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Advances in the Understanding of Plaque Composition and Treatment Options

Year in Review

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Atherosclerosis research has classically followed 2 intertwining lines of investigation concerning atherosclerosis as a local process (the "high-risk plaque") and as a systemic disease (the "high-risk patient"). Over time, the weight of attention has swung, like a pendulum, between these 2 related foci. With optimal medical therapy and attention to risk factors firmly established as fundamental aspects of management, in the past year, we have nevertheless perceived a shift in the pendulum toward renewed focus on the local plaque. We contend that this shift results from a convergence of major advances in understanding the biology of plaque progression, novel sophisticated invasive and noninvasive imaging modalities for the in vivo characterization of plaque composition and inflammation, and emerging data and technologies that have renewed interest in locally targeted interventions. Here, we review the dynamic and exciting progress that has occurred over the last 12 months in this arena, while acknowledging future work that remains to be done to refine and validate new imaging modalities and therapies. (J Am Coll Cardiol 2014;63:1604–16) © 2014 by the American College of Cardiology Foundation

Atherosclerotic plaque is the local manifestation of a systemic disease. As such, research in this field has generally followed 2 intertwining lines of investigation, focused either on the local process (the "high-risk plaque") or the systemic disease (the "high-risk patient") (1). Over time, the weight of collective attention has swung like a pendulum between these related foci. Two decades ago, observations on the natural history of coronary plaque (2) and newly available intravascular tools such as intravascular ultrasound (IVUS), virtual histology, palpography, and thermography fueled interest in the local plaque. Emphasis on understanding, diagnosing, and treating atherosclerosis as a systemic disease then took hold as medications, rather than locally targeted therapies, demonstrated efficacy in reducing myocardial infarction (MI) and death. In the last decade, this shift was punctuated by results of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation) trial in which an initial strategy of local therapy (revascularization) conferred no advantage for prevention of the composite of death or nonfatal MI above and beyond optimal medical therapy (3).

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On this backdrop of optimal medical therapy and risk factor modification, now established as the bedrock of atherosclerosis management, efforts over the past year to understand, diagnose, and treat the local atherosclerotic plaque have gained momentum (Fig. 1). Central to this resurgence of interest in the high-risk plaque is the arrival of diverse new tools for invasive and noninvasive plaque imaging. Informed by advances in our understanding of both the pathology of the local plaque and the molecular mechanisms of systemic atherosclerosis, these novel imaging approaches provide opportunities to describe, not only the anatomy, but also the biology of the plaque in vivo. In this narrative review, we aim to synthesize key findings over the past year in atherosclerosis, plaque biology, plaque imaging, and emerging therapies.

Defining the High-Risk Plaque

Pathological observations. Core insights informing our paradigm of the plaque at high risk of rupture have traditionally derived from pathological observations of ruptured and nonruptured plaques post-mortem (4). Adding to this body of published data, a recent analysis of 295 plaques in 213 sudden cardiac death victims identified aspects of plaque composition and burden as markers of risk. In this study, Narula et al. (5) compared 105 stable plaques, 88 thin-cap fibroatheromas (TCFA), and 102 ruptured plaques with respect to features of plaque morphology: fibrous cap thickness, percent luminal stenosis, plaque area, necrotic core area, macrophage area, and calcification. Fibrous cap

thickness was the best discriminator of plaque type, measuring <54 μm in ruptured plaques, 54 to 84 μm in most TCFA, and >84 μm in stable plaques. Upon exclusion of cap thickness, the best discriminators of TCFA were macrophage infiltration and necrotic core.

In seeming contradistinction to the earlier observation by Ambrose et al. (2) that incident MI tended to emerge from previously nonobstructive plaque, the majority of TCFA in this pathological study exhibited >50% stenosis, and 70% of ruptured plaques showed >75% stenosis. This pathological observation is consistent with angiographic findings in a substudy of the COURAGE trial in which nonrevascularized, ≥50% lesions predicted subsequent acute coronary syndromes (ACS) (6) and IVUS findings in the PROSPECT (Prospective Natural-History Study of Coronary Atherosclerosis) in which nonculprit lesions responsible for subsequent ischemic events were associated with large plaque burden and reduced minimal luminal area despite apparently mild luminal narrowing at angiography (7).

Reconciling these observations may be important to defining the high-risk plaque, as reviewed recently by Puri et al. (8). It is possible that seemingly nonobstructive plaque at initial angiography represents the "tip of the iceberg," with significant plaque burden not detected by angiography because of positive (outward) remodeling. Alternatively, MI may be associated with rapid plaque progression in the preceding weeks to months, with acceleration of plaque progression mediated by subclinical cycles of plaque rupture and healing (9) or intraplaque hemorrhage (as seen in carotid plaque) (10).

Molecular and cellular basis of plaque progression. Advances in understanding of the cellular and molecular basis for plaque progression have helped to define markers of plaque vulnerability with potential application to both imaging and therapy.

A first theme has been refinement of our understanding of the role of macrophages, monocytes and inflammation in plaque progression. Macrophages and monocytes have been understood classically to contribute to plaque progression through phagocytosis of cholesterol droplets and debris, yielding a sequence of foam cell generation, foam cell death, and formation of the necrotic core, as well as contributing to inflammation and plaque rupture (11). In mouse models, monocytosis develops after MI or stroke in a sympathetic nervous system–dependent manner, a potential mechanism for accelerated atherosclerosis (12). Whether plaque accumulation of macrophages and monocytes results from infiltration has now become the subject of controversy following recent surprising results suggesting that local proliferation (rather than infiltration) accounts for the majority of these cells within plaques (13,14). There is also suggestion that neutrophils may precede monocytes at sites of vascular inflammation, on the basis of the finding in a mouse model that neutrophil-derived cathelicidins induce adhesion of circulating monocytes (15). Circulating leukocyte membrane microparticles that become elevated in humans with unstable carotid plaque may be footprints of this process (16). Furthermore, there is growing evidence that molecular inflammatory mediators associated with leukocyte activation may relate to risk of atherosclerosis disease progression. A key example is interleukin (IL)-6, an inflammatory cytokine associated with increased C-reactive protein production that is released by activated leukocytes and vascular smooth muscle cells at sites of vascular injury. The potential role of IL-6 signaling in atherosclerosis progression was bolstered by recent observations of significant variation in coronary artery disease (CAD) risk with the Asp358Ala allelic variant of the IL-6 receptor (17,18).

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
CAD = coronary artery disease
CI = confidence interval
HDL-C = high-density lipoprotein-cholesterol
IL = interleukin
IVUS = intravascular ultrasound
LDL-C = low-density lipoprotein-cholesterol
MACE = major adverse cardiac event(s)
MI = myocardial infarction
ROS = reactive oxygen species
TCFA = thin-cap fibroatheroma

A second key theme of publications has been the role of free hemoglobin and oxidative stress in plaque progression. When free hemoglobin is released into plaque as a consequence of intraplaque hemorrhage, heme iron is a potent generator of reactive oxygen species (ROS). Binding of free hemoglobin by circulating haptoglobin attenuates oxidative activity and promotes clearance of hemoglobin by macrophages via the CD163 scavenger receptor. Unchecked, oxidative activity related to free hemoglobin may contribute to plaque progression. In a study of human aortic plaques, a genetic polymorphism at the haptoglobin locus (*Hp2-2*) linked to defective attenuation of heme iron–mediated oxidation was associated with a significant increase in apoptotic macrophages, oxidized phospholipid, and malondialdehyde-like oxidation-specific epitopes (19). In addition, among patients with diabetes mellitus in the Nurses' Health Study, the *Hp2-2* genotype was associated with a significantly increased risk of coronary heart disease (relative risk 7.90, 95% confidence interval [CI]: 4.43 to 14.10, $p = 0.004$) (20).

Free hemoglobin within plaque may influence differentiation of macrophages into different subtypes and their capacity to engage in reverse cholesterol transport. Evaluating pathological specimens of human atherosclerotic plaque, Finn et al. (21) demonstrated that macrophages with high expression of mannose and CD163 receptors, devoid of neutral lipids typical of foam cells, preferentially exist at sites of intraplaque hemorrhage and that intracellular hemoglobin in a rabbit model is necessary to drive differentiation of this macrophage subtype, M(Hb). Whereas M(Hb) was associated with increased ferroportin expression, reduced intracellular iron, reduced ROS, increased liver X receptor alpha (LXRα) activation and cholesterol efflux via ATP binding cassette (ABC) transporters, degradation of ferroportin using hepcidin increased