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Aberrant Endothelial Cell Reactivity in Atherogenic Inflammation And Ischemia

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Abstract: Endothelial cells appear to constitute a primary target in activation responses to Ischemia to the blood vessel wall that interact with thrombogenesis and atherogenesis. Leukocyte and cytokine action would permit the progression of various pathways in evolution of plaque development based on a vascularized core in the tunica intima. The tunica intima involves systems of repair and response that allow the execution of agonist action towards formulation of various injury patterns. The classic complications of atherosclerotic plaques would integrally participate in the central evolutionary development of the atheromatous plaque based on concepts of Ischemia and injury on the one hand and on aberrant activation and reactivity of the vascular wall and endothelium on the other. It would seem that the main theories in atherogenesis as put forward are different aspects of a process that centrally evolves in terms of a vascular wall injury. Atherosclerosis would involve both incrustation and imbibition pathways of progression based on a response to injury of the vessel wall.

Key words: Reactivity, endothelial cell , Ischemia ,aberrant

INTRODUTION

Platelet Activating Factor (PAF) induces a series of reactions on the part of endothelial cells that coordinate phases of response implicating platelets, polymorphonuclear leukocytes and cytokines related closely to circulatory flow and vascular permeability. A role for PAF that involves dysfunctional progression of endothelial reactivity would be central to various processes of atherogenesis as vasculogenic events. The roles of PAF in angiogenesis would be implicated in the progression of atherogenesis that is initiated through endothelial reactivity. Such progression appears counteracted by the protective action of apolipoprotein A-1 in coronary artery disease[1].

The role of thrombogenesis as an event initiating various subsequent phases in atherogenesis might specifically redefine PAF interactions that primarily involve endothelial cell injury. Retraction of endothelial cell margins and cytokine production would call into operation platelets and polymorphonuclear leukocytes.

Endothelin-1 as a potent vasoconstrictor isolated from endothelial cells plays an important role in atherogenesis implicating oxidized low-density lipoproteins[2]. Inhibition of proatherogenic factors including CD40L may involve suppression of the inflammatory response. Endothelial activation may lead to an adhesive and dysfunctional endothelium [3].

An essential aspect of PAF actions appears to lie with the amplification and propagation of interactions of endothelial cells as cytokine-induced reactivity. PAF acetylhydrolase is linked to low-density lipoprotein and proinflammation and promotes atherothrombosis in systemic lupus erythematosus[4]. Endothelial cells are centrally operative in the development of inflammatory responses that may underlie the atherogenesis of blood vessels[5]. The mechanisms linking prothrombotic events to dysfunction of the endothelium and to atherosclerosis are ill-defined but may involve tissue factor on endothelial cells that actives factor VII[6] . It might be significant that circulatory flow through microvessels is a dynamic component in the subsequent evolution of atherosclerosis-associated Ischemia to organs such as the heart and kidney.

The heart is involved in response to various septic and hemorrhagic and post-traumatic shock syndromes and would typify reactivity to PAF on the part of both endothelial cells and cardiomyocytes. A correlation exists especially between markers of insulin resistance and endothelial dysfunction, leading to myocardial Ischemia[7].

Fibrinogen is also an independent risk marker for atherosclerosis[8]. It may be significant that PAF appears an upstream operative factor in cytokine production and mediated action. Platelets and polymorphonuclear leukocytes would act as subsequently induced mediators that propagate and transform endothelial injury to anatherogenic process of deposition that is initially progressively angiogenic.

Angiogenesis: It is in terms of angiogenesis as induced by PAF that one might implicate processes of pro-atherogenesis Initiated at sites of endothelial cell injury affected by cytokine production.

Only in terms of initial endothelial surface injury can

there develop a propagated series of phasic reactivities that amplify subsequent progression of the atherosclerotic plaque.

Angiogenesis would constitute diverse conditions activating subsequent platelet and leukocyte interaction with the injured endothelium.

Ischemia/Reperfusion: Dysfunctional endothelial nitric oxide synthase may not only impair endothelium-dependent relaxation but also accelerate atherogenesis through superoxide production [9].

Ischemia/reperfusion injury would involve the production of free oxygen radicals and nitric oxide underlying leukocyte reactivity and effect injury to the vessel wall. Cell necrosis as a source of cytokines such as Interleukin 1Beta and Tumor Necrosis Factor α might be implicated in atherogenesis that progresses initially as endothelial injury. CD 44 is shed from the surface of macrophages and endothelial cells, with subsequent stimulated release of interleukin-1beta from the endothelial cells in a positive feedback fashion[10].

Endothelial cells: The pavementation of endothelial cells and transmigration by polymorphonuclear leukocytes would implicate a series of subsequent events that amplify endothelial injury. In such a context, angiogenesis, as induced by PAF would implicate endothelial cell proliferation as pathways promoting cholesterol deposition.

A complex interplay of action and reaction might call into operation a series of pathways that develop secondary to endothelial cell injury. It is in terms of such injury that cytokines promote leukocyte migration transendothelially as specifically induced angiogenesis.

Angiogenic stimulation of various components of the atherosclerotic response is related to pathobiology of hypertension, diabetes mellitus and smoking.

Septic shock appears to typify hemodynamic processes that evolve as endothelial cell injury. Cytokine production in endothelial cell injury appears central to angiogenesis and atherosclerosis concurrent with development of abnormal hemodynamics. Transforming growth factor-beta1 is implicated in atherogenesis by inducing extracellular matrix proteins[11].

Thrombogenesis would entail the deposition of atheroma as a specific, morphologically defined plaque lesion.

Platelet activating factor: The various reported modes of action of PAF appear related to biology and pathobiology of platelets and leukocytes in the microvasculature. Indeed, the microvascular response to a deficient supply of oxygen would elicit a series of endothelial reactivities that propagate angiogenic and dysregulatory responses. On the other hand, an oxidative response to inflammation model has been proposed in atherogenesis[12].

Reactivity of endothelial cells appears to be a propagated phenomenon that elicits variable response to a multitude of agonists. Endothelial dysfunction is implicated as an early marker for atherosclerosis[13].

Thrombogenesis would evolve in terms of endothelial injury or of stasis that progresses relative to cytokine action. It might be significant that endothelial reactivity would subsequently provoke increasingly aberrant reactivity of platelets and polymorphonuclear leukocytes. Only with regard to an angiogenic response can one envision pathways of progression of injury to the vessel wall specifically conducive to development of a complicated atherosclerotic plaque. Plasma thrombomodulin may serve as a marker for endothelial injury [14]. Interferon gamma appears centrally implicated in inducing endothelial cell dysfunction and in arteriosclerosis through dysregulation of nitric oxide synthase production[15].

Blood flow: It is relative to stasis and turbulence that angiogenesis would subsequently involve a proatherogenic cascade of events that further injures endothelial cells and also induces subsequent proliferation of adjacent endothelial cells. Proliferation of such injured cells that become activated and aberrantly reactive would involve deposition of cholesterol in atherogenesis.

Plaques of atherosclerosis would implicate angiogenesis as core events that progress initially as endothelial activation and reactivity.

Endothelial activation would induce increased cytokine transcription in response to agonists such as PAF that is reflected in increased receptivity expression. Increased transcription and receptivity patterns of endothelial activation might evolve in terms of an injury that specifically typifies disease processes such as thrombosis, atherosclerosis and even angiogenesis. In the presence of low shear, nonlaminar blood flow, a gene expression profile may be induced to predispose the endothelium to the development of atherosclerotic lesions[16]. The recognition of angiogenesis consequent to endothelial activation would constitute a full array of possible subsequent lipoprotein molecular binding events or of thrombogenesis as potent stimulators for further progression of the vascular wall injury.

Atherogenesis: Angiogenic stimulation might play a role as a core phenomenon that sets in motion evolving

thrombogenesis and atherosclerosis cycles of increasing severity.

Interactive consequences of an atherogenesis related to a thrombogenic tendency and to an activated endothelial response to the atheromatous plaque would evolve in terms of cyclical deposition of lipoprotein or cholesterol.

Endothelial cell damage might implicate a receptivity that subsequently activates also calcium ion mobilization. Fibrogenesis would participate in an injury/repair cycle of events that further propagates as endothelial cell injury. One might further characterize the features of the atherosclerotic plaque in terms of injury that is maintained by an ongoing cycle of angiogenesis. C-reactive protein in particular may elicit a proinflammatory and procoagulant milieu within the tunica intima and also damage endothelium[17]. Central plaque core hemorrhage in an angiogenic response implicates subsequent thrombogenic events that typify concurrent atherosclerosis.

Evolved atherosclerotic plaques: Resolution of pathways of evolution in atheromatous plaque deposition would involve angiogenic responses based on aberrant receptivity and activation of injured endothelial cells affected by thrombosis. Advanced glycation endproducts in diabetics may induce oxidative stress, augment endothelial dysfunction and trigger inflammation and proliferative events in the vessel wall; these greatly accelerate atherosclerosis in these patients [18].

The three classic theories in atherogenesis would emphasize the role played by stress injury and as reflected by encrustation of thrombus, imbibition, the turbulence of blood flow and thrombogenesis that all participate in such response to injury.

Reparative pathways somehow involve the ongoing characterization of an atheromatous plaque possessing a vascularized or angiogenic core. The special attributes of plaque generation would distinguish the realized evolution of a vascular wall injury that complements initial endothelial cell activation and subsequent responses arising from dynamics of cellular injury.

Aberrant receptivity: Hypertension in particular would characterize endothelial cell injury beyond simple concepts of aberrant receptivity. One might view the underlying tunica intima as central to an angiogenic response that is provoked by thrombogenic stimuli.

Participation of various components in the tunica intima involves the generation of the atheromatous plaque that enlarges as induced leukocytic transmigration. Macrophages and leukocytes constitute a source of ongoing cytokine production that specifically implicates cell injury as the plaque evolves.

Gene transcription: Gene transcription events would implicate an aberrant tunica intimal response primarily characterized by angiogenesis in the face of endothelial cell injury. The flow of blood over the generated plaque would serve as a source of cytokine and of numerous other activating events that are operative largely in terms of progression of the plaque.Influx of lipoprotein fractions within endothelial cells would reflect integral attributes of activated endothelium that subsequently implicate tunica intima angiogenesis.

Plaque neovascularization appears implicated in atherogenesis and may involve collagen XVIII that maintains vascular permeability. Loss of this basement membrane proteoglycan may stimulate angiogenesis [19].

A response mechanism intrinsically implicating injury as a central event might categorize events in the generation of the atheromatous plaque. In particular, the thrombogenic attributes of flowing blood would constitute a variable spectrum of injury and activation events derived from such agonists as PAF. Platelets are a source of thrombogenesis implicating a tendency for persistent injury to endothelial cells in the first instance[20]. Hypercholesterolemia, diabetes and hypertension increase oxidative stress which impairs endothelial function[21].

Complications of atheromatous plaques: Calcification, fissuring, intraplaque hemorrhage and ulceration of atherosclerotic deposits attest to an ongoing series of events that involve flowing blood as an integral tissue component in vascular wall injury. The Angiotensin-converting enzyme/Angiotensin II system strongly promotes intimal hyperplasia in atherosclerotic plaque development[22]. One might view the various complications of the atheromatous plaque simply as a fixed pattern of evolution that is initiated with activation and injury to the endothelium. Endothelium protects vessels through vasodilation, suppression of growth of smooth muscle cells and inhibition of inflammation largely via nitric oxide action. Nitric oxide inhibits oxidation of low-density lipoproteins and opposes the action of endothelium-derived vasoconstrictors[13] . It is in such terms that subsequent complications of the plaque are generated in terms of its vascularized core as an ongoing response to the injury.

Thrombosis: Thrombosis appears a transformation induced by injured endothelial cells that further progress

in terms of such thrombosis.

It would appear that thrombosis is a source of activation and of injury to endothelial cells in a manner that would enhance tunica intimal reparative processes in the generation of plaque enlargement.

Basic fibroblast growth factor and platelet derived growth factor are linked to endothelial cell activation and the development of atherosclerotic plaques[23].

Dynamics of enlargement of the atheromatous plaque would also characterize multiplicity of atheromatous foci. A histamine-cytokine network would involve a chronic inflammatory response implicating smooth muscle cells, endothelial cells, macrophages and monocytes and T lymphocytes in intimal atherogenesis [24]. Multiple plaques would enlarge as the endothelial cell bed is exposed to a persistent stream of flowing blood. Blood flow appears to account for the generation of the atheromatous plaques as multiple enlarging foci further aggravating the tunica intima injury and thus provoking a reparative response. In addition, the actual reparative events are aberrant in terms of an exuberant process that is enhanced by thrombogenesis. Both embolization of platelet aggregates and receptor-mediated platelet adhesion to the postischemic microvascular surface may impair microvascular circulation and induce chronic inflammation and plaque rupture [25].

A fixed sequence in atheromatous plaque generation would allow for a variable response on the part of endothelium and the vascular wall components as mediated by the overlying stream of flowing blood. Leukocytes in particular would elicit a series of induced responses that variably participate in progression of a disease process influenced by blood lipid content.

Vascular wall blood supply: Vascular blood supply to the vessel wall by the vasa vasorum would probably implicate border zone patterns of insufficiency in blood supply particularly at the level of the tunica intima. Indeed, a whole series of events as reflected in the diabetic and hypertensive state would involve fixed and variable response patterns primarily generated by injured and reactive endothelium. Increased endothelial cell apoptosis may initiate atherosclerosis and apoptosis of vascular smooth muscle cells and macrophages would localize lesions that are likely to rupture [26].

CONCLUSIONS

Thrombogenesis and endothelial cell reactivity to injury would constitute both fixed and variable patterns of response that participate with local vascular responses in inducing atherosclerosis. Vascularized cores of atherosclerotic plaques appear a mechanism in reparative response to vascular wall injury centered on tunica intima with overlying reactive and injured endothelium.

Leukocytic infiltration of the vascular wall would constitute another dynamic participant in promoting cytokine production, cell injury and deposition of both lipoproteins and thrombus. The classic complications involving the atheromatous plaque appear integral components of vascular core response and reparative events in the tunica intima. An aberrant transformation of the reparative process further involves integral development of the plaque centered on vascular patterns of reactivity initiated by endothelial cell activation and injury.

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