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MECHANISMS OF ATHEROSCLEROSIS: NEW INSIGHTS AND NOVEL THERAPEUTIC APPROACHES

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This compendium describes some exciting new developments in our understanding of vascular processes related to atherosclerosis. The majority of this work stems from the Houston Methodist Research Institute's Center for Cardiovascular Regeneration and is aligned with the center's mission of generating fundamental insights that transform cardiovascular care. Within this framework, we intend to elucidate the mechanisms of cardiovascular biology and disease, making seminal contributions to the lexicon of knowledge in our discipline. In addition, we strive to translate these fundamental insights into useful drugs, diagnostics, or devices that transform cardiovascular care.

The work featured herein highlights the different perspectives and insights of our center's faculty. Despite the differences in their areas of expertise and preferred technologies, their work is connected by common themes. One of those themes is the importance of the endothelium for cardiovascular health. The endothelium is a diaphanous film of tissue that exerts tremendous control over vascular homeostasis. By virtue of a panoply of paracrine factors secreted by the endothelium, it modulates vessel wall interaction with the circulating blood elements. The healthy endothelium is much like a vascular Teflon, secreting factors that suppress the adherence of leukocytes and platelets. The endothelium also controls vessel tone through its production of vasoconstrictors (such as endothelin) and vasodilators (such as adrenomedullin, natriuretic peptide, and endothelium-dependent hyperpolarizing factor).[1-4] In addition, the endothelium generates factors that suppress the proliferation of the underlying vascular smooth muscle cells. Endothelium-derived nitric oxide (NO) is paradigmatic of the vascular factors that maintain homeostasis as it suppresses adhesion of leukocytes and platelets, inhibits vascular smooth muscle proliferation, and induces vasodilation.[5] Thus, endothelium-derived NO is an antiatherogenic molecule.

The article by Drs. Ghebremariam and Sukhovershin describes in detail the mechanisms by which NO suppresses the progression of atherosclerosis and by which the action of NO becomes impaired. Reactive oxygen species (ROS) neutralize NO, antagonizing the beneficial vascular effects of this molecule. The generation of ROS in the vessel wall is increased by hyperlipidemia, hyperglycemia, and insulin resistance. These metabolic perturbations also are associated with increased plasma levels of asymmetric dimethylarginine (ADMA), which, based on accumulating data, is a novel risk factor for cardiovascular morbidity and mortality.[6] In addition, preclinical studies suggest that reduction of ADMA levels enhances the vascular generation of NO. Indeed, transgenic animals that have lower levels of ADMA generate more vascular NO, have lower blood pressure and vascular resistance, and manifest insulin sensitivity.[7,8] Thus, a novel clinical approach for treating vascular disease and diabetes mellitus might be to pharmacologically reduce plasma ADMA levels.

"You are only as old as your endothelium" were the wise words of Dr. Rudolph Altschul in 1954.[9] Indeed, as the endothelium ages, it becomes less like Teflon and more like Velcro as the senescent endothelium generates less vasoprotective nitric oxide and more reactive oxygen species. Under the influence of this oxidative stress, the endothelium expresses more adhesion molecules and becomes more adhesive for leukocytes. The senescent endothelium has difficulty aligning with the tractive force of fluid flow and has less proliferative capacity.[10] The article by Nazari-Shafti and Cooke describes the focal senescence that occurs at the bends, branches, and bifurcations of blood vessels where disturbed flow accelerates endothelial turnover. In these areas, endothelial cells are more likely to be senescent. Indeed, the focal senescence in these sites may explain their predilection for plaque formation. Thus, endothelial senescence may be a primary cause for the initiation and progression of atherosclerotic plaque.

Accordingly, a forward-leaning therapeutic development program might focus on methods to rejuvenate the endothelium. One approach would be to restore the length of telomeric DNA since telomere length is a determinant of cellular age.[10,11] In somatic cells, the telomere shortens with each cell division. If one could extend telomere length in somatic cells, the effect might be to forestall or even reverse senescence. Indeed, there is proof-of-concept for such an approach. We have previously used a lentiviral approach to integrate the gene encoding human telomerase in senescent endothelial cells.[10] The effect of telomerase expression in these cells was dramatic, with substantial improvements in endothelial function and replicative capacity.[10] The problem with this approach is that the integration of constitutively active telomerase in an endothelial cell could promote malignancy. More recently, we have used transient transfection with modified mRNA encoding human telomerase to rejuvenate somatic cells. Although the RNA transfection is transient and telomerase activity is only detectable for 72 hours, sufficient telomere extension occurred to substantially improve replicative capacity in somatic cells.[12] Thus, vascular rejuvenation is possible. Our center is now developing RNA therapeutics for telomere extension in age-related diseases.

Endothelial activation describes the effect that cardiovascular risk factors have on the vascular wall to make it more proatherogenic. Inflammatory cytokines and oxidized low-density lipoprotein cholesterol cause the endothelium to generate more adhesion molecules (such as VCAM-1) and chemotactic factors (such as MCP-1) that promote monocyte adhesion and infiltration into the vessel wall.[13,14] This vascular inflammation is one of the initiating events in atherosclerosis. Tobacco smoke has similar effects on endothelial-monocyte interaction.[15] However, nicotine itself has some unexpected effects on the vessel wall. In the article

by Cooke on nicotine and atherosclerosis, the potent angiogenic effects of nicotine and their relationship to tobacco-related diseases is explored. Surprisingly, there are receptors for nicotine on endothelial and vascular smooth muscle cells, and stimulation of these receptors causes vascular cells to proliferate. Endothelial cells are stimulated to generate capillaries, which may contribute to the neovascularization and growth of plaque.[16] Nicotine stimulates vascular smooth muscle cells to proliferate and to synthesize extracellular matrix, both of which promote plaque growth. The discovery of nicotine receptors on the vasculature may explain some of the adverse effects of tobacco. This insight also provides a new therapeutic avenue for treating tobacco-related diseases.

Additional new insights into plaque neovascularization and plaque growth come from the work of Longhou Fang, who has discovered a link between lipid metabolism and angiogenesis. He has characterized the apoA-I binding protein (AIBP), which augments high-density lipoprotein (HDL) functionality by accelerating cholesterol efflux. This molecule appears to play an important role in the reverse cholesterol transport that removes lipid from the vessel wall. Of great interest, AIBP also inhibits angiogenesis by depleting lipid rafts in endothelial cells, thereby suppressing activation of the potent angiogenic receptor VEGFR2. Dr. Fang's work was facilitated by his pioneering development of a zebrafish model for atherogenesis.[17]

Elevated levels of HDL cholesterol have been associated with lower risk of cardiovascular disease. This has been believed to be due to the role of HDL cholesterol in "cholesterol counter-transport," the term used to describe the effect of HDL lipoprotein to remove cholesterol from the vessel wall. The salutary effect of having high HDL cholesterol has led to trials of drugs designed to increase HDL cholesterol plasma levels. Unfortunately, these trials have been disappointing.[18] It seems that pharmaceutically induced elevations in HDL cholesterol may not be uniformly beneficial to cardiovascular health. Drs. Pownall and Gotto review the epidemiological and clinical data on HDL and its relationship to cardiovascular disease and provide a mechanistic explanation for surprising results of the trials designed to raise HDL cholesterol. They also provide a potential new therapeutic pathway for lipid lowering. A new observation from the Pownall laboratory reveals the dramatic cholesterol-lowering effect of a bacterial protein with small molecule analogues that may provide a new therapeutic approach.

Throughout the last 25 years, the cardiovascular community has made great progress in understanding the process of atherosclerosis, identifying the risk factors for atherosclerotic vascular disease, and developing, testing, and implementing effective therapies such as statins.[19] This progress has ultimately saved millions of people from premature death and disability. However, our work is not done. Cardiovascular disease remains the major cause of death globally. This fact justifies continued expenditure of time and money to delineate the mechanisms of vascular pathobiology. The insights gained from this work will lead to new transformative therapies that will lessen the scourge of cardiovascular disease.

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