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REVIEW

STATE-OF-THE-ART PAPER

Coronary Artery Calcification

From Mechanism to Molecular Imaging

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ABSTRACT

Vascular calcification is a hallmark of atherosclerosis. The location, density, and confluence of calcification may change portions of the arterial conduit to a noncompliant structure. Calcifications may also seed the cap of a thin cap fibroatheroma, altering tensile forces on the cap and rendering the lesion prone to rupture. Many local and systemic factors participate in this process, including hyperlipidemia, ongoing inflammation, large necrotic cores, and diabetes. Vascular cells can undergo chondrogenic or osteogenic differentiation, causing mineralization of membranous bone and formation of endochondral bone. Calcifying vascular cells are derived from local smooth muscle cells and circulating hematopoietic stem cells (especially in intimal calcification). Matrix vesicles in the extracellular space of the necrotic core serve as a nidus for calcification. Although coronary calcification is a marker of coronary atheroma, dense calcification (>400 HU) is usually associated with stable plaques. Conversely, microcalcification (often also referred to as spotty calcification) is more commonly an accompaniment of vulnerable plaques. Recent studies have suggested that microcalcification in the fibrous cap may increase local tissue stress (depending on the proximity of one microcalcific locus to another, and the orientation of the microcalcification in reference to blood flow), resulting in plaque instability. It has been proposed that positron emission tomography imaging with sodium fluoride may identify early calcific deposits and hence high-risk plaques.
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Rudolph Virchow, a 19th century pathologist, recognized that vascular calcification occurred as the result of an ossification process (1). About a century later, Tanimura et al. (2) described a stepwise process of intimal vascular calcification and alluded to the role of "extracellular matrix vesicle-like structures" in intimal calcification. Calcium in the coronary arteries has been used as a surrogate marker of coronary atherosclerosis since the 1940s, an era when cardiologists would greet their patients wearing large red googles, to maintain dark adaption so they could see coronary calcium on the fluoroscopy screens (3,4). Improvements in technology, especially high-speed multislice computed tomography (CT) scans, has allowed objective measurement of both the density and extent of coronary calcification (usually calculated by using the method of Agatston et al. [5]). Indeed, the coronary calcium score has been widely used to compute the future risk of an acute coronary event (6).

Macroscopic vascular calcification seen on clinical CT scanning evolves from nanometer foci in inflamed atheroma that are detectable at histopathology but are too small to be seen on clinical CT scanning with

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its spatial resolution of approximately 0.5 mm (7). Calcification begins within the necrotic core of the atheroma. Extracellular vesicles (8) are released by dead or dying macrophages and smooth muscle cells (SMCs). These vesicles provide the scaffolding for initiation of calcification. Control of the local concentration of calcium and phosphate are lost. In the case of phosphate, for example, enzymes such as alkaline phosphatase, adenosine triphosphatase, and reactive oxygen species (9) create free phosphate from the breakdown of larger molecules. Ultimately, the local concentration of free calcium and phosphate in autophagosomes reaches a sufficient concentration to allow formation of calcium phosphate crystals (10,11), which are visible by electron microscopy (12), via active processes that resemble osteo/chondrogenic conversion. The focus of the present review was on vascular calcification from mechanism to molecular imaging.

INTIMAL CALCIFICATION: DIFFERENT FROM MEDIAL CALCIFICATION

Intimal calcification resembles endochondral bone formation in long bones (cartilage metaplasia). Although initiation of calcification does not require participation by specific cells, progression of the lesion is likely driven by chondrocyte-like cells and associated with the expression of inflammatory factors, such as cytokines. Cytokines are produced by tissue macrophages and foam cells (13) in response to the harsh environment in atherosclerotic plaque due to the noxious effects of oxidized lipoprotein. Calcified atheroma in low-density lipoprotein (LDL) receptor–deficient and apolipoprotein (apo) E–deficient mice exhibit cartilage metaplasia and chondrocyte-like cells, which express specific chondrocytic markers such as Sox9, collagen II, and collagen X (14–16). Many disease processes, including dyslipidemia, hypertension, systemic inflammatory diseases (lupus), diabetes, and kidney disease, influence the biology of atherosclerosis, vascular remodeling, and vascular calcification (17–20).

Medial calcification has a different mechanism driven by the action of osteoblast-like cells. Bone morphogenetic protein (BMP)-2/muscle segment homeobox homologue/wingless-type MMTV integration site family member (Wnt) signaling, which is characteristic of intramembranous bone formation, occurs prominently in medial calcification. This signaling causes direct transdifferentiation of vascular cells to osteoblast-like cells, independent of Runx2/cbfa1 (21), as confirmed in an LDL receptor -/- mouse model (22). In addition, osteoblast-like cells resulting in medial calcification may also be derived from chondrocyte-like precursor cells, as has been observed in matrix γ-carboxyglutamic acid protein (MGP) -/- mice (23) and in adenine-induced uremic rats (24,25). Whether patients develop medial or intimal calcification is determined by local factors (26). Both osterix and Wnt/β-catenin signaling cause osteo-chondroprogenitor cells to evolve to osteoblast-like. Conversely, suppression of osterix and Wnt/β pathways or induction of Sox9 induces differentiation of progenitor cells down the chondrocyte pathway (27,28).

At least 4 cell types may lead to vascular calcification: 1) pericytes in microvessels; 2) pericyte-like calcifying vascular cells in the aortic intima; 3) SMCs in the media; and 4) myofibroblasts in the adventitia (29–32). In medial calcification, medial SMCs undergoing osteochondrogenic differentiation are the major contributor (33). In intimal calcification, nearly 90% of chondrocyte-like cells originate in the bone marrow (34), and transdifferentiation of local SMCs to chondrocytes contributes minimally (15).

ATHEROSCLEROTIC LESION AND DEVELOPMENT OF NECROTIC CORE

Atherogenesis is initiated by the focal retention of apo B–containing lipoproteins in the subendothelial extracellular matrix, particularly chondroitin sulfate proteoglycans (35–38). The retained lipoproteins cause local inflammation, resulting in the release of chemoattractant peptides (39). Monocytes attracted to the site enter the tissue, undergo conversion to tissue macrophages, and phagocytize/catabolize the lipoprotein cholesterol complex. In the process of catabolism, the lipoprotein cholesterol complex is aggregated and oxidized. Oxidized lipoprotein cholesterol is particularly toxic to the macrophage, and, if present in sufficient quantity, could cause death of the lipid-laden macrophage (foam cell). This macrophage cell death is initially due to apoptosis (40). However, if the atheroma has a large intensely inflamed necrotic core, normal apoptotic cell clearance mechanisms (efferocytosis) are incomplete, allowing dead cell detritus to contribute to the necrotic core, with release of toxic material into the local environment (41). T cells accelerate the noxious process by producing antibodies that recognize oxidized LDL, adding fuel to the inflammatory fire. SMCs migrate into the intima, proliferate, and

ABBREVIATIONS AND ACRONYMS

apo = apolipoprotein

BMP = bone morphogenetic protein

CT = computed tomography

FDG = fluorodeoxyglucose

LDL = low-density lipoprotein

MGP = matrix γ-carboxyglutamic acid protein

Msx2 = muscle segment homeobox homologue

NaF = sodium fluoride

OPG = osteoprotegerin

RANK = receptor activator of nuclear factor κB

RANKL = receptor activator of nuclear factor κB ligand

SMC = smooth muscle cell

VSMC = vascular smooth muscle cell

Wnt = wingless-type MMTV integration site family member