Complicated atheromatous plaque as integral atherogenesis

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Genesis of plaque lesion as atherosclerosis is based on the involvement of endothelium and smooth muscle cells

The development of atherosclerotic plaques can be thought of as a variable side-effect responsive to the onset dynamics of blood flow and endothelial injury in particular. Endothelial dysfunction marks the extent of atherosclerosis.[1] The response to injury of the endothelium seems to be a reappraisal of dynamics of a process in terms of increased permeability to lipids. Hypercholesterolaemia can induce a variable degree of injury to endothelial cells that is associated with, in particular, the increased permeability of these cells. Chemokines are an essential response mechanism relative to the entry of lipids to the subintima that further progresses as macrophage receptivity and secretory activity. Vascular inflammation induced by the proinflammatory cytokine/nuclear factor κBpathway is important in atherogenesis.[2]

The localisation of individual plaques demonstrates the evolving nature of a lesion that implicates a primary proliferative response of the medial smooth muscle cells in the first instance and subsequent injury to the endothelium. The circulating endothelial progenitor cells are implicated in angiogenesis, and the smooth muscle progenitor cells promote atherogenesis.[3]

The concurrently evolving consequences of endothelial injury in parallel with further proliferation and ingrowth of smooth muscle cells within an incipient focus of lipid deposition and of foam cells demonstrates the ongoing processes of receptivity, centred particularly on the endothelial surface. Arterial thrombosis is the principal complication of atherosclerosis leading to stroke and myocardial infarction.[4]

THE MACROPHAGE

The macrophage is an exquisitely sensitive system in the development of parallel pathways in the evolution of both increased endothelial damage and proliferation of smooth muscle cells.[5] Neutrophil activation is linked to progression of atherosclerosis.[6]

The chemotactic attraction of monocytes by monocyte chemoattractant protein-1,[7] can self-propagate as a system of amplified effect that converts the initial collection of foam cells in the intima to an evolving atherosclerotic plaque. Recruitment of leucocytes from the bloodstream into the vessel intima is a crucial step in the development of the disease.[8] In terms of the dynamics of such evolution, the subintima would participate in the interactive processes of production and further expansion of a lesion that haemodynamically responds to injury to the endothelium.

The haemodynamics of blood flow does prove to be a source of progression in the generation and further expansion of a plaque that calls into operation further cellular elements such as lymphocytes and more monocytes and macrophages. Coexisting hypertension and dyslipidaemia synergistically increase the risk for cardiovascular events.[9]

The transformation of circulating monocytes to macrophages seems to be a preparatory mechanism in the further development of irreversible pathological change, which constitutes the established plaque. The accumulation of lipid, in particular, can result in oxidant injury and oxidation of the low-density lipoproteins (LDL).[9a]

The central role of progression of injury to the endothelium relates, in particular, to the effects of hypercholesterolaemia that further compounds the increased endothelial permeability.[10] Endothelin 1 stimulates the proliferation of smooth muscle cells and promotes hypertension and atherosclerosis.[11] The deposition of lipids as oxidised LDL in the subintima may account for a further characterisation of the dynamic ingrowth of smooth muscle cells and fibroblasts within the core of the atherosclerotic plaque.[11a]

ATHEROMATOUS PLAQUES

The alternate formation of either fibrous plaques or lipid-core plaques seems to be the result of the dynamics of transfer of oxidation end products relative to an injured endothelium.[12] Further implication of thrombus in the subsequent denuded endothelial areas would further compound the deposition process relative to onset and progression of injury, both to the subintima and the subjacent medial smooth muscle cells. There are positive multiplication interactions between low-density lipoprotein cholesterol and smoking for coronary atherosclerosis.[13]

The ingrowth of smooth muscle cells as progenitor cells, in particular, into the region of plaque generation may constitute a responsive element to primary haemodynamics of a disturbed blood flow pattern.

It may be significant that a multiplicity of processes would participate in the incorporation of lipids within the atherosclerotic plaque. Inflammation plays a part in all stages of atherogenesis.[14] In terms of such an event, it is further significant to consider the complications of such a plaque lesion as active pathways of progression of a series of injuries that compound endothelial and subintimal involvement. Statins exert anti-inflammatory action independent of cholesterol levels, implicating increased endothelial cell production of nitric oxide.[15]

In such terms, formation of an aneurysm indicates a tendency for weakness of the wall of the artery that is focally involved by formation of an atherosclerotic plaque. In a similar mechanism, injury to the endothelium would actively promote the migration and chemotactic attraction of circulating monocytes in a manner that is directly conducive to transformation of these monocytes to tissue macrophages.

Endothelial dysfunction is a key event in atherosclerosis.[16] Furthermore, the formation of foam cells seems to be a transition stage in the development of the tissue macrophage by transformation of the circulating monocyte. Nuclear factor κBmay be implicated in the formation of macrophage-derived foam cells.[17]

CHEMOKINES

Chemotactic cytokines seems to be part of a central mechanism in the overall process of propagation of a plaque that generates accumulation of lipid-laden macrophages. There is increasing epidemiological evidence for chronic inflammation in atherosclerosis implicating microbial Toll-like receptor agonists.[18] All these events may be in subsequent progression of the incipient atherosclerotic plaque as expressive phenomena that interactively integrate thrombus incorporation with mitogenic and growth factor action on the one hand, and of

multiplication of smooth muscle cells on the other.

It would further seem that the full expressive development of a stenosing plaque requires the atrophy of smooth muscle media in the native blood vessel wall in a manner conducive to a directly induced expansion of the generated atherosclerotic plaque.

The active generation of the plaque is a side-effect of expansion as well as of multiplication of cellular elements in a manner that is linked directly to the participation of blood vessel intima and media focally and along the relevant length of the blood vessel involved. Cathepsins and angiotensin II are implicated in remodelling of the extracellular matrix of the inflamed arterial intima.[19] The full involvement of blood vessel tunica media may be an expression of a process akin to deposition, but in a manner that actively implicates multiplication of fibroblasts and angiogenesis as essential factors in plaque genesis.

PLAQUE GENESIS

The genesis of plaques is one that usually involves whole multiple segments of a given artery that is linked to the elastic and muscular elements of the larger arteries of the body.

In this way, stenosis may participate in a mechanism linking haemodynamic stress to blood vessel compromise, and this may involve damage to the subintima, particularly the tunica media.

It might also be relevant to consider the primary role of the tunica media as the principal participant in the evolution of an injury that compromises secondarily endothelial function. Dyslipoproteinaemia is a cardinal feature of the metabolic syndrome that accelerates atherosclerosis. This consists of high plasma concentrations of triglyceride and apolipoprotein B-containing lipoproteins, and low levels of high-density lipoprotein.[20]

Endothelial functionality seems to be a secondary side-effect to a fundamental process of multiplication of smooth muscle cells in a manner that would further redefine the consequences of the generated atherosclerotic plaque later.

COMPLICATED PLAQUE AS INTEGRAL ATHEROGENESIS

The various complications affecting atheromatous plaque seem to arise as integral events in the parent process of atherogenesis that initially involves the endothelium and subintima. The endothelium is a dynamic cellular interface that regulates humoral and biomechanical stimuli on vessel tone and remodelling.[21]

The various components in the genesis could be considered as an atheromatous plaque as variable aspects of a central event primarily based on interactivity between blood components and an injured endothelium. A series of pathway events in the subsequent evolution of such injury to the endothelium that characterise the nature of the complicated plaque in that individual patient would evolve.

ANGIOGENESIS

Angiogenesis seems to be a parent event in the development of a lesion that is situated in a blood vessel wall away from the vascular lumen. The whole series could be considered as hypoxic events underlying the evolving plaque as a stimulus for such angiogenesis of new fragile blood vessels.

The tendency for blood vessel rupture seems to be a consequence of the aberrant hypoxic stimulation of neoangiogenic vessels subjacent to the plaque. In such a context, the further evolution of such angiogenesis could be recognised in terms of a transforming injury to the endothelium and in the further growth of related atheromatous plaque.

Events subsequent to haemorrhage into the area of the evolving plaque would contribute to further injury to subintima and possibly further progression of endothelial damage.

Plasminogen activator inhibitor type 1 is an important physiological regulator of fibrinolysis and modulates both inflammation and atherosclerosis.[22]

A strict categorisation of events in atherogenesis could prevent a clear perception of pathways of progression in the pathobiology of a lesion that primarily varies in accordance with effective reproduction of the damaged blood vessel wall. Matrix metalloproteinases 2 and 9 are implicated in atherogenesis and aneurysm formation.[23]

The fatty streak and the subsequently developing atheromatous plaque are two different aspects of a parent process of accumulation that is associated with progression of the injury to the endothelium in the first instance.

Only the subsequent progression of the injury that shifts to involve more prominently the subintima could account for the transforming quality of the fatty streak to an atheromatous plaque.

The proliferative and mitogenic stimuli may be recognised as simple aspects of a central process of integrative pathology involving, in particular, the development of a core of injured tissue centred on the subintima.

The characterisation of events in the genesis of atheroma seems to involve the chief attributes of the endothelium in influencing the underlying smooth muscle cells in the media. Subsequent neovascularisation of the plaque determines intraplaque haemorrhage, lipid-core expansion and plaque rupture.[24]

DAMAGED ENDOTHELIUM

In this context, damaged endothelium seems to correlate with the development of a synthetic-phenotype for the smooth muscle cells that negates advancement of proliferative events in the first instance. Such a side-effect of synthesis and secretion by the smooth muscle cells could account for a progression of a lesion initially characterised by deregulation of endothelial function and particularly by increased endothelial permeability. p53 regulates growth arrest, cell senescence and apoptosis of vascular smooth muscle cells.[25]

The contrasting theories of monoclonality and of response to injury seems to be based on the prominent involvement of smooth muscle cell proliferation in the characterisation of the process of atherogenesis. The full development of the plaque could be considered as largely in terms of the subsequent establishment of potentiality for complications, particularly in the development of angiogenesis, in the base of the plaque. Subendothelial deposits of lipoproteins provoke a cascade of pathogenic responses, including also progressive endothelial dysfunction.[26] Oxidised phospholipids stimulate endothelial cells to produce inflammatory cytokines including interleukin 8.[27]

COMPLICATED PLAQUE

The features of complicated plaque could be considered as a central attribute of a lesion that allows progression of haemodynamic injury to the endothelium,[28] on the one hand, and of increased deposition of atheromatous material in the subintima, on the other. Atherosclerotic plaques occur at sites of disturbed blood flow; this activates extracellular matrix-specific signals that determine patterns of integrin dominance.[29]

Such dual targets of injury are relevant to the integral evolution of a lesion that is capable of response to injury largely in terms of neoangiogenesis. Vasa vasorum neovascularisation is related to advanced and ruptured plaques, especially in the proximal left anterior descending coronary artery.[30]

In such terms, therefore, the blood components circulating in the vascular lumen and in contact with the injured endothelium, and the neoangiogenic vessels that subsequently rupture, could expose the injured vessel wall to multiple

processes comprising pro-proliferative and mitogenic stimulation.

EVOLVING PATHOBIOLOGY

In terms inherent to the subsequent characterisation of the plaque as a focus of evolving pathobiology, a realised event in progression of injury, largely in terms of the subintima, might be implicated.

Oxidative modification of LDL in the subendothelial space is a critical event in atherogenesis.[31]

The subintima represents aspects of involved pathology originally centred on the endothelium. In the further characterisation of such subintimal pathology, the neoangiogenesis would represent a redefinition of the site of injury as transformed dynamics of transferred progression.[32]

The atheromatous plaque might better be viewed as a redefined pathway involving further characterisation of the injury in terms of events, such as the widely recognised possible complications of the plaque. Oxidative modification of lipids and inflammation differentially regulate apoptosis and proliferation of vascular wall-derived cells during atherogenesis.[33]

Stenosis, fissuring, ulceration and superimposed thrombosis in relation to the complicated atheromatous plaque represents different processes arising directly from the parent atherogenesis side-effect. The recategorisation of the sites of injury to the blood vessel wall components could be recognised in terms of realised pathways of integral representation of the inflamed endothelium and of the smooth muscle cells.[34] Baseline levels of C reactive protein are an independent cardiovascular risk factor for atherogenesis.[35]

GROWTH FACTORS

Growth factors and inflammatory reactivity constitutes a basic promoting platform in the induction of mitogenesis and cytokine-mediated action that self-amplify injury to the endothelium and subintima.[36] Further progression of injury seems to be a consequence of cytokine action, particularly in terms of production of chemokines by macrophages entrapped within the atheromatous plaque.

The oxidised low-density lipoproteins constitutes a whole series of propagated effects in relation to free oxygen radicals and oxidation injury to tissue components of the blood vessel wall.[37] The further promotion of such injury is significant in that it results in the production of inflammation that compromises viability of various cellular and tissue components making up the plaque. In such terms, perhaps, secondary waves of injury to the plaque region results in a necrotising core to the lesion that further accentuates the deposition of lipid material. Changes in the elasticity of arteries occur early in atherogenesis and may be promoted by oxidative stress.[38]

Perhaps, in the realisation of such damage to the blood vessel wall, nitric oxide and endothelin production could result in various mitogenic stimuli that further accentuate the lesion as further propagated by repeated deposition of thrombi.

The considerable complexity of production of a lesion, such as a centred plaque on the subintima, might variably develop in terms of a subsequent injury of all three layers of the blood vessel wall. Plaque rupture is regulated by a balance between proliferation and apoptosis of vascular smooth muscle cells.[39]

CONCLUDING REMARKS

It would seem that integral genesis of a plaque lesion as atherosclerosis of the vessel wall incorporates a multiplicity of pathways based on a variable extent on the involvement of endothelium and smooth muscle cells.

Such injury progressions can induce vascular wall dynamics of atherogenesis in terms of processes such as thrombosis and neoangiogenesis.[40] Plaque angiogenesis may be associated with the development of unstable plaques.[41]

Platelets are particularly implicated in the propagation of injury to the endothelium and subintima that facilitates sustained production of growth factors and inflammatory mediators.

The complications of atheromatous plaque constitutes an integral side-effect in the genesis of a lesion that both compromises the viability of the endothelium and further propagates injury to the intima and tunica media of the vessel wall.

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