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The Elusive Vulnerable Plaque: Translational Biology Potential

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Abstract

The vulnerable atherosclerotic plaque plays a major role in acute coronary artery syndrome, which is a major cause of death in the United States. However, the pathobiology of the vulnerable atherosclerotic plaque is not completely understood. A better understanding of the mechanisms of how the atherosclerotic plaque forms and becomes vulnerable will allow us to devise therapies to treat this lesion, which will help prevent acute coronary artery syndrome. This paper therefore, discusses new technology and translational biology that allows better insight into the atherosclerotic vulnerable plaque.

Keywords: Atherosclerosis; Review; Imaging; Translational research; Inflammation; Matrix Metalloproteinases

Each year, there are 785,000 new and 500,000 recurring incidences of acute coronary syndrome, accounting for greater than 50% of all cardiovascular deaths. It is estimated that an additional 195,000 silent MIs occur each year. This would suggest that >20% of first and recurrent MIs are silent [1]. The difficulty with treating this disease effectively lies in the poor understanding of plaque rupture biology. In most cases, fibrous cap rupture and ensuing thrombus formation signals the initial event. This brief review will summarize new technologies and information on translational biology regarding the pathology of the vulnerable plaque.

The vulnerable plaque has four major areas of concern. The first area is the thin fibrous cap that overlies the necrotic core, as rupture of this cap is thought to be the primary cause of acute coronary syndrome. Second, the vulnerable plaque positively remodels with a rich vasa-vasorum containing a necrotic lipid core and increased macrophage numbers [2-4].

Figure 1: Bone morphogenetic protein (BMP) is controlled by important factors related to diabetes. Diabetes patients have increased vascular calcification.

The third area of concern is the role of inflammation, smooth muscle cell apoptosis, matrix metalloproteinases, macrophages and other leukocytes, neovascularization, and intraplaque hemorrhage in advanced coronary lesions [5,6]. Lastly, ruptures occurring in the center of the cap account for approximately 37% of events. Macrophages usually concentrate at the corners of plaques and are sparse in the center of the cap. In

addition, the densest collagen structure is typically at the cap center [7].

Clinical imaging studies have demonstrated three major factors associated with plaque rupture. In the PROSPECT trial, investigators prospectively studied 697 patients with Acute Coronary Syndrome by catheter and Intravascular Ultrasound (IVUS) imaging evaluations. In this trial, major adverse events was defined as composite of cardiac death, cardiac arrest, MI, ACS, revascularization by CABG, PCI, or rehospitalization by CABG or PCI or rehospitalization for angina. Culprit lesion was defined as a lesion that appeared under stress testing that associated with myocardial ischemia defined by changes in electrocardiogram. They reported a 20% cumulative rate of major adverse events at 3 years. However, surprisingly at follow up events from the culprit lesions were 12.9% and non-

Figure 2: At 3 year follow up in the PROSPECT trial, events from the culprit lesions were 12.9% and from non-culprit lesions were 11.6% (p=not significantly different). This figure graphically illustrates the progression of atherosclerosis over time, leading in many patients to a myocardial infarction with ventricular damage. In the next 3 years, the less high grade lesions (non culprit) have a CV event rate very similar to the original culprit lesion.

Multivariate analysis of the non-culprit lesions identified three characteristics that were significantly associated with future adverse events. Non-culprit lesions that were associated with recurrent events had a plaque burden of >70%, a minimal luminal area of <4 mm^2, and were classified as thin cap fibroatheromas by radiofrequency IVUS imaging. At the patient level, insulin-requiring diabetes was the strongest predictor of major adverse events associated with non-culprit lesions [21].

Figure 3: This Infraredx near infrared spectroscopy with intravascular ultrasound (IVUS) illustrates an intermediate lesion with a large lipid core.

New research in imaging and structural evaluation of the vulnerable plaque has made important advances over the last 5 years. The human use of IVUS, Optical Coherence Tomography (OCT), and Near Infrared Spectroscopy (NIRS) has ushered in a new exciting era of investigations on the vulnerable plaque and vascular aging [8,9]. In addition, biomechanical research has contributed important 3D imaging of plaque geometry, circumferential, and fluid induced shear stress information [10-14]. One of the most exciting new areas in vulnerable plaque research has been the identification of microcalcifications in the vulnerable plaque [15,16]. Microcalcifications can be seen with OCT in human coronary plaques and have been correlated with microCT images and autopsy findings [17,18].

Figure 4: An optical coherence tomography (OCT) image illustrating small microcalcifications in the thin plaque cap in a mild to intermediate coronary lesion.

The role of microcalcifications on plaque vulnerability has most recently been studied by Vengrenyuk [19], Maldonado [20], and Kelly-Arnold [18]. Maldonado *et al* [20] studied 92 major coronary arteries with microCT at a resolution of 6.7 microns [20]. They found that 85% of microcalcifications were <50 microns, mostly in lipid pools. Only 0.2% of the microcalcifications were in the fibrous cap proper. In studies by Kelly-Arnold *et al.* [18], 66 human coronary fibro-atheromas, defined as thickened vessel walls with visible lipid pool and necrotic core, were studied by microCT scanning. They were detected by 2.1- micron high resolution microCT scanning in 92 human coronary arteries sections obtained from the National Disease Research Interchange. Their results found that most microcalcifications were <15 micron and were invisible at 6.7 micron resolution. They concluded that nearly all fibrous caps have microcalcifications with only a small subset having the potential to rupture. In contrast, earlier studies by Vengrenyuk *et al.* [19] suggested that microcalcifications were derived from apoptotic macrophages in the cap and necrotic core producing a possible vulnerable cap. They concluded that for thin caps without microcalcifications, the rupture threshold cap thickness would be around 30 microns. This is much less than the reported 65 microns from earlier research. More research is needed in this important area of the vulnerable plaque pathobiology.

Recent developments in molecular biology have shed important light on the mechanisms of the development of vascular calcification. Data from Yao et al. [22] reports that the endothelium can produce osteoprogenitor cells that have the potential to increase vascular calcification. Increased vascular calcification is seen in patients with diabetes and disorders with enhanced bone morphogenetic protein levels. Both contribute osteoprogenitor cells to the vascular calcification [22]. Diseases and drugs that impact Bone Morphogenetic Protein (BMP) levels would alter osteoprogenitor cells that are linked to vascular calcification seen with vascular aging and increased plaque rupture risk. Changes in the level of osteoprogenitor cell activity may affect the levels of microcalcifications found in the vulnerable plaque.

In summary, the vulnerable plaque continues to be an elusive target for the treatment of acute coronary syndrome, in part due to an insufficient understanding of the mechanisms underlying the development and rupture of the vulnerable plaque. Clinically the best choices for reducing cardiovascular events continue to be lifestyle changes and risk factor modification with therapies such as statins that have been shown to decrease future cardiovascular events.

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