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Editorial

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OF ICEBERG FORMATION AND TILE-LAYERS: NEW APPROACHES IN ATHEROTHROMBOSIS

It is in a way strange how two of the biggest killers worldwide—myocardial infarction and stroke—are sons of the same mother: the atherothrombotic lesion in the coronary artery or in the cerebral circulation. Ironically, the cardiologist is quite often called to take care of the consequences of the atherothrombosis on the heart and to reduce the size of an infarct as much as possible, as is the internist or the neurologist when dealing with a stroke. However, the real target for both of these conditions is not the heart or the brain, but rather the endothelium of the vessel. If the endothelium is normal, no atherosclerosis or thrombosis can occur; but if the endothelium is abnormal, then the onset of complex biochemical structural/functional changes inexorably leads to the constitution of the atherosclerotic plaque. Of course, there are various genetic, environmental, and lifestyle factors that influence the onset and the development of this dangerous process.

It follows that the atherosclerotic plaque and thrombus can be likened to an iceberg slowly developing underwater, or under the vessels, and only in some occasions extruding into the vessel lumen to such an extent as to completely block it, ultimately causing a stroke—the larger the vessel and the thrombus, the severer the occlusion and its consequences.

The question is, how does the iceberg start developing in the first place? The process all starts with the endothelium losing its protective role due its surface being altered. The endothelial cells in our vessels undergo a life-and-death cycle: each endothelial cell has a life span of about 1 month, and eventually commits “cellular suicide,” ie, is subjected to apoptosis, while new cells arise and “fill in” for those that have disappeared. Thus, throughout a person’s lifetime, the entire endothelium undergoes constant destruction and renewal.

Now picture the endothelial cells as “tiles” forming a “floor” lining the vessel, with an idiosyncratic pair of tilers (perpetually) redoing the floor by haphazardly removing old tiles and laying new ones in their place, so as to avoid any bare spots remaining in





the floor at any time. If, then, the tiler removing the old tiles goes berserk (endothelial dysfunction) and starts working faster than his partner who is laying them, gaps will occur and start coalescing into a larger one. Likewise, when through some pathological process a mismatch occurs between the rate of apoptosis and the rate of regeneration of the endothelial cells, the outcome is a loss of continuity in the vessel endothelial lining, and this triggers the complex biochemical sequence of events that characterize the atherosclerotic process.

Thus, one of the fundamental targets in coronary artery disease (CAD) prevention is to preserve the integrity of the endothelium by reducing the abnormally accelerated rate of apoptosis (ie, calming down the tile-remover gone berserk). This is the key to success, at least as far as secondary prevention of CAD with statins and angiotensin-converting enzyme inhibitors is concerned. Interestingly, both are effective in terms of cholesterol and blood pressure reduction. But there is also another, self-perpetuating, aspect to the complicated scenario of the atherothrombotic process, which is initiated by endothelial dysfunction, and continues with deposition of lipoproteins, invasion of macrophages, and release of proinflammatory molecules from the damaged endothelium. Each of the aspects of this atherothrombotic process offers a potential foothold for treatment. At present, we already have some very powerful drugs that address some of the features of the atherothrombotic process, but many needs are still unmet. Fortunately, new drugs, with new or complementary mechanisms of action, are just around the corner, at various stages of development.

This issue of *Dialogues* provides fascinating insights into the fine print of the pathophysiology of the atherothrombotic process and the means for exploring all of its aspects, as well as into which markers are useful to monitor its progression and predict cardiovascular events and which targets offer the best prospects for therapeutic intervention so as to better and more fully counter the complex processes that trigger—and are triggered by—atherothrombosis. The future looks very bright indeed!

