From Inflammation to Fibrosis: A Stiff Stretch of Highway

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Fibroblast fibrous tissue formation follows an inflammatory cell response that appears at sites of cardiomyocyte necrosis, a “dirty” form of cell death. In replacing these lost cells, such fibrosis preserves the structural integrity of the myocardium. This replacement fibrosis, or scarring, is distinct from a reactive fibrosis that surrounds intramyocardial coronary arteries and which, over time, may extend into the contiguous interstitial space. Absent an inflammatory cell response, such as occurs with cardiomyocyte apoptosis (a “sterile” form of cell death), fibrous tissue does not appear. An abnormal accumulation of type I fibrillar collagen, a stiff structural protein, reduces myocardial distensibility while a pharmacology-based regression of cardiac fibrosis is accompanied by an improvement in diastolic stiffness (reviewed in References 1, 2). It is not the quantity but rather the quality of myocardium that determines its stiffness.

What accounts for reactive fibrous tissue formation involving the vasculature? To address this question the relative importance of hemodynamic factors versus circulating hormones that accompany any experimental model need to be considered. For example, in placing an occlusive band around the abdominal aorta, either above or between the renal arteries or around a single renal artery, the renin-angiotensin-aldosterone system (RAAS) is activated as a result of renal ischemia. The accompanying elevation in arterial pressure is created by the band and RAAS effector hormones. An infusion of either angiotensin (Ang) II or aldosterone (ALDO) is accompanied by arterial hypertension due to multiple mechanisms, which are beyond the scope of this brief commentary. Circulating Ang II and ALDO are each increased in a hypertensive, double transgenic rat harboring human renin and angiotensinogen genes.

The anatomical arrangement of the right and left heart and their common coronary circulation are useful in addressing these issues. Iterations in aorta and pulmonary artery structure are likewise insightful. Over the short term, systemic hypertension poses a hemodynamic overload on the left ventricle (LV) and aorta while sparing the atria, right ventricle (RV), and pulmonary artery. A circulating hormone, on the other hand, gains equal access to both atria and ventricles; it reaches the great vessels via their vaso vasorum, where increments in arterial pressure have been dissipated. In the aforementioned models accompanied by RAAS activation, fibrosis appears throughout the right and left heart and adventitia of the great vessels. This is not the case for hypertension that accompanies an occlusive band placed around the abdominal aorta but below the renal arteries and where RAAS activation does not occur. These studies have further shown the hypertrophic growth of cardiomyocytes is confined to the LV and is regulated by the hemodynamic burden imposed on them during systole and not by RAAS effector hormones, which would be expected to induce hypertrophy of both the RV and LV, as is the case for growth hormone and thyroxin. Fibrosis, whether found in the heart or kidneys in these models, is independent of organ hypertrophy and arterial pressure. Ang II and ALDO provoke the release of other vasoactive hormones, including endothelin-1. When corresponding receptor antagonists are used to interfere with the endocrine properties of these circulating hormones, fibrosis does not appear and this is the case for a small nondepressor dose, which does not prevent hypertension, and a larger depressor dose of such an agent. Pharmacological agents that specifically interfere with these hormones are both cardio- and renoprotective. Furthermore, this contrasts to nonspecific vasoactive agents despite their providing equipotent reductions in arterial pressure. Thus, 3 major lines of evidence link tissue fibrosis to circulating hormones, not hemodynamic factors.

Why do chronic elevations in circulating Ang II or ALDO lead to a proinflammatory vascular phenotype? Whether derived from endogenous or exogenous sources, chronic elevations in plasma levels of these hormones are associated with the appearance of inflammatory cells and fibroblasts within the perivascular space of intramural arteries of the heart and such systemic organs as kidneys, pancreas, and mesentery. An alternate approach focuses on monocytes/macrophages and lymphocytes as requisites to the appearance of vascular fibrosis and that are facilitated by an upregulated expression of adhesion molecules and chemottractant chemokines within the endothelium of the affected vasculature. These include intercellular adhesion molecule-1, vascular cell adhesion molecule-1, platelet-endothelial cell adhesion molecule-1, and monocyte chemoattractant protein (MCP)-1 and osteopontin. MCP-1 is integral to the homing of inflammatory cells into cardiovascular tissue. Within these invading inflammatory cells an activation of a redox-sensitive nuclear transcription factor-nuclear factor-kB is seen.
together with increased mRNA expression of a proinflammatory mediator cascade it regulates, including intercellular adhesion molecule-1, MCP-1 and tumor necrosis factor-α. Also present is an activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a source of superoxide formation; increased NADPH oxidase activity; and 3-nitotyrosine labeling, a stable tyrosine residue indicative of peroxynitrite formation, a reactive nitrogen species and product of nitric oxide and superoxide.19,23,25–28 Thus, the evidence points to an induction of oxi/nitrosative stress in promoting this phenotype.

In this issue of Hypertension, Kuwahara et al32 report on the appearance of macrophages and fibroblasts in the perivascular space of intramural coronary vessels of the RV and LV in response to suprarenal abdominal aorta banding and which is accompanied by upregulated expression of MCP-1 and transforming growth factor-β, the appearance of cardiac fibrosis and echocardiographic evidence of diastolic dysfunction together with elevated LV filling pressure. The importance of this inflammatory cell response in leading to fibrous tissue formation is underscored by an anti-MCP-1 monoclonal neutralizing antibody, which inhibited not only the accumulation of macrophages, but also fibroblast proliferation, the induction of transforming growth factor-β, and the appearance of fibrosis with accompanying diastolic dysfunction. It did not prevent hypertension or LV hypertrophy. These important findings advance our understanding of the role of this chemokine in regulating inflammatory cell invasion, the interaction of macrophages and fibroblasts in leading to the subsequent structural remodeling of the coronary vasculature by fibrous tissue, and a role for fibrosis in altering diastolic distensibility. They further confirm fibrous tissue formation is independent of blood pressure and hypertrophy.

Why the induction of oxi/nitrosative stress? In treating rats with Ang II, ALDO, or another mineralocorticoid, deoxycorticosterone in its acetate form, the accompanying elevations in arterial pressure have been held responsible for the appearance of oxi/nitrosative stress in cardiovascular tissue.33–36 Such evidence, however, is also found in postcapillary venules,37 where elevations in intraluminal pressure are not expected. Additionally, an altered redox state is not seen with comparable elevations in arterial pressure induced by norepinephrine.35 A nonhemodynamic factor needs to be considered.

Ang II and ALDO each reduce cytosolic-free concentrations of Mg2+, or [Mg2+]i, in various cells, including lymphocytes.38,39 This could be based on an efflux of Mg2+ from the cell via a Na+/Mg2+ exchanger, a compartmentalization of this cation within organelles, or its enhanced binding to ATP. [Mg2+]i is the biologically active component of this important divalent cation. A reduction in [Mg2+]i leads to intracellular Ca2+ loading and subsequent induction of oxi/nitrosative stress. Mechanisms responsible for augmented intracellular Ca2+, albeit uncertain, might include reduced activity of Mg2+-dependent Na+/K+ ATPase and ALDO receptor-mediated upregulated expression of T-type Ca2+ channels.40,41 Evidence in support of Ca2+ overload in leading to an altered redox state with activation of immune cells in aldosteronism has recently been reported.42,43 This immuno-

stimulatory state, which precedes the assault on the coronary vasculature by weeks, includes B cell activation with increased expression of immunoglobulins; increased expression of CC and CXC chemokine proteins and receptors; and evidence of autoreactivity.42,43 In the future, decoding the peripheral blood mononuclear cell molecular phenotype (ie, their transcriptome and proteome) may provide noninvasive biomarkers of risk, onset, and progression of vascular remodeling.

What intervention(s) prevent the appearance of this immunostimulatory state? The prevention of adverse vascular remodeling will be based on underlying pathophysiological mechanisms (see Figure). A reduction in arterial pressure is less relevant and indeed would prove an indirect outcome to successful immunomodulation. Emerging evidence suggests the efficacy of various pharmacological interventions acting as immunomodulators. They include attacking the neuroendocrine-immune interface via antagonists to AT1,9,13,16 ALDO,12,15,18,23 or ET1,7,17,19,28 receptors; preventing intracellular Ca2+ loading by dihydroproeridine11 or T-type Ca2+ channel blocker; and assisting endogenous antioxidant defenses with an antioxidant, such as pyrrolidine dithiocarbamate, N-acetylcysteine or probucol,14,23,25,26,31,34 Agents that interfere with the transcription of genes promoting the proinflammatory vascular phenotype, such as 3-hydroxy-3-methylglutaryl coenzyme A reductase10,24,46 and ligands to peroxisome proliferator-activated receptor-γ and -α,47,48 may prove useful. Selective inhibition of a specific phosphodiesterase isomerase may interfere cyclic nucleotide second messenger (cAMP and cGMP) formation to downregulate mitogen- and antigen-induced T cell proliferation, Th-1 and Th-2-derived proinflammatory cytokines, and adhesion molecule expression in these cells.49
Mycophenolate mofetil selectively inhibits T cell proliferation, it has proven renoprotective.

The road from inflammation to fibrosis is a stiff stretch of highway filled with aggressive immune cells and reconstruction sites, where delays in ventricular distensibility can be expected. Modifying the behavior of these reckless cells may prove the best means of traffic control.

References


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