Linking Hemorrhage, Angiogenesis, Macrophages, and Iron Metabolism in Atherosclerotic Vascular Diseases

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Hemorrhage in Coronary Artery Disease

Intraplaque hemorrhage (IPH) is a phenomenon observed in advanced atherosclerotic plaques. Paterson[1] was the first to propose vasa vasorum as the source of IPH. Barger et al[2] described an abundance of plaque microvessels found in diseased coronary arteries compared with healthy ones and proposed that plaque neovascularization plays an important role in the pathogenesis of atherosclerosis. A postmortem study from our group established a critical relationship between erythrocyte extravasation in coronary atherosclerotic plaques (measured by the red blood cell membrane sialoglycoprotein glycophorin A) and necrotic core enlargement and plaque progression.[3] In a different postmortem study, plaque macrophages were found to be 2- to 4-fold more abundant in patients with symptomatic cardiovascular disease, and the adjacent microvessel network was found to be denser.[4] Kockx et al[5] showed that perivascular foam cells in areas of high microvascular density within carotid plaques frequently contained platelets and erythrocytes. Phagocytosis of red blood cells was shown to be a trigger for macrophage activation in both in vitro and in vivo. It was also shown that macrophages were particularly abundant around newly formed leaky microvessels.[5–7] This and other emerging data support the notion that IPH plays a causal role in promoting plaque progression via deposition of free cholesterol from red blood cells.[8–10] The effect of plaque hemorrhage translates into higher plaque burden and vulnerability, which are demonstrable in imaging modalities such as magnetic resonance imaging, intravascular ultrasound, and near infrared spectroscopy.[11,12] Here, we summarize recent progress made in our understanding of the collective role of IPH, angiogenesis, macrophages, and iron metabolism in atherosclerotic plaque progression.

IPH Risk Factors and Mechanisms

In a recent article, Sun et al[13] examined the effect of the blood pressure on carotid plaque IPH diagnosed by magnetic resonance imaging in an asymptomatic cohort, in which the majority of subjects were under antihypertensive therapy. It was found that IPH was more likely to be present in subjects with low diastolic blood pressure. This effect was independent from other risk factors, suggesting that patients with larger decrease in blood pressure under hypertensive therapy were more likely to develop IPH.[13] The importance of hemodynamics and vascular compliance was also shown in the Rotterdam study, in which arterial stiffness assessed by aortic pulse wave velocity was associated with increased risk of IPH (odds ratio, 1.20 [1.01–1.43]).[14] Similarly, Ding et al[15] showed that carotid stiffness was also associated with cerebral microbleeds after adjusting to other risk factors, such as hypertension. Given the abundance of antihypertensive treatment in patients with advanced atherosclerosis, there is a keen interest in further characterizing hemodynamic effect of antihypertensive therapies because different hypertensive regimens might have different effects on IPH. These differences might eventually translate into clinical outcomes.

The primary mechanisms responsible for IPH are thought to be vascular fragility and permeability induced by vascular endothelial growth factor (VEGF).[16] Chen et al[17] described impaired vascular integrity in a model of hereditary hemorrhagic telangiectasia type 2, a disease in which abnormal vessels are prone to hemorrhage and rupture. Using a floxed deletion of ALK1 (activin receptor-like kinase) and VEGF stimulation, the authors tested the hypothesis that VEGF impairs vascular integrity in ALK1-deficient mice through the reduction of mural cell coverage. They showed that in transgenic mice receiving VEGF overexpression vector, the angiogenic foci induced by VEGF had more α-smooth muscle actin–negative vessels in the vessel wall and fewer covering pericytes compared with wild-type control mice. ALK1-deficient brains demonstrated more perivascular fibrin, a 10-fold increase in iron-positive areas and extravascular red blood cells surrounded by macrophages. This work demonstrates reduction of mural cell coverage as a potential mechanism for the impairment of vessel wall integrity in hereditary hemorrhagic telangiectasia type 2 and perhaps other disease.

In atherosclerotic plaques, intimal thickening is thought to induce hypoxia, which is the major stimulus for VEGF-induced angiogenesis. Sluimer et al[18] previously demonstrated hypoxia in human carotid specimens using the bioreductive agent pimonidazole. Hypoxia was strongly correlated with the macrophage marker CD68, angiogenesis, thrombus, hypoxia-inducible factor-1 alpha (HIF-1α), and VEGF in regions of advanced atheroma but was absent in areas of pathological intimal thickening. HIF-1α immunoreactivity and mRNA were detected at sites of inflammation even in areas within a close distance (20–30 μm) from the vessel lumen, well below the diffusion limits of oxygen (100–250 μm). Thus, although hypoxia is thought to be an important stimulus for angiogenesis within atherosclerotic plaque, the presence of HIF-α within a very close distance to the vessel lumen indicates that stimuli for HIF-1α/VEGF other than hypoxia remain a likely possibility.

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Unlike in the ALK1-deficient model highlighted above, another postmortem study found that mural cell coverage was infrequent in microvessels in both normal and atherosclerotic vessels.[19] This suggests that in atherosclerosis, mural cell coverage is likely not the defect causing increased vascular permeability. Rather this particular study found that plaque microvessels had abnormal morphology, aberrant endothelial cell junctions, and leukocyte adherence. Bobryshev et al[20] found abnormal endothelial cell VE-cadherin expression associated with areas of inflammation in human carotid plaques, suggesting the link between inflammation and endothelial incompetence. Thus, the mechanisms of vessel incompetence in atherosclerosis remain incompletely understood but may involve interactions between immune cells and the endothelium.

Microvessels, Vasa Vasorum, and Angiogenesis

The vasa vasorum are microvessels supplying the vessel wall. The vasa vasorum interna originates from the arterial lumen, whereas the vasa vasorum externa is found mostly in the adventitia and arise mainly in branching sites.[21] Angiogenesis and neovascularization originate by sprouting of the endothelium. It is a complicated process with numerous factors affecting it. Angiogenesis in nature is like a double-edged sword; in certain beds and vessel diameters, it is a physiological process, which helps to adapt to stress and injury, whereas in other cases, such as in proliferative retinopathies, atherosclerotic plaques, and neoplasms, it has a deleterious effect.[21] VEGF is the most studied ligand inducing neovascularization with hypoxia serving as a physiological trigger through the induction of hypoxia-inducible transcription factors HIF-1 and HIF-2. MKP-1 (mitogen-activated protein kinase phosphatase-1) is a phosphatase that deactivates MAPK (mitogen-activated protein kinase). MKP-1 was found to be essential for VEGF-induced angiogenesis both in vitro and in vivo.[22] In injured arteries, the vasa vasorum microvessel density is higher and is proportional to the vessel stenosis.[23] Inflammation is one of the processes known to induce VEGF through cytokines released from inflammatory cells. Recently, Zhu et al[24] investigated the role of macrophage AMPK (AMP-activated protein kinase) on arterial neovascularization. AMPK is an energy sensor, activated by various stimuli, including hypoxia, nutrient deprivation, oxidative stress, and shear stress at the site of vessel obstruction. In a model of mice hindlimb ligation, The authors demonstrated that knocking out AMPKα1 reduced capillary density and collateral maturation and caused decrease of macrophage accumulation in the ligated limb. The isolated macrophages from the AMPKα1 knockout showed decreased production of VEGF, FGF2 (fibroblast growth factor 2), TGFβ (transforming growth factor-β), and PDGFB (platelet-derived growth factor subunit B) compared with the wild-type mice. By using a Lys-Cre floxed mice, the authors showed that knocking out AMPKα1 in macrophages produced similar results, thus strengthening the role of macrophages in neoangiogenesis and collateral formation. Whether AMPK plays a role in plaque angiogenesis remains unclear.

Although macrophages have a clear role in angiogenesis, in certain vascular beds they seem to play a less crucial role. Using 2 experimental models–oxygen-induced retinopathy and laser-induced choroidal neovascularization, Liyanage et al[25] showed that macrophage-specific conditional knockout for *Vegfa* or *Hif-1*a did not reduced the total ocular VEGF nor did it significantly affect neovascularization. Another mechanism that triggers neovascularization is flow and shear force changes. Stable laminar flow downregulates DNA methyltransferases and histone deactylases and upregulates histone acetyltranferases in the endothelium. The expression of some miRNAs and transcription factors is also regulated by changes in flow and shear force. These changes in gene expression, by both epigenetic methylation mechanism and transcriptional control, are responsible for proatherogenic shift in angiogenesis.[26] Changes in collateral flow direction after ligation seem to increase angiogenesis, independently of ischemia.[27] The mouse ligated hindlimb model was also used to investigate the effect of exercise on angiogenesis. Schirmer et al[28] showed that exercise-induced angiogenesis is at least in part facilitated by iNOS (inducible nitric oxide synthase) produced by circulating monocytes. The iNOS induction is independent of eNOS (endothelial nitric oxide synthase), which is induced directly by changes in shear forces. Poldip2 (polymerase δ-interacting protein 2) is a protein involved in regulating adhesion, vascular smooth muscle cell migration, and extracellular matrix composition. A heterozygous deletion of *Poldip2* caused decreased production of H_2O_2, decreased metalloproteinases activity, and macrophage infiltration. It also caused decrease in neovascularization and angiogenesis.[29]

Although it is not clear what the importance of the angiogentic mechanisms described above are in the pathogenesis of plaque progression. In vivo imaging of the vasa vasorum in aged hypercholesterolemic mice showed paucity of microvessels inside the plaque, decreased blood flow velocity, and increased leakage in the plaque vasa vasorum when compared with controlled capillaries.[30] The plaque's vasa vasorum also showed increased leukocyte adhesion and extravasation, which as alluded to above might contribute to plaque progression and vulnerability.

Improved resolution of intracoronary imaging using optical coherence tomographic imaging may enable us to analyze intraplaque macrophages and vasa vasorum in living patients. In a recent study, optical coherence tomography was used to assess the endothelial function in patients with mild coronary atherosclerosis.[31] Choi et al[31] demonstrated that the segmental coronary endothelial dysfunction is associated with the presence of macrophages and intimal microvessels in 42 patients with early coronary artery disease. These data suggest that optical coherence tomography may allow us to better understand the role and relationship of angiogenesis to plaque progression in patients with coronary artery disease.

Macrophages and Hemoglobin

Macrophages are a heterogeneous group of immune cells that respond to pathophysiological cues to form distinct functional phenotypes. Besides the classic proinflammatory M1 inflammatory macrophages, distinct subtypes of alternative polarized macrophages (sometimes referred to as M2) have been characterized largely based on in vitro data.[32] M1 macrophages are generated after stimulation with interferon-γ and

lipopolysaccharide, whereas M2 alternative macrophages are seen after stimulation with interleukin-4 and interleukin-13. Alternative macrophages are thought to counterbalance M1 responses by promoting resolution of inflammation and promoting tissue repair.[33] The extrapolation of this paradigm to the in vivo function of macrophages is likely more complex than this simple dichotomy suggests. Multiple alternative macrophage subtypes have been described.[33] One important stimulus for alternative macrophage conversion within human atherosclerosis is IPH.[34,35] Scavenger receptor CD163 upregulation is a distinct characteristic for macrophages that is essential in processing free hemoglobin.[16] Within areas of IPH, oxidative stress leads to erythrocyte lysis, which releases free hemoglobin (Hb).[36] Hb is quickly bound by the plasma protein haptoglobin (Hp), and hemoglobin:haptoglobin complexes are formed and internalized into the macrophage via CD163 receptor, which is exclusive to macrophages. We and others have previously described that intake of hemoglobin:haptoglobin complexes by CD163 expressed on macrophages leads to a distinct phenotype of macrophage termed M(Hb) or M(hem) found in areas of neoangiogenesis and hemorrhage characterized by high surface expression of CD163, reduced proinflammatory cytokine production, and lack of lipid retention, all characteristics that distinguish them from foamy macrophages.[34,37–39] On the basis of these findings, the M(Hb) macrophage phenotype has been termed atheroprotective.

However, analysis of atherosclerotic lesions from human coronary arteries suggests that hemosiderin-laden macrophages have positive correlation with plaque progression and angiogenesis.[3] Thus, it remains uncertain whether the term atheroprotective accurately characterizes the role of this phenotype in atherosclerosis. A recent article from the Joseph Boyle group identified activation of transcription factor 1 pathway as a critical transcription factor driving the differentiation and phenotype of heme-stimulated macrophages M(hem).[40] Foam cell formation was minimized by hemoglobin differentiation by activating a pathway, which involved activation of transcription factor 1 and AMPK. This article showed that heme activates AMPK in human blood–derived and plaque macrophages. Activation of transcription factor 1 is the closest homolog of CREB (cAMP response element–binding protein), and both CREB and activation of transcription factor 1 can be activated by protein kinase A and AMPK.[41] Corsini et al[42] showed a crucial role for CREB in the modulation of VEGF receptor 2–mediated proinflammatory and proangiogenic responses of endothelial cells to gremlin, a noncanonical VEGF receptor 2 ligand. In this article, the authors showed VEGF receptor 2 phosphorylation, and CREB activation mediates the early phases of the angiogenic response to gremlin, including stimulation of endothelial cell motility and permeability, leading to monocyte adhesion to endothelial cells and their extravasation.[32] Published data also show that levels of HIF-α/VEGF and presumably VEGF receptor 2 are elevated in areas of hypoxia within advanced human atherosclerotic plaques, although the roles of gremlin and CREB have not specifically been examined within this context.[18] Activation of CREB within M(hem) as shown by Wan et al suggests that further investigation of this pathway within CD163-positive macrophages may be warranted.[40]

Imaging and Biomarker Studies Relevant to IPH

Both imaging techniques and biomarkers might be useful in the detection of IPH within patients as a method to detect the formation of high-risk plaques likely to cause clinical events especially when they provide complimentary information. Such an approach might allow us to know not only who is at risk but also where in the arterial tree such an event might occur.

An interesting study by Pedersen et al[43] showed that macrophage CD163 expression is correlated with ^{64}Cu-DOTATATE ([1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid]-d-Phe1,Tyr3-octreotate) uptake in positron emission tomography (PET)/magnetic resonance imaging of patients who underwent carotid endarterectomy. DOTATATE, an investigational PET radioligand,[44,45] binds to somatostatin receptor subtype-2, which is upregulated in activated macrophages.[46] The authors showed that the ^{64}Cu-DOTATATE uptake correlated with expression of macrophage markers CD68 and CD163 using univariable analysis, although the correlation with CD163 expression remained significant on multivariable analysis. The propensity of CD163$^+$ macrophages toward ^{64}Cu-DOTATATE uptake suggests that this radioligand can identify a unique subset of CD163$^+$ macrophages in the inflammatory process compared with conventional ^{18}fluorine-fluorodeoxyglucose-PET.[47] Further work is needed to verify the specificity of ^{64}Cu-DOTATATE for CD163-expressing macrophages within the context of atherosclerosis.

Using nanoparticles in diagnosis or treatment for the purpose of imaging or delivering therapeutical agents has gained popularity.[48,49] In an article by Cui et al[50] in studying arteriovenous fistulas, dextranated magnetofluorescent nanoparticles were shown to deposit in pathological endothelium (ie, VCAM-1 [vascular cell adhesion molecule-1] positive) and even predict subsequent neointimal hyperplasia. Adhesion molecules, such as VCAM-1, promote the entry of leukocytes into the plaque, and identifying VCAM-1–positive endothelial cells may be a useful surrogate for angiogenic plaques at risk for further progression through IPH.

Biomarkers are another possible avenue for the identification of the early stages of IPH. Simplicity in obtaining blood samples has advantage for screening large populations and identifying patients at high risk for events. Circulating soluble CD163 (sCD163) is the ectodomain shedding product of extracellular portion of CD163.[51] sCD163 has been proposed to be a product of shedding because shedding can be inhibited by proteinases in monocytic cells with ADAM17/TACE being identified as an enzyme that cleaves CD163. This enzyme responds to various physiological inflammatory stimuli such as Toll-like receptor activation by lipopolysaccharide, oxidative stress, and thrombin. sCD163 demonstrates relatively low affinity for Hb:Hp, suggesting that its purpose may be unrelated to hemoglobin scavenging. We recently demonstrated that sCD163 functions as a decoy receptor for TWEAK, a secreted proinflammatory cytokine of the tumor necrosis factor family, to regulate TWEAK-induced activation of canonical nuclear factor-κB (NF-κB) and Notch signaling necessary for myogenic progenitor cell proliferation.[52] Others

have shown that sCD163 levels are elevated during inflammation and macrophage activation. It has been suggested to be a useful biomarker of macrophage activation in inflammatory diseases, as well as a general risk factor of comorbidity and mortality in chronic inflammatory diseases such as HIV and hepatitis C. Aristoteli et al[53] identified that sCD163 was a significant predictor of coronary artery disease extent independent of conventional risk factors. More recent studies showed that sCD163 is also significantly associated with noncalcified coronary artery disease in HIV patients,[54] as well as carotid artery disease in the setting of HIV and HCV infection.[55] Further work is needed to understand whether sCD163 levels correlate with or are independent of IPH. Moreover, how sCD163 influences atherosclerosis remains to be determined.

Cell–Cell Communication and Angiogenesis

A variety of cells, directly or indirectly involved in inflammation, could interact with macrophages to modulate their phenotype. Adipocytes in the perivascular adipose tissue (PVAT) are thought to be involved in local stimulation of pathogenesis of coronary plaque formation.[56] Proinflammatory cytokines and adipokines are expressed and secreted in epicardial adipose tissue in patients with coronary artery disease. As one of the key chemokines that regulate migration and infiltration of monocytes and macrophages, MCP-1 was suggested to be a crucial factor in this process.[57] A PVAT transplant mouse model was used to demonstrate the importance of MCP-1 for neointima growth after a wire injury by Manka et al.[58] Neovascularization and adventitial microvessel density increases in wild-type PVAT transplant, but not in MCP-$1^{-/-}$ PVAT, confirming a MCP-1–dependent mechanism. The role of PVAT and its relationship to plaque neovascularization remains to be further determined.

Endothelial cells can interact with macrophages in a way that shifts the macrophage polarization, which in turn could modulate arterial endothelium integrity. In a pig study of renal artery stenosis, the role of endothelial outgrowth cells was investigated in shifting macrophage phenotype toward M2.[59] After percutaneous transluminal renal angioplasty, autologous endothelial outgrowth cells were infused via intrarenal delivery. This treatment improved blood flow and angiogenesis and attenuated fibrosis, increased cell proliferation, and decreased M1/M2 macrophage ratio. VEGF played a critical role because the effect was blocked by VEGF blockade. This suggests that infusion of endothelial outgrowth cells after renal angioplasty induced a VEGF-mediated attenuation of macrophage inflammation, preserved the microvessel integrity and function, and decreased fibrosis in stenotic kidney. The influence of plaque microvessels on influencing the behavior of nearby macrophages also deserves particular attention because it is possible that such mechanisms likely influence the behavior of plaque microvessels.

When there is an occluded vessel, macrophage accumulation also becomes crucial in the remodeling process around collateral vessels undergoing arteriogenesis.[60] Another recently published article by Bruce et al revealed that arteriogenesis occurs in collateral arterioles of the murine spinotrapezius muscle after feeder arteriole ligation.[61] By examining a time course of monocyte recruitment to collateral arterioles, the authors were able to demonstrate that the proliferating cells in vessel walls of shear-activated collaterals are likely to be perivascular $CD206^{+}$ mannose receptor–positive macrophages. CD163-positive macrophages found in area of IPH are also $CD206^{+}$, raising the question of whether these macrophages are also proangiogenic.

Iron Metabolism and Regulation in Atherosclerosis

Sullivan[62] hypothesized that iron deficiency could play a protective role against the development heart disease. This hypothesis has been tested in epidemiological studies; however, the results have been inconclusive. How iron deficiency mechanistically would cause such an effect remains uncertain. Iron metabolism plays an important and distinctive role in each of the M1 and M2 macrophages phenotypes discussed above via coordinated differential regulation of iron trafficking genes.[55] M1 macrophages maintain higher intracellular iron levels, whereas M2 macrophages (including CD163-positive macrophages) are able to metabolize heme iron via heme oxygenase-1. The released free iron is either sequestered via ferritin or exported via the ferroportin transporter expressed on the surface of macrophages, resulting in lower cellular iron concentrations.[63]

In animal models, iron deprivation seems to have antiatherosclerotic effects. The iron chelator desferrioxamine has been shown to reduce oxidative stress and inflammation in an atherosclerosis model.[39] Likewise inhibition of the hepatic hormone hepcidin, which degrades ferroportin leading to lower intracellular iron levels within macrophages, reduced atherosclerosis in mice,[64] whereas its overexpression has the opposite effect.[65] An important caveat to these conclusions is that neither model develops atherosclerosis associated with angiogenesis as seen in humans with IPH.

Iron overload has also been studied in human abdominal aortic aneurysm (AAA) and murine Ang II and $CaCl_2$-induced AAA models.[66] In both human and murine models, iron accumulations are positively correlated with 8-hydroxy-2′-deoxyguanosine expression and macrophage-infiltrated area. In animal fed with restricted dietary iron, incidence of AAA formation was decreased with attenuated oxidative stress and inflammation. The authors suggest a possible high expression of transferrin receptor and ferroportin, in the AAA walls and macrophages, respectively, suggesting that dysregulated iron homeostasis genes may cause aortic iron overload.

Iron Metabolism and Atherosclerosis in Human Clinical Studies

Two recent human population studies have shown an association between iron metabolism and atherosclerosis. As the most widely used noninvasive imaging method to assess atherosclerosis and cardiovascular risk, carotid intima-media thickness has recently be reviewed and compared with other noninvasive techniques for coronary artery disease detection.[67] In a study of a cohort of 692 apparently healthy children, association between circulating ferritin levels and carotid intima-media thickness was demonstrated.[68] This is the first time such an association has been reported in a large healthy cohort. In

multiple regression analyses, circulating ferritin levels contributed independently to carotid intima-media thickness change variance, after controlling for other risk factors. This association was remarkably significant particularly in those children whose fathers had higher ferritin levels, suggesting a paternal specific effect on carotid intima-media thickness.[68] This result is potentially intriguing and suggests sex-specific effects of iron metabolism on atherosclerosis risk in progeny.

The iron regulatory hormone hepcidin is a key determinant for body iron distribution. Serum hepcidin is a 25-aa peptide hormone, which has a key role in the systemic regulation of iron homeostasis.[69] In 766 subjects from the Nijmegen Biomedical study, serum hepcidin, hepcidin:transferrin, and hepcidin:ferritin ratios were found to be associated with noninvasive measurements of atherosclerosis in women.[70] The relationship was not nearly as strong in men. Hepcidin binds and subsequently degrades the iron exporter ferroportin, resulting in iron overload within macrophages. The accumulation of iron in the macrophages is a characteristic of the proinflammatory M1 phenotype as discussed above. Interestingly, in alternative macrophages activated by hemoglobin:haptoglobin, a transient increase of intracellular iron could lead to the accumulation of oxidized lipids, which activates liver x receptors α–mediated increases in ferroportin expression with subsequently lowering intracellular cellular iron concentrations.[71] M1 macrophages, on the other hand, by trapping iron, increase expression of scavenger receptors and proinflammatory cytokines, leading to foam cell formation. Collectively, these 2 human studies provide additional evidence that iron metabolism might play a role in atherosclerosis risk perhaps through effects on macrophages. Further studies are needed to fully understand the molecular mechanism on how iron trafficking is differentially regulated.

Conclusions and Future Directions

IPH, angiogenesis, macrophages, and iron metabolism all play critical roles in the development of atherosclerotic disease. We and others have previously shown that IPH is a progression-promoting event in atherogenesis. It alters plaque microenvironment fundamentally by increasing free cholesterol derived from red cell membranes resulting in expansion of necrotic core and disease progression. Blood pressure, hemodynamics, arterial stiffness, and fragility are critical factors closely involved in the predisposition toward IPH. The atherosclerotic microenvironment is an important stimulus driving macrophage differentiation into differential cell types that have distinct effects on disease evolution. Alternative polarized CD163-positive macrophages are often associated with areas of intraplaque angiogenesis and permeability, and this observation raises the important question of whether these cells play an active role in these processes. Iron metabolism may be another crucial factor in the function of these cells relative to atherosclerosis risk both systemically and at the cellular level. Further study is needed to fully understand the important connections between hemorrhage, angiogenesis, macrophages, and iron metabolism and their roles within atherosclerosis.

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