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Exploring Atherosclerosis Unfolding: In-Vivo Insights from Aortic Landscape Surveillance

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Introduction

Atherosclerosis, a systemic disease affecting arterial walls, is consistently present in the aorta [1]. Although aortic atherosclerosis can be extensive, it often remains asymptomatic throughout life. This is primarily due to the larger lumen size of the aorta, which prevents spontaneous ruptures of atherosclerotic plaques (SRAPs) from causing atherothrombotic occlusion. Consequently, examining the luminal wall of the aorta in vivo offers valuable insights into the complete and unabbreviated progression of atherosclerosis. Over the past five years, Komatsu et al. utilized non-obstructive general angioscopy to survey the aortic atherosclerotic landscape in patients with coronary disease, establishing it as the most sensitive technique for in vivo detection and characterization of aortic atherosclerotic plaques [2]. Initially, they identified and described various appearances of atherosclerotic plaques commonly observed during autopsies, including the consistent presence of plaques with features indicative of spontaneous rupture. Some SRAPs visibly affected the plaque cap through erosion, fissuring, rupture, and ulceration, while others impacted non-cap regions of the plaque, causing discoloration of the atherosclerotic surface, suggestive of intra-mural hemorrhage [3]. Subsequently, they safely retrieved debris from SRAPs, which contained large cholesterol crystals (CCs), necrotic gruel with calcium deposits, and cellular infiltrates consistent with the content of atherosclerotic plaque, as observed through confocal microscopy of fresh unprocessed debris from carotid plaques [4,5]. In this issue of Atherosclerosis, Komatsu et al. took an additional step by characterizing the cellular infiltrate in the debris associated with the so-called puff-chandelier lesions [6]. The analysis confirmed the presence of large CCs, contributing to the debris's shimmering chandelier appearance. Additionally, the cellular infiltrate stained positive for CD68, NLRP3, IL-1β, and IL-6, markers typically expressed by activated macrophages. Neutrophils were also detected in a significant portion of the specimens. These findings provide strong circumstantial evidence of an innate inflammatory process triggered by CCs within these plaques [7].

The insights obtained from their in-vivo examination of the atherosclerotic landscape yield several important findings. Firstly, their observations confirm the prevalence of SRAPs in living subjects, highlighting the dynamic nature of the atherosclerotic process. These findings emphasize that as atherosclerosis advances; SRAPs commonly affect both the plaque cap and non-cap regions [8]. This observation is significant as it underscores the fact that the majority of plaques are situated deep within the vessel wall, with only a small portion of their surface exposed to the vessel lumen. While the occasional rupture of the plaque cap in smaller and medium-sized arteries can result in atherothrombosis leading to ischemic stroke and myocardial infarction, the frequent but clinically silent injury to the non-cap regions of atherosclerotic plaque is also consequential, as it contributes to disease progression [9,10]. The presence of large cholesterol crystals (CCs) within the debris expelled from SRAPs highlights their pivotal role in plaque rupture, offering further insights. While it is known that CCs can develop within the lipid-rich core of a plaque in living subjects, it is not widely recognized that CCs cannot continue to grow outside of such an environment. As free cholesterol molecules dissociate from lipoproteins and phospholipid structures, they spontaneously associate to form flexible meta-stable structures. Initially, these structures appear as filaments that gradually broaden into ribbons, twisting into helices and eventually forming tubular structures. In the presence of ample free cholesterol monohydrate, the meta-stable tubular structure expands, and numerous microscopic ridged flat plate CCs begin to detach from its end. This process is accompanied by the release of latent elastic energy, dispersing the CCs into their surroundings [11]. These microscopic flat plate CCs serve as platforms for additional free cholesterol molecules to attach, leading to the growth of macroscopic structures. The presence of calcium debris may accelerate the rate of CC growth [12]. When this process occurs within the core of a lipid-rich plaque, it can cause damage to its walls as the sharp edges of flat plate CCs may puncture or perforate the plaque, and the aggregation of CC fragments can increase pressure and volume within the plaque, resulting in stretching, thinning, and even rupture of its walls. Plaque rupture exposes the plaque contents to either the systemic circulation or the interstitial space. However, since neither environment is rich in free cholesterol, CCs no longer enlarge once released from the plaque core. Therefore, it is plausible to speculate that the large flat plate CCs found in the debris expelled from ruptured atherosclerotic plaque must have formed and enlarged within the plaque core, rendering it vulnerable or even causing its rupture [13,14].

The presence of activated macrophages and, in some cases, neutrophils within the debris expelled from SRAPs sheds light on the events that occurred in the atherosclerotic region prior to plaque rupture, providing another important insight. When SRAPs affect non-cap regions of a plaque, CCs are released from the acellular core directly into the interstitial space. This release may lead to damage to the vasa vasorum, causing intra-plaque hemorrhage and triggering an immune response by complement and macrophages, recognizing the CCs as foreign. Fragments of CCs that are too large to be engulfed by phagocytes result in frustrated phagocytosis and promote chronic inflammatory injury [15]. The presence of CCs and inflammatory infiltrate in the debris associated with puff-chandelier ruptures suggests that these ruptures involve the plaque's cap and shoulder regions, which are exposed to crystal-induced inflammation. These

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observations demonstrate that lipid-rich plaques are constantly at risk of injury, both from within due to the enlargement and aggregation of CCs, and from outside due to acute inflammatory flares triggered by intermittent release of CCs from the core. While most inflammatory flares resolve, leading to sequestration of CCs and progressive arterial sclerosis, there are instances where a flare may precipitate SRAP by further weakening portions of the plaque wall that have stretched and thinned, thus becoming more vulnerable to rupture in conjunction with the enlargement and aggregation of CCs in the core [16,17]. Furthermore, the frequent occurrence of SRAPs associated with the extrusion of atherosclerotic debris throughout the aortic landscape provides a plausible mechanism by which the chronic release of such debris into the periphery can contribute to gradual brain and renal injury that may eventually have clinical implications. While each of these observations in the atherosclerotic landscape supports the significance of CCs in the plaque core as primary drivers of disease progression and SRAPs. Compelling evidence now suggests that CCs also play a role in atherogenesis. When cells such as macrophages, smooth muscle cells, and endothelial cells become loaded with cholesterol, CCs have been observed to form within their membranes and lysosomes. Similar to what occurs in the plaque core, the growth of nascent CCs in cell membranes can lead to membrane dysfunction, while the growth of CCs in lysosomes can disrupt their membranes, resulting in the release of CCs and cathepsins into the cytosol. This, in turn, can activate the NLRP3 inflammasome and trigger apoptosis [18-20].

Conclusion

In conclusion, the work conducted by Komatsu et al. deserves recognition for their in-vivo investigations, which provide further support to the long-held belief derived from autopsy studies, laboratory experiments, and animal models. Their findings reinforce the notion that the transformation of cholesterol into its crystalline form within lipid-rich plaques initiates a cycle of repetitive traumatic and inflammatory injuries. This process ultimately shapes the arterial wall landscape, evolving it from a relatively flat surface to a complex terrain, resembling a volatile volcanic range that is constantly vulnerable to underlying factors.

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