Cellular mechanisms in atherogenesis: new opportunities in cardiovascular disease risk reduction

Gordon A. A. Ferns
Centre for Clinical Science and Measurement, School of Biological Sciences, University of Surrey, Guildford GU2 5XH, UK

Our understanding of the cellular events that lead to coronary atherosclerosis has improved substantially over the last decade. This improved understanding has been due to: (1) the production of cell-specific monoclonal antibodies for immunocytochemistry (Tsukada *et al*. 1986); (2) the cloning and characterization of the genes of several cytokines, growth factors and cell surface receptors that may be involved in atherogenesis, and that have allowed studies of gene expression; (3) the careful use of experimental models including the development of gene 'knock-out' animals (Breslow, 1996).

Ross and his colleagues (Masuda & Ross, 1990*a*,*b*) have demonstrated that leucocyte adhesion to the endothelium is followed by their accumulation within the subendothelial space. Macrophages are converted to lipid-laden foam cells within the artery wall, giving rise to a lesion termed the fatty streak. The initial adhesion event is mediated by pairs of adhesion molecules, one of each pair being on the leucocyte, the other on the endothelial cell. The endothelial adhesion molecules have been shown to be up regulated as an early event in atherogenesis in the hyperlipidaemic rabbit and apolipoprotein E 'knock-out' mouse. Enhanced adhesion may also be stimulated by immunization with bacillus Calmette-Guérin, which is associated with leucocyte activation (Lamb *et al*. 1999), and inhibited by antioxidants (Ferns *et al*. 1993).

The normal endothelium elaborates factors such as prostacyclin and endothelium-derived relaxing factor (or NO) that limit leucocyte adherence (Vane *et al*. 1990). In the hypercholesterolaemic rabbit, although NO continues to be produced, its biological activity is compromised. Organ-bath studies of arteries in the early stages of atherosclerosis have shown that they are less able to respond to vasodilators such as acetyl choline (Andersson *et al*. 1994; Stewart-Lee *et al*. 1994). The latter is likely to be due in part to the interaction of NO with other molecular species such as the superoxide radical. These changes in the properties of the endothelium have given rise to the concept of endothelial dysfunction. Several studies have demonstrated that hyper-cholesterolaemia-induced endothelial dysfunction may be prevented or reversed by the antioxidant vitamin E (Andersson *et al*. 1994; Stewart-Lee *et al*. 1995).

The conversion of the fatty streak into a fibrous plaque necessitates the recruitment of and proliferation of vascular smooth muscle cells (for review, see Ross, 1993). This process is driven by the synergistic interplay of several growth factors. Platelet-derived growth factor is likely to be an important contributor to this process, as it is both chemo-tactic and mitogenic for smooth muscle cells. It is expressed by macrophages, endothelial cells, and smooth muscle cells. The active platelet-derived growth factor molecule is dimeric and exists in three different isomeric forms (AA, AB and BB). Platelet-derived growth factor-BB is expressed by macrophages in atherosclerotic lesions of man and non-human primates (Ross *et al*. 1990) and in the cholesterol-fed rabbit, its neutralization by endogenous antibodies causes a marked reduction in aortic atherosclerosis (Rutherford *et al*. 1997).

Atherogenesis: Endothelial function: Platelet-derived growth factor

References

Andersson TLG, Matz J, Ferns GAA & Anggard EE (1994) Vitamin E reverses cholesterol-induced endothelial dysfunction in the rabbit coronary circulation. *Atherosclerosis* **111**, 39–45.

Breslow JL (1996) Mouse models of atherosclerosis. *Science* **272**, 685–693.

Ferns GAA, Forster L, Stewart-Lee A, Konneh M, Nourooz-Zadeh J & Anggard EE (1993) Probucol inhibits mononuclear cell adhesion to the vascular endothelium in the cholesterol-fed rabbit. *Atherosclerosis* **100**, 171–181.

Lamb DJ, Reynolds L-J & Ferns GAA (1999) Immunisation with bacillus Calmette-Guérin vaccine increases aortic atherosclerosis in the cholesterol-fed rabbit. *Atherosclerosis* **143**, 105–114.

Masuda J & Ross R (1990*a*) Atherogenesis during low-level hypercholesterolaemia in non-human primate. I. Fatty streak formation. *Arteriosclerosis* **10**, 164–177.

Corresponding author: Professor Gordon Ferns, fax +44 (0) 1483 464072, email g.ferns@surrey.ac.uk

https://doi.org/10.1017/S0029665100000574 Published online by Cambridge University Press

Masuda J & Ross R (1990*b*) Atherogenesis during low-level hypercholesterolaemia in non-human primate. II. Fatty streak conversion to fibrous plaque. *Arteriosclerosis* **10**, 164–177.

Ross R (1993) The pathogenesis of atherosclerosis: A perspective for the 1990's. *Nature* **362**, 801–809.

Ross R, Masuda J, Raines EW, Gown AM, Katsuda S, Sashahara M, Malden LT, Masuko H & Stao H (1990) Localization of PDGF-B protein in macrophages in all phases of atherosclerosis. *Science* **248**, 1009–1012.

Rutherford C, Martin W, Carrier M, Anggard E & Ferns GAA (1997) Endogenously elicited antibodies to platelet derived growth factor-BB and platelet cytosolic protein inhibits aortic lesion development in the cholesterol-fed rabbit. *International Journal of Experimental Pathology* **78**, 21–32.

Stewart-Lee A, Ferns GAA & Anggard EE (1995) Differences in the onset of impaired endothelial responses and in effects of vitamin E in the hypercholesterolaemic rabbit carotid and renal arteries. *Journal of Cardiovascular Pharmacology* **25**, 906–913.

Stewart-Lee AL, Forster LA, Nourooz-Zadeh J, Ferns GAA & Anggard EE (1994) Vitamin E protects against impairment of endothelium-mediated relaxations in cholesterol-fed rabbits. *Arteriosclerosis and Thrombosis* **14**, 494–499.

Tsukada T, Rosenfeld M, Ross R & Gown AM (1986) Immunocytochemical analysis of cellular components in atherosclerotic lesions. *Arteriosclerosis* **6**, 601–613.

Vane JR & Botting R (1990) Regulatory functions of the vascular endothelium. *New England Journal of Medicine* **323**, 27–36.

https://doi.org/10.1017/S0029665100000574 Published online by Cambridge University Press