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Coronary Collateral Growth: Clinical Perspectives and Recent Insights

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Abstract

This chapter summarizes recent research on the coronary collateral circulation. The chapter is focused on clinical perspectives and importance of a well-developed coronary collateral circulation, the mechanisms of growth induced by chemical factors and a role for stem cells in the process. Some discussion is devoted to the role of shear stress and mechanical signaling, but because this topic has been reviewed so extensively in the recent past, there is only small mention of its role in the growth of the coronary collateral circulation.

Keywords: arteriogenesis, coronary collateral, ischemic heart disease

1. Introduction

Although arteriogenesis has been studied for approximately a hundred years, there are still fundamental unanswered questions about the causes of collateral vessel growth, and whether different factors control growth at varying points in the maturation process. One line of investigation, spurred by the myriad contributions of Schaper and his colleagues have focused on mechanical shear stress being the main factor that stimulates collateral growth [1–4]. Although this hypothesis is well-founded on a large body of experimental data, it does not explain other observations that show collateral growth in the absence of altered shear stress [5, 6]. Accordingly investigators have proposed that ischemia (via cytokine, chemokine, and growth factor expression), and the consequential inflammation, is the cause of collateral growth, but

assessing it has proven to be difficult due to the unclear lines between ischemic regions, normal circulation, and collateral growth. The hypotheses regarding the causative factor(s) for collateral growth are not mutually exclusive as there are likely many mechanisms that are the principal driver, which vary at various points of the process. For example, even if one maintains that ischemia is the initiating mechanism for collateral growth, it is likely that other stimuli continue the growth of the vessel after the ischemic stimulus has waned. To provide perspective for this chapter, we refer to **Figure 1**, which summarizes four factors that exert important effects in this adaptive process. The bulk of this chapter will focus on the collateral growth from a clinical perspective, the role of stem cells, and chemical factors involved in this process. We will not extensively review the role that shear stress in coronary collateral growth as this has been reviewed ample times in the past. We also will not review the genetic aspects because the bulk of this information has been derived from studies of collateral growth in vascular beds other than the heart, e.g., skeletal muscle and brain [7, 8], although there is some preliminary information about genetic links to collateral growth in patients [9]. **Figure 1** also shows the anatomical structure of a collateral; namely, an arterial-arterial anastomosis that connect large coronary perfusion territories. Collateral growth, also known as arteriogenesis, in the heart involves the abluminal expansion of a preexisting arterial-arterial anastomosis [10]. The degree of expansion is profound—the caliber of collateral vessels can increase over an order of magnitude [10]. This degree of expansion would greatly reduce vascular resistance of these vessels, thereby increasing flow in the area of risk. This increase in flow is the reason why the collateral circulation exerts beneficial effects through the reduction in infarct size (following a coronary occlusive event) and reduction in the incidence of sudden cardiac death.

We also would like to point out an obvious distinction between the growth of collateral vessels (arteriogenesis) and angiogenesis. These processes are often confused as the same, but

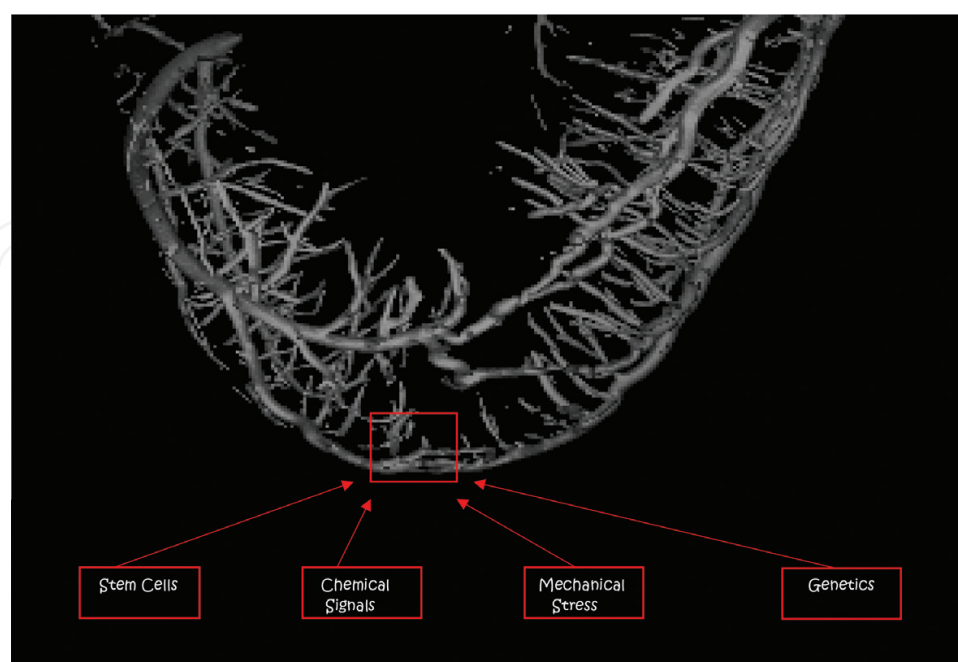


Figure 1. An image of the human coronary circulation depicting large collateral vessels that connect perfusion territories of major arteries and some factors that regulate their development.

they are distinct and have distinguishing characteristics. In *A Brief Etymology of the Collateral Circulation*, Faber et al. describe angiogenesis as the formation of capillaries from preexisting capillaries [11]. In contrast to angiogenesis, arteriogenesis is more the remodeling of preexisting vessels through the “anatomic increase in lumen area and wall thickness.” The causes of arteriogenesis are more physical, specially, mechanical shear stress and ischemic conditions, while angiogenesis is caused by chemical conditions such as hypoxia [11].

2. Clinical perspective

Heart disease is extremely prevalent in the United States, where it accounts for every one in four deaths and almost 735,000 Americans suffer a heart attack each year (Centers for Disease Control, USA). However, there are numerous differences between these individuals in terms of response to treatment, future adverse events, and long-term survival rates. One explanation for these differences involves the presence of good collateral growth in certain individuals. A 5-year study called Osaka Acute Coronary Insufficiency Study (OACIS) assessed both acute and long-term survival in patients and came to three important conclusions: (1) patients with a Rentrop collateral score (RCS) of one or two showed the most promising 5-year survival rates, (2) RCS of three was associated with a worse 5-year survival rate, (3) RCS of three was associated with the best survival rates in a specific subgroup of patients with single vessel disease without previous myocardial infarction (MI) [12]. These first two conclusions can be explained due to the fact a higher baseline RCS can be indicative of a worse background of clinical characteristics such as previous MI or angina pectoris resulting in increased mortality rates, whereas an RCS of one or two was developed in the acute setting negating any adverse effects of chronic ischemia [12]. The third conclusion states RCS of three is more beneficial in the setting of single vessel occlusion and without previous MI, which would liken it to individuals who have RCS of one or two, but without any previous adverse events. In this subgroup, patients are having increased collateral flow, but without the chronic angina pectoris or previous MI improving survival rates [12]. This information leads to an important conclusion where the increased number of collaterals does not equate to decreased mortality rates, but rather is dependent upon a multitude of factors.

2.1. Methods

The literature is replete with the salubrious effects of a well-developed coronary collateral circulation and the potential benefit of a therapeutic process aimed at stimulating coronary collateral growth [13–19]. One patient study focused on coronary collateral growth in patients that had stable coronary artery disease. Specifically, the Möbius-Winkler et al. study looked at the impact of exercise on coronary collateral growth [20]. The patients were put into groups of usual care, moderate intensity exercise, and high-intensity exercise. The main findings of this study were that moderate and high-intensity exercise increased the coronary collateral blood flow. Scientists in this study postulated the cause of the coronary collateral growth. They questioned whether ischemia triggers collateral growth, since a percutaneous coronary intervention was performed before the study began; however, there is a large body of litera-

ture suggesting the PCI procedures may not completely resolve myocardial ischemia. The authors further speculated that the cause could be this increased blood flow and could have been from either increasing work done by preexisting blood vessels or an “improvement in endothelial function of small intramyocardial vessels.” There was a CFI increase of 39% in the group of patients that did high-intensity exercise and a 41% CFI increase in the group that did moderate intensity exercise, which emphasized that exercise increased the coronary collateral blood flow in patients with coronary artery disease [20].

There has been much discussion for stimulating arteriogenesis in patients in order to give them proper blood perfusion to ischemic areas. Collaterals have been found to give patients many benefits over individuals who do not have collaterals, with a long-term mortality reduction, reduced myocardial infarct size, a greater postinfarction ejection fraction, and a reduced risk for rupture of the papillary muscle, myocardial free wall, or interventricular septum [21]. A reduction in infarct size was noted by the decreased peak creatinine levels as the number of collaterals increased depicting a cardioprotective effect [12]. Additionally, specific benefits have been noted between the presence of collaterals and sudden cardiac death and myocardial infarction.

There are three prevalent assessment methods of collateral growth circulation: the Rentrop score, collateral flow index (CFI), and intracoronary electrocardiogram. The Rentrop score can be most easily assessed when using coronary angiography as a visual assessment method. Circulation is then categorized into four different grades: Grade 0, Grade 1, Grade 2, and Grade 3. These categories range from no filling of the coronary collaterals to complete filling of collaterals, respectively. Although successful, the Rentrop method has some limitations due to being easily influenced by blood pressure changes and the force of injections during imaging procedures. Currently, the method considered to be the most accurate is the collateral flow index measurement. This method centers around utilizing a Doppler sensor tipped guide wire to quantify flow velocity in an occluded vessel compared with a normal vessel. Briefly mentioned was the intracoronary electrocardiogram, which is regarded as “simpler, cheaper, and very accurate” [22].

2.2. Benefits of coronary collaterals

Although many in the preclinical models have been employed in the study of coronary collateral growth, there is a relative paucity of clinical studies that have attempted to elucidate mechanisms of growth. One of the first studies done was in 1971 and was published in the *New England Journal of Medicine* [23]. This study only had three successful trials that demonstrated collaterals alleviating cardiovascular mortality. The inconsistency, according to Meier et al., could be rooted in the method by which they measured coronary collateral growth. The 1971 study “qualified” collaterals visually using coronary angiography, but Meier et al. postulates that had a better measurement method such as CFI been used, results could have been more promising [22].

One successful clinical study was performed by Seiler et al., which found that there is a direct correlation between collateral function and atherosclerotic lesions [24]. Patients with chronic

total coronary occlusions had higher CFI values than those patients who did not have this condition. A CFI shift was quantified that patients with coronary occlusions had a CFI of 0.365 ± 0.190 versus 0.180 ± 0.105 of that of patients without occlusions. This study directly demonstrated that “collateral function is a direct indicator of CAD severity.” The clinical importance of these findings suggests that human coronary collaterals can act as a “marker of poor outcome” in diseases such as acute coronary syndromes.

Sudden cardiac death (SCD) has several causes including electrical instability of the heart, specifically QRS complex variabilities can be used as markers for SCD and at times even trigger SCD [25]. The Oregon Sudden Unexpected Death Study (Ore-SUDS) has shown that prolongation of the QRS complex is associated with a large increase of SCD due to both known and unknown causes; therefore, methods to reduce this adverse event in the presence of myocardial ischemia can reduce mortality [26]. Additionally, fragmented QRS (fQRS), which are various RSR patterns in two continuous leads, have a well-established relationship with cardiac fibrosis caused by previous myocardial infarction or ischemia [27]. fQRS patterns have also been associated with increased morbidity and mortality, SCD, and repeat cardiovascular (CV) events and were found more often in individuals with poor collateral growth [27]. The presence of a well-developed collateral network has been shown to reduce QRS prolongation in left coronary artery occlusion and occurrence of fQRS in patients with chronic total occlusion [25, 27]. With this information, it can be concluded that with an increased number of coronary collaterals, patients can avoid QRS complex abnormalities thereby decreasing the chances of sudden cardiac death.

Additionally, the presence of collaterals has shown an increased time from symptom-onset-to-perfusion (>6 hours in good collateral versus poor collateral). This enables patients to increase the amount of time before onset of detrimental cardiac damage [28]. During an acute MI, the presence of a well-developed collateral circulation was seen in infarcted tissue that did not undergo cell necrosis, proving that increased collaterals will increase the chances of myocardial viability [29–31].

Overall, the presence of a well-developed collateral circulation in conjunction with healthy baseline characteristics (absence of repeat MI or angina pectoris) will be protective in patients who may suffer SCD, MI, or bouts of ischemia. Working to induce this collateral growth in patients both mechanically and chemically will prove to be very beneficial in decreasing mortality rates of patients with heart disease and perhaps ameliorate the possibility of recurrent cardiac events.

3. Mechanical factors involved in coronary collateral growth

The precise stimulation of arteriogenesis is yet to be found; however, both mechanical and chemical influences are required to induce the formation of collaterals in the heart. Mechanical shear stress occurs due to increased pressure gradients that form when an occlusion is present [32]. A stenotic artery will increase the pressure prior to the occlusion while decreasing the pressure distal to the occlusion. The increased pressure above the occlusion will cause an increase in blood flow into capillary beds prior to the occlusion increasing the shear stress [32]. The increased movement of blood into pre-existing collaterals and the resultant increased

shear stress leads to several changes in the capillary endothelium. The first of which includes an increase in MCP-1 that serves to attract more monocytes to the proliferative site in order to transform them into the subsequent macrophages. The macrophages play a vital role in releasing cytokines and growth factors required for arteriogenesis. $\text{TNF-}\alpha$, released by macrophages, helps form the inflammatory environment required for the growth of collaterals [33]. Another major factor includes basic fibroblast growth factor (bFGF), which helps with the actual development of collaterals [32]. A more in depth analysis on chemical inducers will be discussed later on in this chapter.

Although mechanical shear stress is thought to be a major contributor to arteriogenesis, it cannot be the sole solution due to the inability of fluid shear stress to completely replace the conducting artery. Fluid shear stress (FSS) has been found to only reach 35–40% of the maximal conductance possessed by the original stenotic artery [34]. An explanation for this phenomenon can be found in the relationships: FSS and blood flow velocity and FSS and cube of the vessel radius. FSS and blood flow velocity have a proportional relationship, while FSS is inversely related to the cube of the vessel radius [34]. The increase in blood flow velocity in the pre-existing collaterals leads to an increase in FSS. Since the shear stress causes growth in the collaterals (meaning an increase in the vessel radius), the FSS begins to decline preventing full recovery of the stenotic artery [34]. This indicates the need for both mechanical and chemical effectors for the production of proper coronary collaterals.

4. Chemical factors involved in coronary collateral growth

In addition to mechanical mechanisms of arteriogenesis, there are several chemical mediators involved in regulation of the process. Many of these chemical factors modulate the functions of the various cell types involved in arteriogenesis, including induction of cell proliferation, chemotaxis, and cellular remodeling. In this section, we will outline the various chemical mediators that are currently known to play a role in arteriogenesis.

4.1. Vascular endothelial growth factor (VEGF)

Vascular endothelial growth factor (VEGF) is known to play a major role in development of new vasculature. Under hypoxic conditions, VEGF production and release stimulates new capillary formation (angiogenesis) via endothelial cell sprouting, proliferation, and migration [35]. Alternatively, under different conditions, it can instead stimulate growth of new arteries, formation of collateral vessels, and modulation of lumen expansion—these actions are collectively referred to as arteriogenesis [35].

In VEGF signaling, there are three primary cell-surface receptors to which it binds: two tyrosine kinase receptors VEGFR-1 and VEGFR-2 and a nonkinase receptor neuropilin-1 (NRP-1) [35–37]. There are multiple isoforms of VEGF, with VEGF-A playing the major role in endothelial cell function via binding to VEGFR-2 [35]. VEGFR-2 is also involved in signaling pathways that lead to arteriogenesis via stimulation of proliferation, migration, survival, and lumenization of endothelial cells [35].

The first of these signaling cascades is activation of phosphatidylinositol 3-kinase (PI3K)/Akt that inhibits apoptosis in endothelial cells thus promoting cell survival [35]. The cascade is initiated by binding of VEGF-A to VEGFR-2 (Flk-1), which initiates receptor internalization via clathrin-coated pits followed by receptor autophosphorylation [35]. Active VEGFR-2 then phosphorylates PI3K, which goes on to phosphorylate the serine/threonine kinase Akt, which will go on to phosphorylate targets to inhibit apoptosis [38].

The second signal cascade is phosphorylation of profilin-1, indirectly via Src/FAK as well as directly via VEGFR-2, which stimulates migration of endothelial cells [35, 37]. Like the previous mechanism, this cascade is initiated by binding of VEGF-A to VEGFR-2. Activated VEGFR-2 then goes on to phosphorylate profilin-1 as well as Src kinase, which also phosphorylates profilin-1 [37]. Phosphorylated profilin-1 then goes on to catalyze the exchange of ADP for ATP on G-actin that stimulates polymerization of actin and resultant remodeling of the endothelial cell cytoskeleton [37]. This remodeling results in formation of actin-rich filopodia extending in the direction of the concentration gradient of VEGF, thus stimulating endothelial cell migration [37].

The third signal cascade is activation of the Raf-MEK-ERK signal cascade, which stimulates proliferation of endothelial cells, network formation, and increase in lumen size via phosphorylation of ERK1/2 [35]. While the exact mechanism of ERK1/2 action on cell proliferation and motility is not yet well understood, it has been suggested that a major component of this signaling cascade is downregulation of Rho-Kinase activity [39].

Finally, it is important to note that VEGF has been shown to be a critical factor in the process of coronary collateral growth. In a study of collateral growth following myocardial infarction in rats, it was observed that when the endogenous functions of VEGF were blocked by anti-VEGF neutralizing antibody, the result was a complete lack of collateral growth and subsequently no increase in coronary flow in the anti-VEGF group [40]. Additionally, upon treatment with dipyridamole (a potent vasodilator), it was observed that the increased coronary flow seen in the control group was in fact due to collateral growth, as there was no observed increase in coronary flow in the anti-VEGF group after the dipyridamole [40]. This study solidifies the importance of VEGF in the process of angiogenesis, particularly as it relates to coronary collateral growth.

4.2. bFGF and PDGF

In addition to VEGF, other growth factors are known to play a role in arteriogenesis—notably basic fibroblast growth factor (bFGF) and platelet-derived growth factor (PDGF) [41]. Basic FGF and PDGF are known to induce mitosis in both endothelial and smooth muscle cells and also exert other mitogenic effects such as promoting cell migration and differentiation [41, 42]. Basic FGF stimulates these mitogenic effects via binding to FGF receptors (FGFRs) expressed on cell surfaces [43]. These FGFRs are a part of the tyrosine kinase receptor family, and following binding of bFGF dimerize and are autophosphorylated to become activated [43]. Activated FGFRs, notably FGFR-2 (FGFR-1 is thought to be a regulator of bFGF concentration available to bind FGFR-2), then continue the signal cascade by activation of cytoplasmic mitogen-activated protein kinase (MAPK), which then is translocated to the nucleus to initiate

transcription promoting the aforementioned mitogenic effects [43]. PDGF, on the other hand, is known to activate multiple other downstream targets including PI3K, phospholipase C (PLC), as well as MAPK to mediate its mitogenic effects [44].

4.3. MCP-1 and macrophages

In addition to endothelial cells, macrophages are also heavily involved in arteriogenesis, but in order to do so must be directed to the correct location [36]. The primary molecule that has been studied as part of this mechanism is monocyte chemotactic protein 1 (MCP-1) [36]. Secretion of MCP-1 is initiated by activation of endothelial cell MAP-kinase-protein-kinase-2 (MK2) by elevation of fluid shear stress [45]. Released MCP-1 subsequently activates monocyte MK2, initiating migration to the correct location [45]. In the last step of the cycle, release of inflammatory cytokines by recruited monocytes cause increased secretion of MCP-1 from the endothelium, resulting in further monocyte recruitment [45]. Of similarly significant importance to MCP-1 are two adhesive molecules, intracellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), which serve to bind the surface of migrating monocytes allowing them to roll along the luminal surface of the vasculature [36].

Once the macrophages have reached their destination, the correct phenotype must be expressed to stimulate new vessel growth [36]. There are two primary phenotypes of monocyte macrophages: M1 macrophages that secrete inflammatory molecules and help fight pathogens and M2 macrophages that play a role in vascular growth and wound healing [36]. These two phenotypes are induced by different cytokines, with interferon- γ causing a shift toward the M1 phenotype, while IL-4, IL-13, and several other factors such as IL-10 and IL-33 causing M2 differentiation. In histological analysis of hypoxia-induced arteriogenesis, the number of M2 macrophages was shown to increase indicating their essential role in development of new vasculature [36].

4.4. NO and eNOS

Nitric oxide (NO) is a potent vasodilator that is produced via the activity of endothelial nitric oxide synthase (eNOS). eNOS has been shown to function in stimulating production of new vasculature, and its expression is also known to be upregulated in response to elevated fluid shear stresses—a principal mechanical stimulus of arteriogenesis [46]. While the exact effects of NO and eNOS on arteriogenesis are still controversial, it has been shown that one contribution of elevated NO due to increased expression of eNOS is a reduction of vascular endothelial cadherin (VE-cadherin), resulting in increased vascular permeability and indirect promotion of macrophage invasion [46]. Additionally, eNOS activity and pharmacological inhibition of eNOS were shown to play a role in mediating vascular remodeling during collateral growth [47, 48].

4.5. Catestatin

Catestatin is a neuroendocrine peptide derived from a specific cleavage of the larger protein human chromogranin A (CgA) [49]. It functions in many different processes within the body including secretion of histamine from mast cells, defense against microbes, vasodilation, and attraction of monocytes. It has also been observed that catestatin acts in a pro-angiogenic capacity, involved in inducing proliferation and migration of endothelial cells

as well as formation of capillary tubes [49, 50]. This is accomplished through stimulating release of bFGF, which in turn will activate MAPK via binding to FGFR-1 as previously discussed [49, 50]. It has also been shown that catestatin activates other signal cascades such as PI3K/Akt, serving an anti-apoptotic role to promote cell survival [50]. Finally, catestatin influences effects in both endothelial progenitor cells (EPCs) and vascular smooth muscle cells (VSMCs) in addition to its direct effects on endothelial cells, inducing chemotaxis to incorporate these cell types into formation of new vasculature [50].

4.6. Neuregulins

Neuregulins (NRG) are another class of molecules produced by endothelial cells. These growth factor ligands bind to erbB receptors expressed on the surface of endothelial cells—this action has been shown to induce angiogenesis [51]. NRG involvement in angiogenesis and arteriogenesis is tied to regulation of $\alpha_v\beta_3$ integrin, thus playing a role in cell migration, proliferation, and differentiation mechanisms as shown in a NRG-erbB knockout mouse model. The mechanism by which this occurs involves another proangiogenic protein, Cyr61, the expression of which is upregulated by NRG-erbB signaling, in addition to mediation via induction of VEGF release and subsequent activation of the ERK signaling cascade [51]. ErbB receptors have also been found to be expressed on EPCs, playing a role in increasing cell survival, and on certain types of VSMCs, though the role NRG-erbB signaling plays here is not well known [51].

4.7. Early growth response 1 (Egr-1)

Early growth response 1 (Egr-1) is a transcription factor of the zinc-finger family that has been shown to be upregulated during arteriogenesis [52]. It plays a major role in modulating the levels of other growth factors that are involved in the process of collateral growth, including playing a role in the recruitment and proliferation of leukocytes [52, 53]. Specific genes that are upregulated by Egr-1 include PDGF and transforming growth factor β (TGF- β), which then indirectly upregulates other factors involved in collateral growth such as VEGF and metalloproteinases [53]. Interestingly, despite the fact that most of these factors have been primarily shown to affect angiogenesis, it has been observed that Egr-1 primarily affects the growth of arterioles rather than capillaries, indicating its primary role in regulation of arteriogenesis [53].

Much like the other factors mentioned here, Egr-1 production is stimulated primarily by elevations in fluid shear stress, in this case by activating the Egr-1 gene promoter [54]. It has been suggested that this is mediated by the Ras-MEK-ERK1/2 signal cascade in which shear stress leads to activation of MEK1, which proceeds to activate ERK1/2 of the MAPK family, and finally ERK1/2 activate the protein Elk-1 that induces transcription of Egr-1 [54]. Interestingly, this pathway can be activated by very low levels of shear stress due to the sensitivity of ERK1/2 [54].

There are many varying chemical mediators of arteriogenesis, many of which share similar signaling pathways leading to their involvement. While some of these mediators have been studied extensively and are relatively well understood, there are others whose mechanisms have not yet been elucidated and require more investigation. There are likely even more chemical mediators involved that have not yet been studied. Going forward, more research

will be extremely valuable in understanding the overall chemical mechanism behind collateral vessel growth and how to apply this knowledge to a clinical setting.

5. Role of Stem Cells in Coronary Collateral Growth

In addition to the aforementioned chemical mediators that mitigate the consequences of vascular occlusive diseases by stimulating collateral growth, in recent years, stem cell-based therapy has been implicated as a possible avenue for vascular regeneration. Stem cells have the unique potential of developing into many different cell types in the body. Under certain physiologic and experimental conditions, they can be manipulated to grow into specific tissues and organ cells with exclusive functionality. This revolutionary discovery for stem cells has demonstrated a clinical potential to create new networks of blood-perfused vessels and treat human patients with cardiovascular and vascular diseases [55]. The current theory is that stem cells may release a series of angiogenic factors, such as VEGF and bFGF, which mobilize vascular endothelial cells through a paracrine effect [56]. In this section, we will summarize the current state of regenerative approaches using stem cells to stimulate coronary collateral growth.

A 2012 study programmed endothelial cells to develop into induced vascular progenitor cells (iVPCs) and assessed their ability to induce coronary collateral growth in a rat model in efforts to increase blood flow to the collateral-dependent region of risk [57]. iVPCs are also known to be less tumorigenic compared with induced pluripotent cells (iPSCs) and are more likely to commit to a line of vascular differentiation (they will not turn into cardiomyocytes) [57]. When the iVPCs were transplanted into myocardium, they formed blood vessels and improved blood flow markedly better than did natural endothelial cells, mesenchymal stem cells, or iPSCs [57]. However, while results showed that partial programming of the endothelial cells was promising enough to sprout new blood vessels in the myocardium, one big challenge persists: how to maintain the partial programmed state of the cells until they get to their intended destination [57].

In addition, current literature posits that bone marrow-derived stem cells and endothelial progenitor cells in arteriogenesis do not physically deposit onto the walls of newly generated arteries but rather play the role of supporting cells [58]. The therapeutic induction of collateral growth from already established arteries improves any blood flow deficiencies caused by blockage in major arteries. Transplanted bone marrow-derived cells act as “cytokine factors” and secrete specific growth factors that mediate their effects through paracrine activity [59]. As Dr. Matthias Heil of the Netherlands puts it, “bone marrow stem cells provide the software and not the hardware in vascular growth” [59]. His group’s study on the hindlimb ischemic model with mice revealed that GFP-tagged bone marrow was not localized to endothelial and smooth cell markers, but around burgeoning collaterals that were secreting chemokines and growth factors [59]. Hence, therapeutic arteriogenesis functions to boost the body’s natural angiogenic ability by stimulating the release of pro-angiogenic factors rather than actually providing the building block for a new artery. A caveat to this is if the processes in the heart are different from those in the peripheral circulation.

While there is a continued debate on whether bone marrow-derived multipotent stromal cells (MSCs) exert their effect via transdifferentiation or through paracrine activity, there is unequivocal

evidence showing that MSCs must first travel to ischemic tissue to achieve a therapeutic benefit [60]. MSCs localize to injured tissues by adhering to endothelial cells and migrating across the cell wall. Homing of MSCs to injured tissues is optimized by an expression of ligands on endothelial cells [60]. A 2009 study showed the importance of epidermal growth factor (EGF) and heparin-binding epidermal growth factor-like growth factor (HB-EGF) in inducing increased expression of these ligands [60]. Specifically, phosphorylation of the EGF-R leads to higher expression of ligands, VCAM-1, and ICAM-1 that enhanced MSC adherence and ultimately stimulated coronary collateral growth in rats that had undergone repetitive instances of myocardial ischemia [60]. Coronary collateral growth was assessed with the ratio of collateral dependent flow (CZ) to normal zone flow (NZ). Exposure of both MSCs and coronary endothelial cells (CECs) to a 100 ng/mL dose of EGF for 16 hours maximally increased expression of adhesion molecules compared with samples untreated with EGF [60]. The CZ/NZ ratio increased in rats whose MSCs were treated with EGF and showed improved cardiac function and decreased left ventricular remodeling compared to rats without EGF treatment of MSCs [60].

Another 2009 study involving a rat model of repetitive myocardial ischemia showed that granulocyte-colony stimulating factor (G-CSF), a glycoprotein responsible for hematopoietic cell proliferation and differentiation of neutrophil granulocytes, also stimulates coronary collateral growth [61]. G-CSF mounts a series of defenses against infectious agents, one of which is promotion of neutrophils to release reactive oxygen species (ROS) [61]. This generation of ROS was studied both *in vivo* and *in vitro* and was shown to directly act on injured cardiomyocytes. Cardiomyocytes under the influence of G-CSF-induced ROS generate angiogenic factors that lead to vascular growth and tube formation in levels comparative to cardiomyocytes induced by VEGF [61]. To the surprise of researchers, this study also demonstrated that G-CSF can promote coronary collateral growth without the impetus of repetitive ischemia and hence this cytokine can act as a surrogate for ischemia [61].

Majority of the recent clinical trials in humans purport that stem cell-based therapy adequately facilitates angiogenesis in patients suffering from peripheral arterial disease and promotes wound healing [55]. Specifically, bone marrow-derived stem cell transplantation has shown to improve ischemic symptoms, such as claudication, ischemic rest pain, and has augmented wound healing in ulcer-related conditions [55]. Nonetheless, these studies have been limited by a lack of care standardization, absence of a control group, small sample sizes, dissimilar inclusion criteria, and inconsistencies in methods of outcome assessment [55]. In other cases, the absence of follow-up procedures has prevented elucidation of long-term effects of treating peripheral artery disease with stem cells [55]. While the central issues of public safety and treatment efficacy linger over the field, progress, albeit limited, has been made in the arena of coronary collateral growth.

6. Summary

The process of coronary collateral growth is being better understood year by year. The role that the many chemical factors, mechanical factors, and stem cells play in the process is still incompletely understood. The study of these factors in “normal” preclinical models may be

an oversimplification, because under conditions with risk factors for coronary disease, there may be shifts in the normal control mechanisms. We advocate that future studies incorporate models of cardiovascular disease and aging to better understand the mechanisms by which this adaptive process is abrogated in the majority of patients with ischemic heart disease.

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