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Atherosclerosis-Time for a New Paradigm?

Mini Review

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Sometimes science progresses by a period of integration after a long period of data accumulation. These leaps can be made as much by the injection of a spurt of imagination - as with the discovery of the structure of DNA or classically the structure of the benzene ring - as by the application of strict scientific method. Looking at old data in a new way is best favoured when different disciplines talk to each other. This is not so easy in an era of increasing academic specialisation. However when different disciplines do talk, an underlying truth buried under a pile of data can sometimes be found to have been staring us in the face without being recognised.

From the time of the initial animal cholesterol-feeding experiments at the start of the last century [1] to the development of cholesterol-lowering drugs in the 1990s, atherosclerosis has been dominated by a story of metabolic disease, centering round the role of low density cholesterol and its oxidised metabolites and the mechanism whereby cholesterol is transferred into the vessel wall forming the centre of a plaque composed of cholesterol crystals, fibrous tissue, smooth muscle hypertrophy and inflammatory cells. According to the cholesterol hypothesis, the inflammatory changes are due to the effects of lipid accumulation rather than being in themselves causative. Much progress has been made in pursuing the cholesterol theory. The Framingham study established LDL cholesterol as one of the risk factors for coronary artery disease [2] and the subsequent development and clinical success of statins has lent support to the paradigm of cholesterol accumulation being the pivotal event in atherogenesis.

It is tempting to stick with an existing idea when much time and effort has been invested in it, all the more when statins work, an effect attributed naturally to their cholesterol- lowering rather than their pleotropic anti-inflammatory actions via the mevalonic acid pathway. These pleotropic effects inhibit leucocyte-endothelial interaction and inflammatory signalling.

However over the last few decades there have been gathering hints that all is not well with the cholesterol story. The hints arise from several sources: atherosclerosis is a focal disease rather than a diffuse one, as one might expect if it was simply a matter of cholesterol uptake by the endothelium [3]. On reviewing the Framigham data, the contribution of cholesterol to risk is dubious if one disregards the extreme outliers due to familial hypercholesterolaemia [4]. LDL cholesterol is not a risk factor in patients over 60 [5] and lastly potent LDL cholesterol-lowering measures other than statins are disappointingly ineffective against cardiovascular end-points [6].

The necessary re-appraisal has come with an appreciation that atherosclerosis is primarily an inflammatory disease [6] as was in fact initially postulated by Virchow. Not only are the histological features of atherosclerosis consistent with an inflammatory mechanism, but inflammatory signalling can be demonstrated in the evolving lesions, and C-reactive protein, a marker of systemic inflammation, is found to be an independent risk factor [7]. Meanwhile in an entirely different context, vascular surgeons had been literally looking at atherosclerosis in the face [3]. They had observed the changes in the elastic character of the vessel walls, the localised distribution of atherosclerosis at points of mechanical stress and flow turbulence and around the ostia of collateral vessels and have noted its premature appearance in patients with stiffened arteries. They have also observed the appearance of a fibrotic-inflammatory response at the distal ends of synthetic

vascular grafts where the relatively rigid graft is anastomosed to the compliant distal vessel [8]. Surgeons think in mechanical terms, and looking at atherosclerosis from a mechanical point of view it seems clear that the disease at least in its localisation, is fundamentally related to mechanical stress.

This makes sense if we recognise that mechanical stress gives rise to inflammation. Orthopaedic surgeons and rheumatologists have long recognised this. Repetition strain disorders or occupational over-use injuries are characterised by repeated mechanical over-strain giving rise to a process of inflammatory healing characterised by persistent inflammation. A common example is tennis elbow. These injuries involve a repeated strain applied to a fibro-muscular unit with an abruptness, a force or a range of movement that exceeds the normal physiological range. They are associated with the over-expression of a number of inflammatory signalling molecules, also found in atherosclerotic lesions [9,10]. The pathogenesis of RSI seems remarkable analagous to what is happening to an artery in a hypertensive patient, particularly when the wall of that artery is stiffened by age, a rise in mean arterial pressure or disease, and subjected to an excessive pulse pressure. So are the inflammatory changes underlying atherosclerosis simply a repetition strain injury, in which the accumulation of oxidised LDL cholesterol in the vessel wall is an epiphenomenon related to the inflammatory response to what is in fact primarily a mechanical injury? This is where tissue culture comes to the fore: endothelial cells in tissue culture are highly mechano-sensitive, responding to repeated shear stress by the release of inflammatory mediators [11], a process which is blocked by statins via their anti-inflammatory actions. In short, the paradigm of atherogenesis has good reason to shift from:

cholesterol deposition>atherosclerosis, to

mechanical strain>inflammation>atherosclerosis

This concept of atherosclerosis as a repetition strain injury affecting the arterial wall points to several areas of future research. In vitro studies examining the origin of this mechanical strain emphasise the role of pulse pressure, peak pressure waveform and underlying arterial wall stiffness (itself rising exponentially with mean arterial pressure) [12]. Should we therefore target pulse pressure and pulse pressure waveform in our treatment of older hypertensive patients? In younger patients mean arterial pressure would be an appropriate target with the objective of preserving large vessel compliance. And if, as seems probable, the elevations of hs-CRP associated with cardiovascular risk represents the pathological consequence of repetitive stress acting on the arterial wall, would measuring hs-CRP help us to distinguish between those patients needing immediate therapeutic intervention from those suitable for a watchful waiting approach? What measures can be used to reduce vascular wall stiffness, a central element in mechanical transmural strain, to which vascular smooth muscle tone makes a marked contribution? [13] And can we develop in future materials for vascular grafts and stents that reproduce the elastic qualities of arteries and thereby reduce the incidence of graft failure due to intimal fibrotic hyperplasia?.

These are areas where in future we may need to look for an integrative cross-disciplinary approach amongst clinical researchers, pharmacologists, protein chemists, vascular surgeons, mathematical modellers and engineers.

Conflict of Interest

None

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