Chapter 23
Coronary Plaque Vulnerability: Molecular and Cellular Mechanisms and Novel Imaging Modalities

George D. Giannoglou
AHEPA University General Hospital, Greece & Aristotle University Medical School, Greece

Konstantinos C. Koskinas
AHEPA University General Hospital, Greece & Aristotle University Medical School, Greece

ABSTRACT

Beyond structural information obtained by traditional imaging modalities, molecular imaging can now visualize inflammation and proteolytic activity in the atheroma in-vivo. In addition, visualization of plaque neovascularization, and measurement of the plaque’s mechanical properties may enhance the identification of rupture-prone lesions. While limited mainly at the pre-clinical level, these novel imaging methods show promise for clinical translation.

ROLE OF MATRIX-DEGRADING PROTEASES IN PLAQUE DESTABILIZATION AND RUPTURE

The thrombotic complications of coronary atherosclerotic disease result mostly from physical disruption of a subpopulation of high-risk lesions (Virmani, Kolodgie, Burke, Farb, & Schwartz, 2000). Local inflammation and proteolytic activity within the plaque influence critically the stability of the atheroma and modulate the plaque’s propensity to rupture and cause an acute coronary event (Libby, 2008).

The status of the extracellular matrix in the atherosclerotic intima is regulated by the fine balance between macromolecule synthesis and enzymatic catabolism. Extracellular matrix macromolecules, especially fibrillar interstitial collagens, confer tensile strength upon the plaque’s fibrous cap and determine the mechanical properties and stability of atherosclerotic arteries, as shown by experiments in genetically altered mice that
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express collagenase-resistant collagen (Deguchi, et al., 2005). Interstitial collagenases, mostly collagenolytic matrix metalloproteinases (MMPs) MMP-1, MMP-13 and MMP-8, attack the intact triple helical collagen molecule and thereby initiate the catabolic cascade of collagen (Sukhova, et al., 1999), (Deguchi, Aikawa, & Libby, 2005). These active collagenases are expressed in human atherosclerotic plaques, but not in normal arteries, and promote plaque vulnerability through the degradation of the major plaque-stabilizing protein, i.e. collagen. Gelatinases MMP-2 and MMP-9 are implicated in later steps of collagen catabolism after the collagenases make the initial attack. In addition to collagen catabolism, plaques also contain potent elastases (MMP-9, cathepsins S and K, neutrophil elastase) which break down elastin fibers (Dollery & Libby, 2006) and may have important roles in adverse outward arterial remodeling and plaque destabilization (Sukhova, Shi, Simon, Chapman, & Libby, 1998), (Lutgens, et al., 2006).

MOLECULAR IMAGING OF PLAQUE INFLAMMATION AND PROTEASE ACTIVITY

In the light of the well-recognized contribution of inflammation and proteolytic activity to plaque destabilization, novel imaging modalities visualizing molecular targets are increasingly appreciated for their potential to assess in vivo biological processes beyond the structural information that is obtained from traditional imaging modalities. While the feasibility and validation of these techniques have been tested at the pre-clinical level, the rapidly emerging strategy of optical and multimodality molecular imaging of inflammation and protease activity has shown promise for clinical translation. These techniques could provide a powerful tool to enhance our understanding of the pathophysiologic processes governing the progression towards high-risk plaque, enable the identification of rupture-prone plaques at earlier stages of their evolution, enable monitoring of novel therapeutic interventions, and allow for individualized therapeutic strategies. Near-infrared fluorescence (NIRF) is a particularly promising technique for the in vivo visualization of protease activity. Detection of the NIR fluorochromes can be performed either non-invasively by fluorescence molecular tomography (FMT), or invasively, using intravascular NIRF catheters.

Non-invasive Imaging of Protease Activity by Near-Infrared Fluorescence (NIRF)

Protease presence in the plaques can be visualized in vivo with radiolabeled small molecule inhibitors or MRI-detectable agents (Amirbekian, et al., 2009). However, because protease molecules may represent inactive zymogen precursors that lack proteolytic capacity, protease activity per se can be visualized by protease-activatable fluorescent probes. The principle of NIRF molecular imaging of protease activity consists of biocompatible agents that emit fluorescent signal after proteolytic cleavage of a peptide sequence specific to their target enzyme. These agents are injected and delivered to the protease-rich plaque environment and cleaved by proteases, including cathepsins -K, -L, -S, and -B, generating fluorochromes that are detectable by NIRF imaging technologies (Chen, et al., 2002). More recently, experimental studies have used the first-generation protease activatable agent and incorporated peptide substrates that are specifically cleaved by selective enzymes, including MMP-2, MMP-9 (Chen, Tung, Allport, Chen, Weissleder, & Huang, 2005), cathepsin-K, (Jaffer, et al., 2007) -S (Galande, Hilderbrand, Weissleder, & Tung, 2006) and -D, thereby allowing the enzyme-specific assessment of protease activity in the atherosclerotic plaque in vivo.