This Week's Citation Classic®

Ross R & Glomset J A. Atherosclerosis and the arterial smooth muscle cell. *Science* 180:1332-9, 1973; and **Ross R & Harker L.** Hyperlipidemia and atherosclerosis. *Science* 193:1094-100, 1976.
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The first paper emphasizes that smooth-muscle proliferation is the key event in atherosclerosis, which begins as a result of endothelium injury that alters endothelial structure and function. The second paper demonstrates early observations in hypercholesterolemia and the ways that lesions of atherosclerosis caused by hypercholesterolemia result in specific forms of endothelial injury and cellular interactions. These precede the development of the intimal proliferative lesions of atherosclerosis. [The *SCI*® indicates that these papers have been cited in over 700 and 425 publications, respectively.]

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These two papers represent the initiation and early steps in the process of our conceptualization of the "response to injury hypothesis of atherosclerosis." When John A. Glomset and I wrote the 1973 article, we were aware of endothelial changes that might precede platelet interactions and of increased cellular interactions, but we chose to emphasize the importance of intimal smooth-muscle proliferation as the key event in advanced lesion formation in atherosclerosis. The research that led to these data included studies demonstrating that smooth-muscle cells are collagen-forming cells,[1] studies showing that it is possible to grow differentiated smooth muscle in culture, and, in the second paper with Laurence Harker, studies incorporating the concept that growth factors released from platelets and ultimately from numerous other cells (including monocyte/macrophages,[2] endothelium, and smooth-muscle cells themselves[3]) may be important in the intimal proliferative response. The platelet-derived growth factor (PDGF) was discovered in our laboratory and first described in 1974.[4] In those days it was not appreciated that PDGF was derived from numerous cells in addition to platelets, nor was it clear how often platelets interacted. Harker and I had, however, observed platelets interacting with artery wall cells in the homocysteinemic baboon,[5] and we subsequently made similar observations in hypercholesterolemic nonhuman primates.

Now it is clear that although platelet interactions may occur, they are not the major event; rather, numerous other cellular interactions, in particular those of monocytes and macrophages, may be of much greater importance in hypercholesterolemia and possibly in hypertension, as well. Occurrence of platelet interactions is probably related to altered rheologic properties of the vessel and altered glycoproteins on the surfaces of endothelial cells as well as monocyte/macrophages, which can lead to increased platelet adherence and all of the subsequent smooth-muscle chemotactic and proliferative responses.

It is clear, however, that growth factors released from all the different cells potentially involved in the development of the lesions of atherosclerosis may play key roles in inducing the intimal smooth-muscle proliferative response that represents the clinically important component of the lesion.[6]

One possible reason that these publications have been highly cited is that atherosclerosis is responsible for approximately 50 percent of all deaths in the US and Western Europe in relation to both myocardial and cerebral infarction. This, by its very nature, has stimulated research in the field, which is now blossoming thanks to the development of cell and molecular biology and the entrance into the field of individuals well trained in these areas.

Many writers continue to misrepresent our view of the response to injury hypothesis, believing that we meant it to always include only platelet interactions; this is not the case. In some instances there may be platelet adherence and release; however, in the majority of cases, the response to injury hypothesis probably means that alterations occur in endothelial function that include permeability changes, release of growth factors, alterations in relaxation or contraction, as well as alterations in the endothelial surface that help induce monocyte and possibly platelet interactions and subsequent release of growth factors. This has led to a revised hypothesis that incorporates recent data and our understanding of the field at this point in time.[6]

1. **Ross R & Klebanoff S J.** The smooth muscle cell. I. *In vivo* synthesis of connective tissue proteins. *J. Cell Biol.* 50:159-71, 1971. (Cited 715 times.)
2. **Shimokado K, Raines E W, Madtes D K, Barrett T B, Benditt E P & Ross R.** A significant part of macrophage-derived growth factor consists of at least two forms of PDGF. *Cell* 43:277-86, 1985. (Cited 55 times.)
3. **Walker L N, Bowen-Pope D F, Ross R & Reidy M A.** Production of platelet-derived growth factor-like molecules by cultured arterial smooth muscle cells accompanies proliferation after arterial injury. *Proc. Nat. Acad. Sci. USA* 83:7311-5, 1986.
4. **Ross R, Glomset J, Kariya B & Harker L.** A platelet-dependent serum factor that stimulates the proliferation of arterial smooth muscle cells *in vitro*. *Proc. Nat. Acad. Sci. USA* 71:1207-10, 1974. (Cited 1,055 times.)
5. **Harker L A, Ross R, Slichter S J & Scott C R.** Homocystine-induced arteriosclerosis: the role of endothelial cell injury and platelet response in its genesis. *J. Clin. Invest.* 58:731-41, 1976. (Cited 425 times.)
6. **Ross R.** The pathogenesis of atherosclerosis—an update. *N. Engl. J. Med.* 314:488-500, 1986.

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