Why is coronary collateral growth impaired in type II diabetes and the metabolic syndrome?

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Abstract

Type II diabetes and the metabolic syndrome are strong predictors of severity of occlusive coronary disease and poorer outcomes of coronary revascularization therapies. Coronary collateral growth can provide an alternative or accessory pathway of revascularization. However, collateral growth is impaired in type II diabetes and the metabolic syndrome. Although many factors necessary for collateral growth are known and many interventions have shown promising results in animal studies, not a single attempt to induce coronary collateral growth in human clinical trials has led to satisfactory results. Accordingly, the first part of this review outlines the known deleterious effects of diabetes and the metabolic syndrome on factors necessary for collateral growth, including pro-angiogenic growth factors, endothelial function, the redox state of the coronary circulation, intracellular signaling, leukocytes and bone marrow-derived progenitors cells. The second section highlights the gaps in our current knowledge of how these factors interact with the radically altered environment of the coronary circulation in diabetes and the metabolic syndrome. The interplay between these pathologies and inadequately explored areas related to the temporal regulation of collateral remodeling and the roles of the extracellular matrix, vascular cell phenotype and pro-inflammatory cytokines are emphasized with implications to development of efficient therapies.

Keywords

collateral growth; diabetes

Introduction

Type II diabetes and the metabolic syndrome, a cluster of risk factors including abdominal obesity, insulin resistance, hyperglycemia, dyslipidemia and hypertension, affect ~30% of the U.S. population with increasing prevalence.[1] Abdominal obesity, a major risk factor for the development of both type II diabetes and hypertension has increased from ~35% to ~75% of the U.S. population over the last 30 years.[1] While there is no significant difference in the prevalence of CAD between patients with or without diabetes or the metabolic syndrome, both type II diabetes and the metabolic syndrome are associated with more severe ischemic coronary artery disease (CAD), and a higher number of the metabolic

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syndrome components have been correlated with worse CAD by coronary angiography.[1, 2] Patients with type II diabetes are ~2 times more likely to die of CAD, whereas patients with all component pathologies of the metabolic syndrome are ~3.6–4.4 times more likely to die of CAD.[3, 4] Moreover, current revascularization therapies, coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA) in type II diabetics and metabolic syndrome patients are associated with higher procedural risk and poorer long-term outcomes then in patients without type II diabetes or the metabolic syndrome.[5–7]

Coronary collateral growth (arteriogenesis) is a physiological adaptive response to transient and repetitive occlusion of major coronary arteries in which small arterioles (native collaterals) with minimal to no blood flow remodel into larger conduit arteries capable of supplying adequate perfusion to tissue distal to the site of occlusion. However, this normal physiological response is impaired in patients with type II diabetes and the metabolic syndrome. Yilmaz, et al. showed that the prevalence of type II diabetes and the metabolic syndrome were higher in patients exhibiting poor coronary collateral development than those exhibiting good coronary collaterals (44% (diabetes), 78.4% (MS) vs. 27.1% (diabetes), 49.2% (MS)). The metabolic syndrome remained an independent risk factor for poor coronary collaterals even after adjusting for type II diabetes.[8] The number or type of metabolic syndrome components other than diabetes were not differentiated in this study. Sasmaz, et al. showed that an increasing number of component pathologies of the metabolic syndrome correlated with increasingly poorer coronary collateral development by angiography using the Cohen and Rentrop grading systems.[9] Mouquet, et al. also found that increasing the number of component pathologies of the metabolic syndrome inversely correlated with coronary collateral development by angiographic grading. In addition, they determined that of the individual components of the metabolic syndrome hyperglycemia, hypertension and insulin resistance negatively correlated with coronary collateral development, with hyperglycemia having the strongest negative correlation and insulin resistance the weakest.[10]

Studies in animal models of diabetes and the metabolic syndrome support the findings in the human. Coronary collateral growth in response to coronary artery occlusion has been shown to be impaired in rat models of the metabolic syndrome [11, 12] and a dog model of dextrose infusion [13]. However, normal collateral development has been reported in a swine model of the metabolic syndrome.[14] The most obvious difference between the rat and dog models and the swine model is that the studies in the rat and dog models used transient, repetitive coronary artery occlusion to stimulate collateral development, which mimics the situation in the human, whereas the swine model is a model of progressive chronic ischemia. Since the exact duration of coronary occlusions has been associated with the extent of collateral growth [15, 16], this difference between the two animal models is the likely explanation for the different outcomes between the rat and dog vs. the swine models.

Many factors critical for collateral growth are known. Although the definitive driving force for CCG is still debated, arguments for both transient, repetitive ischemia (RI) and shear stress have been eloquently laid out in recent reviews.[17, 18] Collateral remodeling is a complex multi-step process, which involves multiple cell types as well as reorganization of components of the extracellular matrix (ECM). This process is coordinated by an array of pro-angiogenic growth factors and anti-angiogenic peptides. Yet clinical trials aimed at restoration of perfusion through collateral growth have yielded unsatisfactory results.[19, 20] Retrospective analysis identified the critical difference between animal models used to identify factors required for collateral growth and patients enrolled in these clinical trials to be the use of healthy animals vs. patients with advanced coronary artery disease, the majority of whom were diabetic and/or fit the criteria for the metabolic syndrome.[20]

However, further studies aimed at collateral growth recovery in animal models of diabetes and the metabolic syndrome have also been only partially successful [11, 12, 21] and not a single subsequent approach has been clinically applicable either due to lack of efficacy or undesired side effects [22].

This review will outline the known deleterious effects of diabetes and the metabolic syndrome on factors which are necessary for collateral growth and highlight the gaps in our current knowledge of how pathways which regulate collateral growth may be altered in diabetes and the metabolic syndrome to negatively effect collateral development.

What we do know

Pro-angiogenic growth factors

Of the growth factors, the vascular endothelial growth factor (VEGF) and the fibroblast growth factor (FGF) have been most consistently associated with collateral growth. Increased VEGF and FGF levels have been shown to correlate with collateral growth.[23, 24] Administration of VEGF and FGF to normal animals resulted in robust collateral development.[25, 26] VEGF inhibition also blocked collateral formation thus demonstrating that it was required for collateral development.[26] Yet therapeutic clinical trials aimed at restoration of perfusion through collateral growth using growth factors have failed.[19, 20] Retrospective analysis identified the probable reason for this to be the assessment of efficacy of treatment with VEGF and FGF in healthy animal models whereas the patients enrolled in the clinical trials had advanced coronary artery disease and the majority were diabetic or fit the criteria for the metabolic syndrome.[20]

The serum level of VEGF was subsequently found to be elevated in diabetic and metabolic syndrome patients with or without significant ischemia compared to non-diabetic controls. [27–30] Moreover, their downstream signaling as well as multiple other parameters which critically affect collateral remodeling have been shown to be significantly altered. These will be addressed sequentially in this review. Thus, it is not surprising that VEGF and FGF monotherapy did not result in restoration of collateral growth in diabetes and the metabolic syndrome. In fact these results highlight the importance of using appropriate animal models, which closely approximate the human patient population. Like in the human metabolic syndrome patients, treatment with VEGF alone failed to increase coronary collateral growth in a rat model of the metabolic syndrome, the Zucker obese fatty rat (ZOF).[12]

Another factor whose role in coronary collateral development has now been defined is angiotensin II (Ang II). Angiotensin type I receptor (AT1R) blockade impaired coronary collateral growth in normal, healthy rats but significantly improved coronary collateral growth in metabolic syndrome rats.[11] This was associated with the effect of AT1R blockade on the regulation of oxidative stress and redox-sensitive signaling and is of specific relevance to treatment of diabetic and metabolic syndrome patients with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).

Endothelial (dys)function

Endothelial dysfunction is a hallmark of diabetes and the metabolic syndrome and is characterized by decreased synthesis of vasodilators including nitric oxide (NO), prostacyclin and endothelial hyperpolarizing factor(s) (EDHF), increased synthesis of endothelial-derived vasoconstrictors, such as endothelin-1 (ET-1), increased expression of adhesion molecules, VCAM-1 and ICAM-1 and increased vascular permeability (reviewed in Guerci et al, 2001).[31] NO has been shown to be critically required for collateral growth in multiple studies.[23, 32] Accordingly, coronary collateral growth has been shown to be severely impaired in animal models of diabetes and metabolic syndrome with documented

endothelial dysfunction assessed as impaired endothelium-dependent vasorelaxation, the ZOF and the JCR (Russell, JCR:LA-cp) rats.[11, 12] These observations parallel human studies where diabetes and the metabolic syndrome strongly correlate with endothelial dysfunction [31] and impaired collateral growth [8–10] indicating that impaired endothelial function is a serious impediment to collateral development.

Oxidative stress

Another salient feature of diabetes and the metabolic syndrome in humans and animal models is elevated basal oxidative stress (defined as elevated reactive oxygen species (ROS) and/or more oxidative redox state).[11, 21, 31] Oxidative stress within the context of these pathologies has been shown to be mediated by several different mechanisms among which are the increased activation of oxidases including the membrane-bound NAD(P)H oxidases and mitochondrial oxidases, and to a lesser extent xantine oxidase and myloperoxidase, decreased NO synthesis and inactivation or decreased expression of antioxidant defenses, Co/Zn superoxide dismutase (SOD) and catalase in a variety of cell types including inflammatory cells (monocytes, macrophages, neutrophils and T-cells), endothelial cells (ECs), vascular smooth muscle cells (VSMCs), and cardiac myocytes.[31, 33] Repetitive coronary occlusion leads to an increase in ROS above the baseline level.[11] In normal, healthy animals, the amount of ROS generated by repetitive coronary occlusion is necessary for coronary collateral development.[11] However, in the metabolic syndrome animals where baseline levels of ROS are elevated, the amount of ROS generated by repetitive coronary occlusion is much higher and is not compatible with coronary collateral development.[11]

It has now been clear for several years that an optimal amount of ROS or an optimal redox state of the cell (redox window) is absolutely required for coronary collateral growth. This topic was recently extensively reviewed.[18, 34] Briefly, our own and Chilian's group have demonstrated that reduction of ROS below the lower boundary of this window reduces collateral growth but increasing ROS above the upper boundary of this window is likewise incompatible with collateral development.[11, 21, 35, 36] Either decreasing superoxide ($O2^{-\bullet}$) with a flavin-containing oxidase inhibitor (DPI) or increasing $O2^{-\bullet}$ with an SOD inhibitor (DETC) abrogated coronary collateral growth in normal, healthy rats.[35] Furthermore, decreasing oxidative stress by apocynin or AT1R blockade in normal rats impaired coronary collateral growth, but significantly improved coronary collateral growth in the metabolic syndrome rat model where basal and repetitive occlusion-induced oxidative stress is elevated.[11, 21]

Of the possible sources of ROS, the sources most important for the regulation of coronary collateral growth have not yet been entirely resolved. Strong evidence now points to the mitochondrial sources of ROS. In a recent study, the mitochondria-targeted antioxidant MitoQ nearly completely restored coronary collateral growth in the ZOF rat.[36] Several studies suggest that membrane NAD(P)H oxidases are also important sources of ROS within the context of collateral growth.[21, 37] Whether the cross-talk between membrane NAD(P)H oxidases and the mitochondria, phenomenon known as ROS-induced ROS release, is functionally relevant in collateral growth remains to be determined.

In which cell type(s) in the heart the regulation of oxidative stress during collateral development is important, and whether this point is clinically relevant remains to be determined. With the overwhelming failure of large antioxidant clinical trials (HOPE, MRC/BHF Heart Protection) the question whether any antioxidant type intervention will translate into successful therapy in humans also remains unresolved. However, multiple factors specific to coronary collateral growth and the animal models used in the successful antioxidant studies outlined above provide some hope for the use of antioxidants in coronary

revascularization through collateral growth. First, whether the antioxidant interventions actually succeeded in reducing oxidative stress in patients enrolled in the HOPE and the MRC/BHF trials was never ascertained.[38] Second, emerging evidence suggests that reduction in mitochondrial oxidative stress is critical for collateral growth; the antioxidants in these trials were not targeted to the mitochondria, and therefore could not have reduced mitochondrial oxidative stress. Third, collateral growth or myocardial perfusion per se were not the end-points in these trials; therefore, a multitude of additional factors, including unstable angina and heart failure contributed to total outcomes. Finally, the JCR and ZOF rats, in addition to mimicking the pathology the human metabolic syndrome, also display the specific cardiovascular abnormalities typically found in diabetic and metabolic syndrome patients at the time of coronary revascularization including impaired endothelium-dependent and -independent vasorelaxation, cardiac and vascular hypertrophy, wide-spread atherosclerosis, and diffuse myocardial micro-infarctions, and thus, provide relevant models for studying effects of antioxidants.[39]

Intracellular signaling pathways

A number of signaling pathways have been shown to be important in the regulation of collateral growth. Signaling downstream of the VEGF receptor, Tie-2 has been outlined for some time and includes activation of the mitogen activated protein kinases (MAPKs: ERK1/2, p38 MAPK and JNK) and Akt.[40] We have shown that p38 MAPK and Akt were required for coronary collateral growth.[35, 41] A recent study demonstrated that a Raf family member, Rap-2, is required for collateral growth in response to femoral artery occlusion.[42] The ERK1/2 MAPKs have also been definitively implicated in collateral growth in healthy animals.[43, 44] Upstream, a joined regulator of the MAPK pathways and Akt, the non-receptor tyrosine kinase Src, is required for coronary collateral growth.[21] Downstream, Akt and ERK1/2 have been shown to activate eNOS.[40] On the other hand, we have shown p38 MAPK to activate matrixmetalloproteinases (MMPs) 2 and 9 which were also required for coronary collateral growth.[45]

Activation of other growth factor receptors, including the FGF, EGF and PDGF receptors as well as of the AT1R likewise results in activation of the MAPK and the Akt pathways. Angiopoietin-related growth factor enhances collateral growth via activation of ERK1/2 and eNOS in a mouse model.[46] Inflammatory cytokines and growth factors, including VEGF, have been shown to induce MMP 2 and 9 expression and activation.[47–49] Independently of growth factor receptor activation, statins activated Notch1 and promoted angiogenesis and collateral growth through Akt-dependent stimulation of γsecretase in a mouse model of femoral artery occlusion.[50]

Another series of studies demonstrated the importance of cell-ECM interactions during collateral growth. Upregulation of $\alpha v\beta 3$ and $\alpha 5\beta 1$ integrin expression and focal adhesion kinase (FAK) activation has been observed in growing collaterals.[51] The Rho/Rho kinase pathway has been strongly implicated in collateral growth.[44] A Rho antagonist inhibited collateral development.[52] Another study identified the actin-binding Rho activating protein, Abra, to be essential for collateral growth.[53]

However, a key limitation of all of these studies is that the signaling intermediates identified to be required for collateral growth were identified in normal, healthy animal models. Only a handful of studies have investigated signaling pathways in diabetic or metabolic syndrome patients and animal models. The Flt-1 kinase activity was found to be intact in monocytes from diabetic patients.[27] These data suggested that the signaling defect was downstream of the VEGF receptor itself. We have demonstrated that in contrast to the healthy animals, p38 MAPK, Akt, Src, and MMP 2 and 9 were not activated in response to repetitive coronary occlusion in the metabolic syndrome rat model.[11, 21, 41, 45] Restoration of their

activation, either by interventions that lower oxidative stress or delivery of constitutively active kinases, significantly improved coronary collateral growth in the metabolic syndrome. [11, 21, 41] These signaling mediators as well as MMP 2 and 9 have been shown to be redox-sensitive, thus it is likely that lack of their activation in the metabolic syndrome is a result of elevated oxidative stress which resulted in either aberrant upstream redox-dependent signaling or their direct oxidative modification. On the other hand, Akt activation could be impaired due to insulin resistance and resultant impaired IRS-1 signaling, which has not been investigated in collateral development. As a whole, identification of signaling pathway alterations in diabetes and the metabolic syndrome and determining whether their manipulation could be clinically useful for coronary revascularization through collateral growth remains largely unexplored.

Leukocytes

A positive association between leukocytes, especially monocytes, but also resident macrophages, T-cells, mast cells and to a lesser extent NK cells and neutrophils and collateral development has been documented in normal, healthy animal models (reviewed in Meisner et al, 2010).[54] This is consistent with the relatively extensively documented positive role of inflammatory cytokines in collateral growth in normal animals. Transforming growth factor-β (TGF-β) [55], tumor necrosis factor-α (TNF-α) [56, 57], monocyte chemotactic protein-1 (MCP-1) [58], interleukin-20 (IL-20) [59], IL-8 [60] and granulocyte-colony stimulating factor (G-CSF) [61, 62] have been positively associated with collateral growth either through correlative studies or because their exogenous addition in normal animals resulted in increased collateral formation. However, not all cytokines are beneficial for collateral growth. For example, IFNβ inhibited collateral growth and VSMC proliferation through cell cycle arrest and induction of monocyte apoptosis, while IFNβ inhibition stimulated VSMC proliferation and collateral growth in a mouse model.[63] High levels of IFNγ were associated with low collateral number in humans.[64]

Several studies suggest that impaired recruitment of monocytes underlies impaired collateral growth in diabetes. A higher number of circulating monocytes was correlated with better collateral networks in a study of diabetic patients.[65] Monocyte chemotaxis, at least to VEGF-A, was decreased in monocytes derived from diabetic patients vs. age-matched non-diabetic controls.[27] However, monocyte migration was not negatively affected by diabetes.[66] However, while a correlation between impaired collateral development in diabetes and decreased number of circulating monocytes has been established, the effect of inflammatory cytokines on collateral growth has not been studied in either animal models of diabetes or the metabolic syndrome or in human patients. The effectiveness of cytokines on collateral formation was assessed in a single clinical trial, in which G-CSF failed to elicit significant improvement in patients with moderate or severe intermittent claudication [67]; however, whether these patients were diabetic is impossible to determine from the published results of the study. Therefore, if or how the role of inflammatory cytokines might be altered within the setting of diabetes or the metabolic syndrome remains unknown.

Bone marrow-derived progenitor cells

Of the bone marrow-derived progenitor cells endothelial progenitor cells (EPCs) have received the most attention with respect to treatment of ischemic disease. Despite a decade of intense research, fairly little is known about the mechanism by which EPCs enhance collateral development. Due to recent studies which have demonstrated failure of endogenous EPCs to trans-differentiate into ECs or VSMCs, they are now proposed to participate in collateral growth more so by secretion of paracrine factors than by providing the structural components of newly formed vessels (reviewed in Meisner et al, 2010 and Tongers et al, 2010).[54, 68]

The number of circulating EPCs inversely correlated with insulin resistance and the metabolic syndrome in humans with or without overt type II diabetes [69] and in diabetic animal models[70]. EPCs derived from peripheral blood mononuclear cells taken from diabetic patients exhibited decreased capacity to incorporate into endothelial tubes in vitro, reduced adhesion and ability to form vascular-like structures in matrigel plugs, and reduced ability to stimulate recruitment of pericytes and smooth muscle cells.[71] Despite these observations, the potential benefit of EPCs or other progenitor or stem cells on collateral growth remains difficult to determine due to varying successes of EPC-based therapies to date.[54, 68] A recent study in which ECs were reprogrammed into vascular progenitor cells capable of differentiating into both ECs and VSMCs showed impressive ability to stimulate collateral growth [72] and may indicate that broadening the scope of research to a wider stem/progenitor cell population might be beneficial.

What we do <u>not</u> know

Temporal regulation of coronary collateral growth

Collateral growth is a temporally tightly regulated process, which progresses through distinct phases. In the initiation phase, the morphology of the vessel remains largely intact, ECs and VSMCs increase expression of chemoattractants and adhesion molecules, ICAM-1 and VCAM-1, and vascular permeability is increased, which allows for accumulation of circulating progenitor and inflammatory cells in the vascular wall. This is followed by an inward remodeling phase characterized by an increase in cell proliferation, VSMC switch to the synthetic phenotype, degradation of the internal elastic lamina and the basement membrane by MMPs, and EC and VSMC migration into the lumen of the pre-existing vessel in a process akin to neointima formation. This is followed by reestablishment of the basement membrane, the internal elastic lamina and the endothelium, clearance of the neointima and outward expansion leading to a large increase in collateral diameter. The final phase or vessel maturation is characterized by VSMC return to the contractile, non-proliferative phenotype, ECM synthesis to support the enlarged lumen and pruning of smaller vessels that had originally taken part in the remodeling but are phased out secondary to competitive flow.[17, 54]

It is obvious that very different and sometimes diametrically opposite processes (ECM degradation vs. ECM synthesis, cell proliferation vs. cell senescence) occur at different times during collateral vessel formation. Very few studies have investigated the precise timing of events associated with and required for collateral growth. Our previous studies support the notion that timing of activation of signaling pathways required for collateral growth is critically important for positive vs. negative outcomes. While transient p38 MAPK activation was compatible with coronary collateral growth, sustained p38 MAPK activation induced by infusion of a hypertensive dose of Ang II was not.[11] Sustained Akt activation was required for coronary collateral growth, while transient Akt activation was insufficient to promote coronary collateral growth.[41] MMP 2 and 9 activation has also been shown to be transient and confined to early stages of collateral remodeling correlating with ECM degradation.[45, 73] However, many important temporal relationships remain explored. It is likely that the majority if not all signaling pathway activation will be under strict temporal control, which may be altered in diabetes and the metabolic syndrome. Likewise, because ECM proteolysis during collateral growth is temporally tightly regulated, it is likely that protease activity will likewise be tightly regulated. Apart from MMP 2 and 9, the potential role of other MMPs and related proteases in collateral growth has not been explored. However, any attempt to target signaling pathways or proteases to improve CCG in diabetes or the metabolic syndrome will first have to understand their temporal regulation and how it may be altered in these pathologies.

Another unresolved temporal issue concerns the action of growth factors and anti-angiogenic peptides. Considerable evidence suggests that growth factors do not play an equally significant role during the entire process of CCG. In a canine model of CCG, VEGF concentration in interstitial fluid increased rapidly in the early days of CCG, but then decreased back towards baseline, yet collaterals continued to form.[74] These findings suggest that growth factors are important for initiation of collateral growth, but other factors are necessary for continuation of collateral remodeling through the later stages of growth. With the still unresolved question of whether ischemia or shear stress is the driving force for collateral growth, one possibility is that as collateral vessel enlarges, ischemia lessens, and HIF-1α expression, and thus, VEGF transcription decreases. At the same time, the increase in blood flow increases sheer stress, which activates eNOS, leading to increased NO and its downstream signaling. NO levels during the progression of collateral remodeling have not been measured. While VEGF, as is typical of growth factors, stimulates expression of adhesion molecules, proliferation and migration of monocytes, ECs and VSMCs, NO has been shown to be a potent inhibitor of vascular cell proliferation.[75, 76] Therefore, it seems clear that knowing the exact timing of action of these two factors both of which are absolutely necessary for collateral growth but have opposing biological effects would be critical to their efficacious application. To further complicate matters, the timing of upregulation of anti-angiogenic peptides, angiostatin and endostatin, in either healthy people and normal animal models or diabetic and metabolic syndrome animal models and patients during collateral growth remains completely unknown.

Similar considerations might apply to cytokines. Different cytokines preferentially exert different functions with different affinities towards different cell types. For example, the main role of MCP-1 appears to be the attraction, transmigration and activation of monocytes, the beneficial function of which appears to be confined to the early phase of collateral remodeling (reviewed in Ruiter et. al, 2010).[54, 77] Therefore, MCP-1 delivery during the late phases of collateral growth could be hypothesized to be at best pointless and potentially detrimental. On the other hand, the main effects of TGF-β include induction of cell differentiation and cell senescence. Cell differentiation might be relevant, for example, to progenitor and stem cell differentiation or to VSMC phenotype switching from the synthetic phenotype in the early phase of collateral remodeling to the contractile phenotype in the late phase of contractile remodeling. Since TGF-β induces cell senescence, its delivery during the proliferative phase of collateral growth would seem to be detrimental.

Finally, various progenitor cells have been shown to participate in CCG; however, therapeutic clinical trials using progenitor and stem cells have yielded a range of results from significant improvements to little effect.[54, 68] Different types of progenitor cells have been shown to play a variety of roles in the process of CCG, from production of important paracrine factors to trans-differentiation into structural cellular components of the vessel.[68, 72] Therefore, it is likely, that not only the type of cells delivered, the method and dose of delivery but also the exact timing of delivery may be critical for determining these outcomes.

Overall, there is a critical need for systematic and definitive characterization of the temporal distribution of and interplay between factors essential for collateral growth during the process of collateral development so that interventions aimed at recovery of collateral growth in diabetes and the metabolic syndrome can be targeted to the correct temporal window and therefore effective.

Extracellular matrix remodeling

Temporally regulated ECM remodeling is of paramount importance in collateral development. The ECM presents a mechanical barrier to the migration of ECs and VSMCs.

Also, the ECM is a repository for pro-angiogenic growth factors, including VEGF and FGF, as well as for anti-angiogenic peptides, angiostatin, endostatin and thrombospondin. Thus, ECM degradation can facilitate the release of these angiogenic factors thereby either promoting or arresting collateral development depending on which specific ECM substrates are being degraded with significant implications for diabetes and metabolic syndrome.

First, the composition of the vascular ECM itself is altered in diabetes and the metabolic syndrome. Increased ECM synthesis and decreased MMP activation [78, 79] resulting from increased accumulation of advanced glycation end products (AGEs), byproducts of hyperglycemia, results in more ECM being deposited within the vascular wall. Secondly, the ECM exhibits higher type I collagen content. In addition to decreasing MMP activation, hyperglycemia also increase ECM cross-linking, in part through AGE formation.[80, 81] The cumulative result of these alterations is stiffer ECM, which is much more resistant to degradation and cell migration. In addition to hyperglycemia, elevated oxidative stress in type II diabetes and the metabolic syndrome further augments the ECM cross-linking, but has also been shown to increase the susceptibility of certain types of collagens to proteolytic cleavage.[82] These profound alterations in the ECM could significantly impact CCG in diabetes and the metabolic syndrome by limiting cell migration and by regulating the local availability of pro-angiogenic growth factors and anti-angiogenic peptides. In addition, aside from cross-linking the ECM, AGEs bind to their receptor, RAGE and initiate intracellular signaling cascades, which result in increased production of ROS, IL-1 and TNF-α [83, 84], thus resulting in further augmentation of the pro-inflammatory, high oxidative stress phenotype with potential profound consequences on collateral growth.

Matrix metalloproteases (MMPs and ADAMs) are the principal enzymes responsible for ECM degradation. However, while MMPs have been extensively studied within the context of cancer angiogenesis, very little is known about MMPs and ADAMs in collateral growth. Until recently, a single study correlated increased MMP 2 and 9 expression with the early phase of coronary collateral growth.[73] Our recent study extended this finding to demonstrate that MMP 2 and 9 were in fact required for coronary collateral growth but were not activated in a rat model of the metabolic syndrome.[45] MMP 2 activity was likewise decreased in the myocardium of diabetic patients which was associated with impaired coronary collateral formation.[85] However, MMPs are a family of over 25 proteases the potential role of which in collateral remodeling, apart from MMP 2 and 9, remains entirely unexplored.

In addition to removing the structural barrier, ECM degradation can result in the release of growth factors and anti-angiogenic peptides from their binding proteins and the ECM where they are sequestered in their latent forms. MMP 2 and 9 have been shown to increase the bioavailability of TGF-β, VEGF and FGF during cancer angiogenesis.[86–89] Other, MMPs have been shown to be able to generate anti-angiogenic peptides, endostatin and tumstatin by degrading type XVIII and IV collagen in some types of basement membranes in vitro and during cancer angiogenesis.[90] Whether similar events occur during coronary collateral growth and if or how they may be altered in diabetes and the metabolic syndrome is unknown. It has however been shown that endostatin and angiostatin are increased in diabetic patients with coronary artery disease.[85] Chronic hyperglycemia also attenuated coronary collateral development and impaired proliferative properties of myocardial interstitial fluid by production of angiostatin.[13]

Vascular cell (EC and VSMC) phenotype switching

To participate in collateral remodeling, ECs must switch from the normal, adult quiescent phenotype to an "activated", migratory and proliferative phenotype. EC activation within the context of collateral growth involves the expression of monocyte adhesion molecules,

VCAM-1 and ICAM-1. Excessive VCAM-1 and ICAM-1 expression, however, is a hallmark of endothelial dysfunction, which is highly negatively correlated with collateral growth. The question of excessive endothelial activation/dysfunction as it relates to collateral formation within the context of diabetes and the metabolic syndrome is addressed in other sections of this review.

In addition to expression of adhesion molecules, ECs undergo phenotypic changes, which result in increased vascular permeability, as well as in their assuming a proliferative and migratory phenotype. While the signaling pathways which regulate EC proliferation and migration in angiogenesis are rather well-established and are often presumed to translate to collateral growth, they have not been adequately explored in collateral growth, and especially not in animal models of diabetes or the metabolic syndrome. Since ECs are in close proximity and communication with the basement membrane and the VSMC layer, it is reasonable to assume that they would be profoundly affected by the altered composition and remodeling of the ECM as well as by VSMC alterations in these pathologies.

Extensive VSMC participation is a distinguishing feature of collateral remodeling. In the canine heart, the diameter of the lumen of enlarged collateral vessels may be as much as 20 times larger than the native vessel.[73] Our recent work has shown a 10-fold increase in SM-α-actin correlating with maximal coronary collateral growth in the normal, healthy rat model[21] and consistent with previously reported 10-fold increases in SM-specific contractile protein expression in rodents.[91, 92] This increase is not observed in the metabolic syndrome rat model, correlating with lack of collateral formation.[93] Growing, actively remodeling collaterals are characterized by highly proliferative, synthetic VSMC characterized by loss of SM-specific contractile protein expression and VSMC migration into the lumen of growing collaterals. In contrast, the VSMC in mature collaterals exhibit the normal adult contractile phenotype, characterized by low proliferation rates and high expression of SM-specific contractile proteins.[73]

VSMCs may serve as integrators of signals between different cell types in the vascular wall and the ECM. Diabetes and the metabolic syndrome are characterized by oxidative stress and endothelial dysfunction, which result in decreased NO levels. In VSMC, NO activates PKG which has been shown to be required for maintenance of the VSMC contractile phenotype.[94] Thus, endothelial dysfunction and oxidative stress in diabetes and the metabolic syndrome may also critically effect VSMC phenotype. Therefore, VSMC phenotypic modulation in response to transient, repetitive coronary occlusion may be a critical determinant of collateral development. However, a definitive cause-effect relationship between VSMC phenotypic switching and collateral remodeling has not been established. Furthermore, it is not known how or if this process is altered in pathological states where collateral remodeling is impaired, such as in diabetes or the metabolic syndrome.

Pro-inflammatory cytokines

Inflammatory cytokines have been positively correlated with collateral development in normal healthy animals as outlined. However, since their effect on collateral growth in diabetes and the metabolic syndrome has not been investigated, whether this positive effect will translate into these clinically relevant situations remains an open question.

One of the major characteristics of diabetes and the metabolic syndrome is the persistent baseline inflammatory state characterized by increased expression of pro-inflammatory cytokines, including TGF-β, TNF-α and MCP-1, augmented expression of adhesion molecules, VCAM-1 and ICAM-1, and increased adhesion and extravasation of inflammatory cells, especially monocytes into the vascular wall.[95–98] This situation leads

to decreased production of NO and increased production of ROS and as such is a major contributor to elevated oxidative stress and endothelial dysfunction consistently observed in the vasculature and the myocardium of diabetic and metabolic syndrome patients as well as in their animal model counterparts (reviewed in Guerci et. al, 2001).[31] Pro-inflammatory cytokines, TGF-β, TNF-α and MCP-1 have been positively correlated with collateral development in normal, healthy animals. However, TNF-α and MCP-1 have been shown to induce endothelial dysfunction in diabetes.[96, 97] Endothelial dysfunction has been very strongly negatively correlated with collateral growth. [8–10, 12, 31] Thus, it will be interesting to see how the positive effects of these and other inflammatory cytokines on collateral growth in normal, healthy animal models translate into diabetic and metabolic syndrome animal models and human patients.

Conclusion

In conclusion, it is important to emphasize that collateral growth is a complex process the success of which critically depends on the spatially and temporally coordinated interplay between many factors. Therefore, understanding of individual components in isolation, while an important first step, will not lead to sufficient understanding of the process or to therapeutically applicable findings.

Although many individual factors which regulate coronary collateral formation are known, many unresolved questions specifically regarding the regulation of coronary collateral growth in type II diabetes and the metabolic syndrome remain. These remaining gaps in our understanding have been the subject of the second part of this review and include: 1) inadequate knowledge of if or how factors known to be required for collateral development in healthy animal models are altered in diabetes and the metabolic syndrome, 2) inadequate knowledge of the temporal regulation of cellular and molecular processes that underlay collateral remodeling, and 3) inadequate knowledge of how interventions shown to be beneficial for collateral growth in healthy animal models will interact with the significantly altered coronary circulation in diabetes and the metabolic syndrome. These questions will have to be answered before efficacious therapies aimed at coronary revascularization through collateral growth can be developed. Of course, it is reasonable to assume that other factors, which have not yet been explored within the context of collateral remodeling, may also be important for this process and that interaction with these factors will have to be taken into account.

Acknowledgments

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