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 elastin 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 intimate 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. Although 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 contains 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 mucopolysaccharides. 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 investigators which indicate that the most frequent location of intracellular lipid in atherosclerotic lesions is in the cytoplasm of these cells. Implicit in these observations has been the assumption that migration into or proliferation 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 editorial 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 antibody to low-density lipoprotein.4 In the rat, when we first reported lipid-filled plaques in the coronary arteries, we also demonstrated

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**Figure 1**

*Functions of the multifunctional mesenchymal cell.*
the accumulation of lipid in the aortic endothelium and in the superficial medial cells.\textsuperscript{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.\textsuperscript{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.\textsuperscript{7} This produces severe aortic and coronary disease in 9 months or less.\textsuperscript{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 associates\textsuperscript{9} and Constantidines\textsuperscript{10} have demonstrated that many, if not most, of the cells in the thickened intima of the truly atherosclerotic 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.\textsuperscript{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.

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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.—RENÉ DUBOS: The Dreams of Reason: Science and Utopias. New York, Columbia University Press, 1961, p. 134.
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