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Review article

Post-MI cardiac repair: The role of angiogenesis in heart rejuvenation – A review

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Abstract

After a myocardial infarction (MI), the heart's limited regenerative capacity is outstripped by substantial myocytes degeneration and significant arterial damage. Cardiac repair involves a complex, well-coordinated sequence of events, including a strong angiogenic response in the heart's peri-infarct border zone, leading to fibroblast proliferation and scar formation. Effective vascular formation post-MI helps limit myocytes hypertrophy and reduces scar formation by decreasing collagen deposition, thus improving heart function. Robust data from conventional in vitro thrombotic approaches and animal models show that multiple synchronized signaling pathways, including Wnt, PI3K, Notch, and ion channel regulation of cytoplasmic Ca^{2+} levels, control angiogenesis of endothelial precursor cells (EPCs) and existing endothelial cells (ECs). Factors like hypoxia, VEGF and FGF family growth factors, nitric oxide synthase, inflammation, and miRNAs are crucial in angiogenic pathways, significantly impacting the infarcted heart. Post-MI, paracrine and autocrine cell-to-cell signals, predominantly delivered by extracellular vesicles carrying pro-angiogenic proteins and non-coding RNAs like miRNAs, are vital for cardiac repair. This review overviews major angiogenic pathways and their effects on post-infarction myocardial angiogenesis, emphasizing the roles of endothelial nitric oxide synthase and growth factors like VEGF and FGF. It also explores signaling pathways triggered by MI, focusing on ROS regulation, Ca^{2+} influx, and miRNAs in endothelial cell activation and subsequent angiogenesis. Additionally, the review discusses troponin's role as a biomarker for myocardial infarction, highlighting its function as a potent angiogenesis inhibitor.

Introduction

Myocardial infarction is a main cause of death and sickness globally. It is occurring due to insufficient oxygen supply and blood flow as a result of coronary artery blockage [1]. The unfavorable remodeling of the left ventricle (LV) after myocardial infarction serves as the foundational structure for ischemic heart failure (IHF), involving intricate alterations in left ventricular size, shape, function, as well as molecular and cellular structure both in the short and long term [2]. The advancement of this process to clinical heart failure (HF) is largely determined by the size of the initial infarction and the efficiency of the post-MI reparative process, even though several pathophysiological elements converge reconstruct the cardiac muscle following an infarction of the myocardium. Limiting the extent of an infarction usually involves rapid coronary reperfusion in clinical practice. But therapeutic intervention in the subsequent restoration procedure which is mostly propelled by severe inflammation of tissues, which is then actively suppressed and resolved has proven to be far more difficult. However, a number of

promising goals for therapy that could have a favorable impact on cardiac wound healing and repair have been found in recent studies. The multiplicity of cellular and molecular mechanisms regulating post-MI healing are extensively examined in this study, with a focus on their translational implications for reducing unfavorable remodeling and the development of ischemic heart failure [3]. Approximately 10% of myocardial infarction (MI) patients endure with significantly impaired left ventricular (LV) function, placing them at risk for adverse LV remodeling and heart failure [4].

Myocardial infarction (MI) can proceed to heart failure due to a number of reasons, such as ischemia-induced oxygen deprivation, cardiomyocyte depletion, and eventual hypertrophy and fibrosis. These negative outcomes worsen the illness, causing it to worsen even more and ultimately result in heart failure [5]. The inflammatory response triggered by tissue damage in acute MI results in the replacement of the necrotic region with granulation tissue, eventually forming a scar rich in collagen [6].

In the course of myocardial infarction (MI), the presence of ischemia and the subsequent healing process in cardiac tissue initiate a series of signaling cascades. Among these include an increase in intracellular calcium (Ca^{2+}) and reactive oxygen species (ROS), as well as a disturbance in the control of endothelial NO synthase (eNOS) [7-9], and the activation of hypoxia-induced factor 1α (HIF-1α). This activation of HIF-1α is crucial for the development of new blood vessels from old vasculature, a process known as angiogenesis [10], primarily orchestrated by endothelial cells (ECs). In addition to endothelial cells (ECs), other cell groups within the heart, including cardiomyocytes, macrophages [11], fibroblasts, and monocytes, have been found to actively participate in post-infarction angiogenesis [12], as demonstrated through various investigations. Their participation in this process is due to their expression of significant amounts of vascular endothelial growth factor (VEGF), it is thought to be the primary reason that promotes the development of new blood vessels. This expression, along with other growth factors, continues for up to one week after the ischemia event. In addition, endothelial cells (ECs) near the infarcted area demonstrate elevated expression of vascular endothelial growth factor receptor 2 (VEGFR2), potentially elucidating the turning on of ECs and the initiation of neovascularization [11].

This explanation of EC turning on the initiation of development in fresh vascular structures may be further complemented by considering other cofactors in cardiac angiogenesis. Extensive research has highlighted a rise in pro-angiogenic paracrine and autocrine signals following myocardial infarction. These signals arise from the actions of various factors such as Insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), fibroblast growth factor 2 (FGF2), and hepatocyte growth factor (HGF) [13], hormones (including estradiol and estrogen), tumor necrosis factor α (TNF-α), monocyte chemoattractant protein-1 (MCP-1) and interleukins (IL2, IL6, IL17) [14].

Similarly, additional research has demonstrated an intensified release of vesicles from various heart cell populations, containing proteins and non-coding RNA, including microRNAs. These molecular components initiate diverse signaling pathways and alterations in intracellular calcium concentrations ($[Ca^{2+}]$), among other signaling events, intricately regulating the complex process of angiogenesis and recently reviewed [15]. Nevertheless, the multitude of signaling pathways involved in post-MI angiogenesis presents challenges in delineating a final strategy for the best possible angiogenic response, as recently discussed. An overview of recent literature is provided by this review. Elucidating the roles of various signaling pathways and miRNAs in Angiogenesis and the stimulation of endothelial cells following myocardial infarction [16].

Angiogenesis

The act of creating newly formed vascular structures, or angiogenesis, is essential for controlling a number of physiological processes, such as the menstrual cycle, Regeneration of tissue and healing from injuries following surgery, and the healing of injuries [17]. Angiogenesis is a closely regulated process that is impacted by a variety of stimulators and inhibitors. An imbalance in these variables has been connected to several diseases, including asthma, arthritis, psoriasis, cancer, age-related deterioration of the eyes, and cardio-cerebral disorders. As such, controlling angiogenesis is seen to be a desirable and effective treatment approach for various clinical diseases [18].

Process of angiogenesis

Angiogenesis is classified into two primary types: sprouting angiogenesis and intussusceptive angiogenesis [19].

Sprouting angiogenesis

It is the process of developing new vascular structures from an already-established capillary network, as opposed to vasculogenesis, which includes the assembly of blood vessels from precursor cells. Typically, endothelial sprouting occurs in response to hypoxia, damage, or triggered by oncogenic signaling activation of Growth regulators that are angiogenesis. A common angiogenic agent, vascular endothelial growth factor stimulates the vascular endothelial growth factor receptors expressed on endothelial cells to start sprouting angiogenesis. With concentration-dependent effects on EC proliferation and gradient-dependent effects on migration, vascular endothelial growth factor is essential for the majority of the steps involved in the creation of new vessels [20, 21]. When endothelial motility and proliferation are induced by the mitogenic signal, the resulting immature vessels have higher permeability. But as they get older, they leave behind fresh extracellular matrix (ECM) that draws in pericytes, which keep the vessels stable [22]. Specialized

endothelial cells have metabolic transcriptome flexibility during sprouting, producing metabolic angiogenic factors such ALDH18A1 and SQLE as well as proteolytic characteristics that allow them to break down the extracellular matrix (ECM) [23]. Tip cell selection appears to occur randomly, potentially linked to varying expression levels of VEGF receptors, and is characterized by dynamic movement where stalk and tip cells can interchange positions during sprouting. This process relies on functional Notch signaling and the presence of Dll4 ligand. Spatial gradients of sFlt contribute to the refinement of erupting developing vessel in conjunction with vascular endothelial growth factor. Stalk cells multiply behind the tip cells and develop lumens, facilitated by the GTPase-interplay protein Rasip1, it is essential to the polarity of cells, endothelial cell, intersection upkeep and adhesion to the extracellular matrix. Tip cell anastomosis, similar to fusion of the bronchial duct, eventually establishes the system necessary for blood circulation. Tip cells exhibit enrichment in several extracellular matrix and elements of the basement barrier, such as Nid1 and Nid2, TGFβ pathway genes, and secreted factors like Apln and Angpt2 [24].

Intussusceptive angiogenesis

A variation of angiogenesis, distinct from sprouting, is intussusceptive angiogenesis. Initially observed during pulmonary microvascular reorganization following birth, this process involves the separation of two new vessels from a previous vessel after the creation of a trans-vascular core between two endothelial cells situated opposite each other within the vessel lumen [25]. Pre-existing vessels split into two new vessels subsequent to the formation of a trans-vascular pillar between two endothelial cells positioned opposite each other within the vessel lumen. Because it doesn't initially depend on proliferation, intussusceptive vasculature is a quick process of vascular remodeling that can happen in a matter of hours or even moments. Research has demonstrated that vessel formation can also happen in tiny arteries and veins outside of capillary plexuses [26]. The absence of growth of endothelial cells in this type of vessel propagation is noteworthy because anti-angiogenic agents targeting endothelial cell proliferation may not be effective. Nevertheless, given that VEGF seems to be a major contributor to in regulating intussusceptive angiogenesis, inhibitors targeting the VEGF signaling pathway could potentially block this mode of angiogenesis [27].

Key angiogenic pathways and their impact on post-infarction myocardial angiogenesis

Ischemic promote elements

Hypoxia-responsive transcription factors like hypoxia-inducible factor 1-alpha (HIF1-alpha) facilitate cellular adjustment to hypoxia, governing angiogenesis during development and in the postnatal period. Activated by hypoxia, HIF1-alpha stimulates various genes, including proangiogenic ones like VEGF and the chemokine that mobilizes precursor cells Factor 1-alpha Derived from Stromal Cells (SDF1-alpha), positioning it as a primary instigator of angiogenesis triggered by ischemia [28]. HIF1-alpha and its counterpart HIF2-alpha are expressed early after myocardial infarction (MI) in inflammatory cells, endothelial and cardiomyocytes cells, persisting for up to 4 weeks in rats. Mice exhibiting intrinsic expression of HIF1-alpha in cardiomyocytes exhibit enhanced cardiac function post-MI, linked with increased VEGF expression and myocardial angiogenesis. The HIF pathway's indirect activation through inhibition of Prolyl Hydroxylase Domain proteins (PHDs) and Factor Inhibiting HIF (FIH) highlights the pathway's critical role in post-ischemic angiogenesis. In rats, consumption of a non-isoform-specific PHD inhibitor increases endothelial permeability in the peri-infarct area, preventing cardiac function decline and left ventricular (LV) dilatation after MI [29]. Additionally, the combined shRNA-mediated downregulation of PHD-2 and FIH in mice post-MI improved left ventricular (LV) function and promoted neovascularization [30]. This underscores the multifaceted role of the HIF1-alpha pathway in angiogenesis during tissue ischemia. Furthermore, HIF1-alpha regulates the recruitment of endothelial progenitor cells (EPCs) to ischemic regions and angiogenesis by establishing gradients of stromal cell derived factor-1 (SDF-1) [31]. Deletion of HIF-2alpha in endothelial cells resulted in increased angiogenesis; however, the newly developed vessels exhibited inadequate maturation, consequently impairing epithelium permeability. These characteristics of endothelial HIF-2alpha are especially pertinent in post-MI angiogenesis, where the longevity and functionality of the emerging microvasculature are essential for effective epithelium perfusion [32].

Growth factors

The elevated levels of several growth factors that promote angiogenesis is seen in the ischemic heart. For instance, myocardial upregulation of HGF after ischemia [33] is noteworthy, and its pro-angiogenic properties in pre-clinical models of MI are well-established. Furthermore, growth factors that promote angiogenesis and lessen cardiac dysfunction following MI include Nerve Insulin-like Growth Factor-1 and Growth Factor [34]. On the other hand, the VEGF and FGF families of growth factors have been the most thoroughly investigated among those linked to post-MI angiogenesis [35].

The VEGF growth factor family

The members of the VEGF family have a notable impact on the process of post-MI angiogenesis. VEGF operates by attaching to its receptor VEGF receptor 2 (VEGFR2) (Figure 1), therefore encouraging the survival, growth, and movement of endothelial cells [36]. VEGF's angiogenic capabilities observed throughout the angiogenesis of malignancies or vascular development have prompted a swift assessment of its part in angiogenesis following MI. In

both humans and rodents, VEGF is promptly induced in the ischemic heart, triggered not only by hypoxia but also by mechanical stretch [37]. Various empirical research has demonstrated the proangiogenic benefits of administering VEGF in porcine or rodent models [38] of myocardial infarction (MI), resulting in an enhancement of heart function. Nevertheless, VEGF by itself stimulates the development of underdeveloped, permeable, and chaotic blood vessels and can hinder Platelet-Derived Growth Factor (PDGF)-BB signaling, which is a vital pathway for vascular maturation. VEGF-R2, upon activation by VEGF, interacts with PDGF-receptor beta to impede signal transmission, resulting in the alteration of mural cell recruitment and vessel stabilization (Figure 2) [39].

Placental Growth Factor (PlGF), another member of the VEGF family of growth factors, exhibits a preference for binding to VEGF Receptor 1 (VEGFR1). PlGF triggers angiogenesis in ischemic tissues through two primary mechanisms. Firstly, PlGF activates VEGFR1, resulting in the transphosphorylation of VEGFR2 and the augmentation of VEGF-dependent signaling (Table 1) [40].

VEGF-B's role in post-MI angiogenesis remains contentious. While initial findings suggested a VEGFR1-dependent proangiogenic effect in murine hindlimb ischemia [41], subsequent studies proposed that VEGF-B might induce angiogenesis specifically in the murine infarcted heart, but not in other tissues, dependent on VEGFR1 and neuropilin-1. Conflicting reports from Bry et al. suggested coronary artery growth without angiogenesis in transgenic rat hearts but not in transgenic mouse hearts. Zhang et al. demonstrated VEGF-B's dispensability for vessel growth but essential role in survival via anti-apoptotic signals in endothelial and mural cells. VEGF-C, primarily linked to lymphangiogenesis, also activates angiogenesis post-ischemia, potentially via indirect promotion of PDGF-B expression and vessel maturation [42].

FGF family of growth factors

This renders it difficult to understand the mechanisms underlying the angiogenic effects of FGF family growth factors because there are four tyrosine kinase receptors, a high number of FGF ligands (22 in humans and mice), and a rather redundant FGF system. This intricacy makes it difficult to understand how these growth cues encourage angiogenesis. The endothelial cell mitogen known as acidic FGF (aFGF or FGF1) was first identified in the brain tissue of cows. Microvascular endothelial cells were then shown to express basic FGF (bFGF or FGF2), which may have an autocrine effect on the cells' survival and proliferation. FGF2 may partially exert its effects indirectly, even though it appears to directly increase endothelial cell proliferation and angiogenesis in vivo. For example, FGF-2 induces endothelial cells to express VEGF, while FGF-2's proangiogenic actions are counteracted by inhibiting VEGF. FGF-2 also has the ability to induce the expression of additional proangiogenic cytokines, such as MCP-1/CCL2 and HGF [45]. Multiple studies have shown that both FGF-1 [46] and FGF-2 [47] stimulate angiogenesis in the ischemic heart and facilitate cardiac repair following myocardial infarction (MI) [48]. In the rat cornea, VEGF-stimulated neovascularization produces unorganized, leaky small capillaries, whereas FGF-2-induced angiogenesis produces stable, mature blood vessels [49]. Because of the interaction between FGF-2 and PDGF-BB signalling, blood vessels become more stable and mature more quickly. This is most likely due to the induction of PDGF-BB receptor expression. Both a pig myocardial infarction (MI) model and a hind limb ischemia [50] model show enhanced angiogenesis and vascular stability in response to co-administration of FGF-2 and PDGF-BB. By increasing angiogenesis and improving myocardial perfusion, this co-administration improves heart function [51]. It has recently come to light that FGF-9 plays a major role in the stability and development of vessels. Research has demonstrated that FGF-9 is elevated in vascular smooth muscle cells as new vasculature mature, highlighting its function in facilitating vessel muscularization as opposed to endothelial proliferation and angiogenesis in and of itself. FGF-9 administration induced the development of long-lasting, multilayered and perfused, new vasculature in a model of hindlimb hypoxia. Despite the lack of evidence about its effectiveness in preclinical models of myocardial infarction (MI), FGF-9's characteristics make it an attractive target for proangiogenic therapy, either on its own or in conjunction with other medicines that target endothelial cells [52].

Nitric Oxide Synthase (NOS)

The creation of nitric oxide (NO) requires the enzymes known as NO synthase (NOS) and play a significant function in the angiogenic response to hypoxia and ischemia, partly because of the HIF1-alpha and VEGF pathways described earlier. Although research on peripheral limb ischemia provides a large amount of the evidence for these pathways, following an infarction of the heart (MI), NOS enzymes are also involved in cardiac remodeling and angiogenesis. The efficiency of statins, which are known to stimulate angiogenesis via the eNOS-dependent mobilization of endothelial progenitor cells (EPCs), is similarly diminished in animals lacking endothelial NOS (eNOS$^{-/-}$mice). These mice also exhibit reduced angiogenesis post-MI [53]. Moreover, rats with myocardial infarction (MI) who received the transcriptional eNOS activator AVE9488 showed increased eNOS levels, decreased infarct size, and sustained numbers of circulating endothelial progenitor cells (EPCs). According to recent research, the well-established role of eNOS in cardiac angiogenesis is not the only one that NOS enzymes and their control play in the process. Both inducible and neuronal NOS were markedly increased in mouse hearts after MI. Inducible NOS-/-mice showed a decrease in nitrotyrosine production after MI, and inducible NOS was required for tetrahydrobiopterin (BH4), a NOS cofactor, to increase

myocardial angiogenesis following MI. These findings imply that a major factor influencing BH4's effect on myocardial angiogenesis is inducible NOS coupling remodeling post-MI [54].

Table 1. Members of the VEGF family and their biological functions (Source data: Jingjing Li *et al.* 2022) [43].

Categories	Splice variants	Receptors	Biological functions
VEGF-A	$VEGF_{121}$, $VEGF_{145}$, $VEGF_{165}$, $VEGF_{183}$, $VEGF_{189}$, $VEGF_{206}$	VEGFR-1, VEGFR-2, NRP-1, NRP-2	Angiogenesis, vasculogenesis
VEGF-B	$VEGF\text{-}B_{167}$, $VEGF\text{-}B_{186}$	VEGFR-1, NRP-1	Embryonic angiogenesis
VEGF-C	None	VEGFR-2, VEGFR-3	Angiogenesis, lymphangiogenesis
VEGF-D	None	VEGFR-2, VEGFR-3	Angiogenesis, lymphangiogenesis
VEGF-E	None	VEGFR-2, NRP-1	Angiogenesis,
VEGF-F	None	VEGFR-2	Angiogenesis
PIGF	PIGF-1, PIGF-2, PIGF-3, PIGF-4	VEGFR-2, NRP-1, NRP-2	Angiogenesis, vasculogenesis

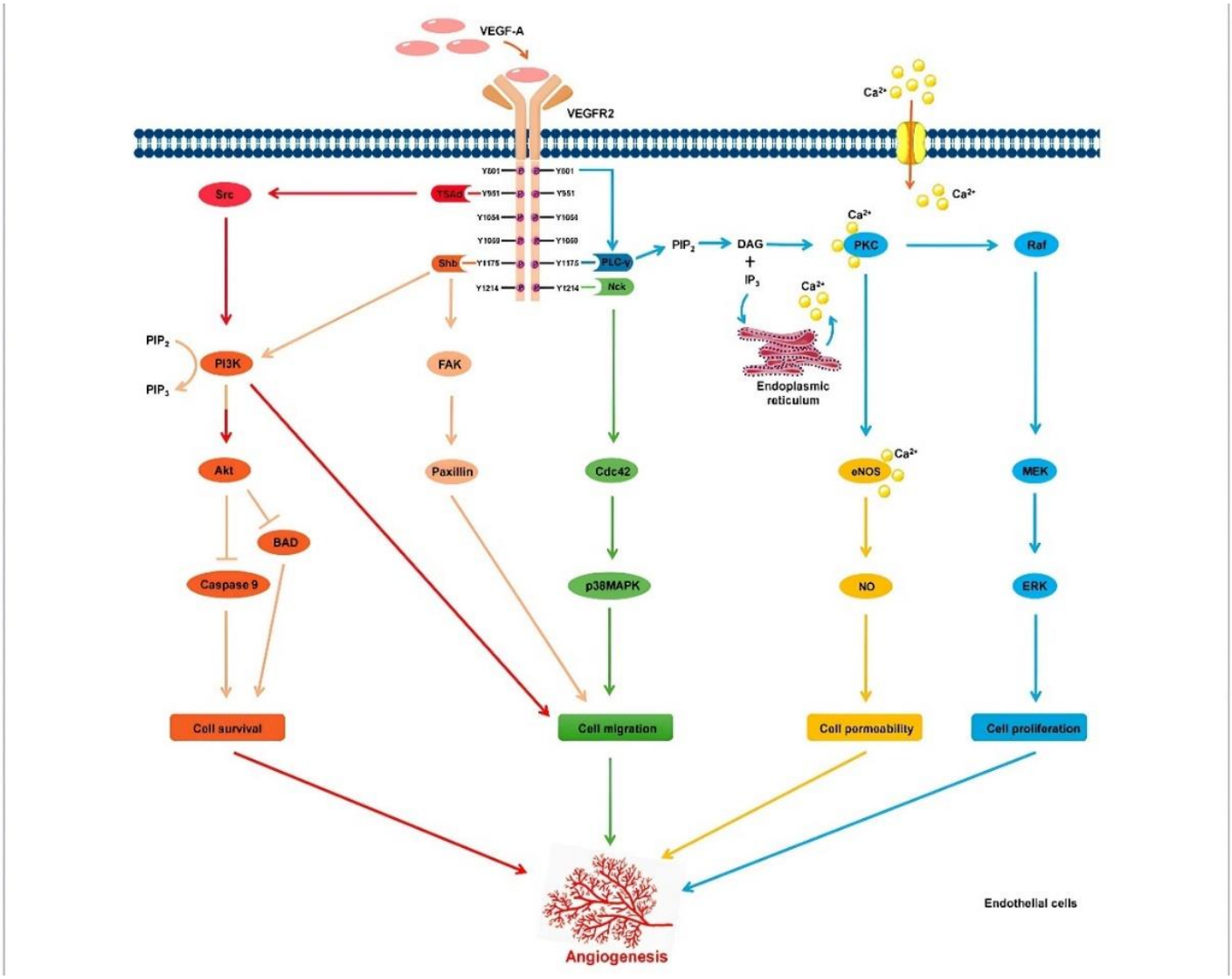

Figure 1. A schematic illustration of VEGFR-2 signaling pathways: When VEGF-A stimulates VEGFR-2, it leads to dimerization and autophosphorylation of particular intracellular tyrosine residues. This activation triggers downstream signal transduction pathways, resulting in the proliferation, migration, and survival of endothelial cells, as well as increased vascular permeability. (Source data: Jingjing Li *et al.* 2022) [43].

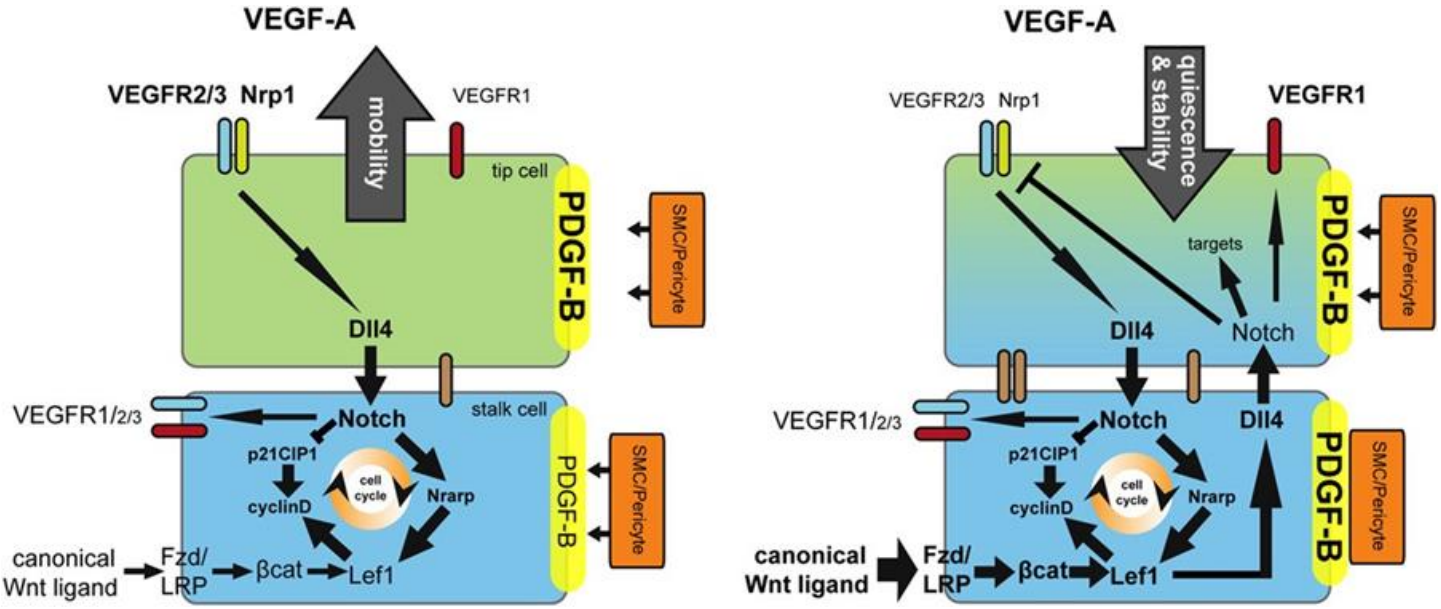

Figure 2. Various effects of Wnt/β-catenin signaling during vascular development. Left: Basal endothelial Wnt/β-catenin signaling during sprouting angiogenesis. In stalk cells, Notch signaling activation downregulates the cyclin-dependent kinase inhibitor p21^CIP1^, leading to cell cycle arrest. Nrarp upregulation promotes Lef1-dependent Wnt/β-catenin signaling, encouraging cell cycle progression despite Notch signaling. However, Notch signaling in stalk cells also reduces the expression of VEGFR-2, VEGFR-3, and neuropilin-1 (Nrp1) while increasing the decoy receptor VEGFR-1. Additionally, PDGF-B is highly expressed in tip cells, facilitating the recruitment of SMCs and pericytes. Right: Effects of sustained Wnt/β-catenin signaling during sprouting angiogenesis. Prolonged Wnt/β-catenin signaling upregulates its target gene Dll4, enhancing Notch signaling and promoting a stalk cell gene signature in adjacent tip cells by functionally downregulating VEGFR-2, Nrp1, and VEGFR-3, and upregulating VEGFR-1. This process fosters vascular quiescence and stability. Vascular stability is further supported by the Wnt targets claudin-3 and PDGF-B, which increase junctional stability and the recruitment of SMCs and pericytes, respectively. (Source data: Marco Reise and Stefan Liebner 2012) [44].

Inflammation

It is unclear exactly how immune cells, fibroblasts, vascular cells, and cardiomyocytes contribute to the inflammatory response during infarct recovery, as well as how each of these cell types plays a role in triggering different inflammatory pathways. Local myocardial cells detect tissue death following an infarction and initiate a process of inflammatory reaction, which draws in different subsets of circulating leukocytes.

Cardiomyocytes

The primary source of the post-infarction inflammatory reaction is apoptotic heart muscle cells. Because they emit molecules known as damage-associated molecular patterns, or DAMPs, into the infarcted area. Furthermore, in response to stimuli like TLR ligands, ROS or IL-1, Additionally, cardiomyocytes that remain in the ischemic border zone may initiate inflammation by generating and releasing cytokines. Intercellular adhesion molecule-1 (ICAM-1) is expressed by live cardiomyocytes in the infarct border zone, according to immunohistochemical investigations and in situ hybridization tests. These cells may also produce chemokine's and cytokines. It is yet unknown, though, exactly how inflammatory mediators produced by cardiomyocytes contribute to the development and spread of post-infarction inflammation [55].

Endothelial Cells

The most prevalent noncardiomyocytes in adult mammals, endothelial cells, make up a sizable portion of the heart's highly vascularized mass. Leukocyte extravasation the need for blood to flow into the area of injury it has been established that following myocardial infarction, endothelial-specific activation of the transcription factor forkhead box O4 stimulates influx of neutrophil into the infarcted heart. Endothelial adhesion molecules are quickly upregulated with the release of DAMPs [56] by dying cardiomyocytes, which starts sticky contacts with active leukocytes. Weibel-Palade bodies [57] contain P-selectin, which is quickly mobilized, while ischemia endothelium has elevated levels of E-selectin. Selectins bind to their leukocyte ligands on the endothelial surface once they are expressed, ensnaring monocytes and neutrophils assisting in their rolling along the venular endothelium. Activated vascular cells additionally function as an important supply of chemokine's and cytokines [58].

Neutrophils

Neutrophils are the first immune cells to enter the infarcted heart in response to a number of stimuli, such as DAMPs, cytokines, chemokine's, intrinsic lipid-mediated responses like prostaglandin E2 and leukotriene B4, histamine, and complement components [59]. Reperfusion speeds up and intensifies their penetration into the infarct, which is mostly focused in the border zone. The stimulation of adhesive contacts between leukocytes and endothelial cells is necessary for the extravasation of neutrophils [60] in the infarcted heart. The active endothelium catches circulating neutrophils carrying selecting ligands, which cause them to roll along the endothelial layer. Rolling neutrophils identify chemokine's attached to glycosaminoglycans on the surface of endothelial cells during this process. Leukocyte integrin's [61] undergo conformational changes as an outcome of associations between the expressed CXCR2 receptor and CXC chemokine's on neutrophils, strengthening sticky contacts and leading to the arrest and adhesion of neutrophils to the endothelial surface. Multiple experimental findings suggest that leukocyte firm adhesion is primarily reliant on neutrophil integrin's such as macrophage-1 antigen (Mac1) and lymphocyte function-associated antigen 1 binding to endothelial intercellular adhesion molecules. Then, neutrophil transmigration takes place as leukocytes actively move in the path of microvascular relationships before moving across basement membrane regions with low expression levels of matrix proteins [62].

Lymphocytes

Numerous reports from big animal and rodent models [63] of myocardial infarction (MI) attest to the early infiltration of lymphocyte subsets into the infarcted heart. Research using a rat model [64] of MI showed that after the infarction, cytotoxic T lymphocytes were activated, and results obtained there was evidence *in vitro* that these cells could be harmful to healthy cardiomyocytes [65]. It is unclear, therefore, if T cell infiltration leads to the progression of ischemia injury in vivo. According to recent data, some lymphocyte subpopulations might be quite important orchestrating role in the inflammatory response. Zouggari *et al.* showed that B cells are essential for initiating the inflammatory cascade because they facilitate the mobilization of proinflammatory Ly6Chi monocytes by genetic and antibody-mediated depletion techniques [66].

Monocyte subpopulations

There are two different waves of monocyte recruitment that have been found during myocardial infarction healing. Firstly, proinflammatory Ly6Chi monocytes are recruited early, thanks to the MCP-1/CCR2 axis being activated [67]. The resolution of the post-infarction inflammatory response may thus be facilitated by the selective recruitment of anti-inflammatory monocyte subpopulations at a later stage. Elevated levels of IL-1 within the infarct area may cause infiltrating monocytes to respond proinflammatory in the early hours after the infarction. Notably, monocytes that invade the infarcted myocardium come from the spleen as well as the bone marrow. The spleen is a significant source of mononuclear cells that can be quickly distributed to inflammatory areas [68].

Fibroblasts

Even in the absence of injury, cardiac fibroblasts are plentiful in the adult mammalian heart. They usually remain in a quiescent condition, where they may help to maintain the extracellular matrix network [69]. Damage-associated molecular patterns (DAMPs) can, however, activate fibroblasts and cause them to release large amounts of chemokine's and inflammatory cytokines. Fibroblasts may react to reactive oxygen species (ROS) and interleukin-1 (IL-1) in the setting of myocardial infarction, changing into a proinflammatory phenotype and becoming a significant source of chemokine's and cytokines. The exact role of fibroblasts is still unknown, though, because a number of other cell types can also activate proinflammatory responses during the early stages of infarct recovery [70]. The activity throughout the duration of the inflammatory phase of heart repair fibroblasts inhibits the expression of Actin makes muscles α-smooth and postpone the conversion of fibroblasts into myofibroblasts, thus promoting a phenotype associated with matrix degradation [71].

mi-RNA

In recent years, microRNAs (miRNAs) have gained prominence as key regulators of the post-transcriptional expression of genes [72], particularly in cardiovascular biology and post-myocardial infarction (MI) angiogenesis. For instance, miR-92 has been discovered as a modulator of integrin-α5 expression in endothelial cells, which regulates post-MI angiogenesis [73]. In a similar vein, human miR-424 and its equivalent in mice, miR-322 are upregulated in response to hypoxia, indirectly facilitating stabilization of HIF-1α, thus promoting angiogenesis following ischemic events [74]. MiR-100 has been identified as capable of inhibiting angiogenesis by suppressing the expression of Rapamycin Vertebrate Target in Ischemic Tissues. Additionally, several other miRNAs, including miR-126 [75], miR-503 [76], and miR-24 [77], are known to regulate post-ischemic angiogenesis, underscoring the significance of these molecules in the process of neovascularization following myocardial infarction. Targeting miRNAs for after MI, therapeutic angiogenesis may present a viable substitute, given the technical feasibility of miRNA supplementation or inhibition [78].

Reactive Oxygen Species (ROS): Regulation of angiogenesis

Both a cause and an effect of the control of normal or abnormal angiogenesis might be oxidative stress [79]. In a recent study, superoxide dismutase's mitochondrial antioxidant isoform was precisely overexpressed in

endothelial cells using a unique conditional binary transgenic mouse model. In a mouse model of myocardial infarction, this study showed that these mice showed enhanced arteriolar density and coronary capillary in the post-MI ischemic zone in addition to better left ventricular performance [80]. In coronary ECs, a targeted reduction in ROS within the mitochondria of endothelial cells (ECs) induced the biogenesis of mitochondrial complex I and upregulated the expression of proteins linked to oxidative phosphorylation pathways, including COX6A1, NDUFA9, NDUFB1, NDUFB3, NDUVB7, and NDUVV3 [81]. These findings ultimately promoted the development of coronary angiogenesis. Earlier research, on the other hand, revealed that minimum levels of ROS appeared to increase the production of growth factors and cytokines, including VEGF, via HIF-1α in the damaged myocardium, suggesting that regulated oxidative stress could be advantageous for angiogenesis during tissue repair [82]. By controlling cell survival, proliferation, and EC apoptosis, this promoted angiogenesis. Notably, VEGF can cause NADPH oxidase, namely the Nox2 subunit, to produce ROS in ECs. As a result, mice lacking Nox2 revealed a marked suppression of genes involved in angiogenesis and experienced a poorer prognosis after myocardial infarction compared to control mice. These findings highlight the intricate regulation of angiogenesis in response to oxidative stress [83].

Ca^{2+} signaling in angiogenesis

As an essential second messenger, the Ca^{2+} ion controls a number of key functions of endothelial cells (ECs), such as angiogenesis, permeability control, proliferation, migration, and the production and release of vasoactive substances [84]. Numerous investigations have demonstrated the role of various cationic channels in angiogenesis, including store-operated Ca^{2+} (SOC) channels and transient receptor potential (TRP) channels. The use of transgenic mice and several research methodologies have confirmed these findings [85]. In particular, a multitude of studies have demonstrated the involvement of TRPC channels and SOC entry-related proteins, including Orai1 [86], Orai3 [87], SARAF [88], and STIM1 and 2 [89, 90], in the activation of endothelial cells and the process of angiogenesis. Their involvement in myocardial infarction (MI)-induced angiogenesis is yet unknown, though. Strong evidence suggests that proangiogenic growth factors, like VEGF, alter the signal transduction pathways that cause angiogenesis by raising intracellular Ca^{2+} levels via the activation of non-excitable Ca^{2+} channels. One week following the intervention in rats with MI, there was a notable rise in Orai isoforms and TRP channels in the peri-infarcted hearts [91]. One week after the intervention, rats with peri-infarcted hearts showed a large increase in Orai isoforms and TRP channels in the context of myocardial infarction (MI). With the use of $TRPC1EC^{-/-}$ animals lacking TRPC1 specifically in endothelial cells, a recent study examined the function of TRPC1 in post-ischemic angiogenesis. Reduced ejection fraction and fractional shortening showed that the heart function of these $TRPC1EC^{-/-}$ animals was more significantly compromised than that of TRPC1fl/fl mice. The infarcted regions of the hearts in $TRPC1EC^{-/-}$ animals exhibited a notable decrease in capillary density, as demonstrated by anti-CD31 staining. In addition, TRPC1fl/fl mice had improved cardiac performance after MI compared to $TRPC1EC^{-/-}$ mice because HIF-1α expression increased TRPC1 expression in primary mouse coronary artery endothelial cells. This enhancement was linked to lower infarct rates and higher capillary density reduced infarct size, and enhanced ejection fraction [92].

The role of Wnt signaling in angiogenesis

Wnts are potent angiogenesis-promoting agents, and the advancement of many disorders, including cancer, depends on their signaling pathways as well as normal development [93]. Cellular functions including proliferation, survival, differentiation, migration, and apoptosis depend on wnt pathways [94]. Wnt signaling is necessary for the development of multiple organ systems, such as the kidney, female reproductive tract, and placenta. The Wnt pathway is also essential for vessel remodeling and angiogenesis [95]. According to recent research, angiogenesis occurs in a variety of organs under both normal and pathological circumstances and is influenced by both canonical and non-canonical Wnt signaling pathways [96]. Vascular endothelial cells require both canonical and non-canonical wnt signaling, which is mediated by a number of regulators including R-spondin3 [97] and Fzd7 [98]. The transcriptional regulation of VEGF by Wnt/β-catenin signaling has been demonstrated, with seven TCF binding sites identified in the VEGF gene promoter. Additionally, defects in APC, which result in constitutively active β-catenin and Wnt signaling, can lead to the overexpression of VEGF [99]. Angiogenesis is driven and regulated by matrix metalloproteinases (MMPs) and interleukin-8, both of which are transcriptionally regulated by the β-catenin/TCF complex. Furthermore, new data suggests that the canonical Wnt ligands Wnt7a and Wnt7b can both trigger β-catenin-mediated signaling via Gpr124 (Figure 3) [100]. The role of SFRP family proteins has been demonstrated to regulate angiogenesis via regulating both canonical and non-canonical Wnt signaling [101].

The role of troponin in myocardial infarction

Troponins are regulatory proteins essential for the contraction of cardiac muscles. The detection of elevated troponin levels in the blood is a key diagnostic and prognostic tool for myocardial infarction (MI) [103]. This review explores the significance of troponins in the context of MI, including their biological function, diagnostic utility, and implications for patient management. The anti-angiogenic role and mechanism of troponin I remain unclear. Recent studies have suggested, that during

contractions of the muscle, the human troponin I receptor site suppresses actomyosin ATPase also contributes to its anti-angiogenic properties. This activity appears to be regulated by the down regulation of vascular endothelial growth factor expression, which in turn leads to reduced expression of intracellular adhesion molecule 1 and block the angiogenesis of the cardiomyocytes [104]. One important component of the thin thread that regulates the contraction of muscles is the cTn complex. There are three different versions of it: cTnC, which binds Ca^{2+}; cTnI, which prevents actomyosin from acting as an ATPase; and cTnT that interfaces with actomyosin. The cTn complex controls the contraction of cardiomyocytes by controlling the interaction between actin and myosin.

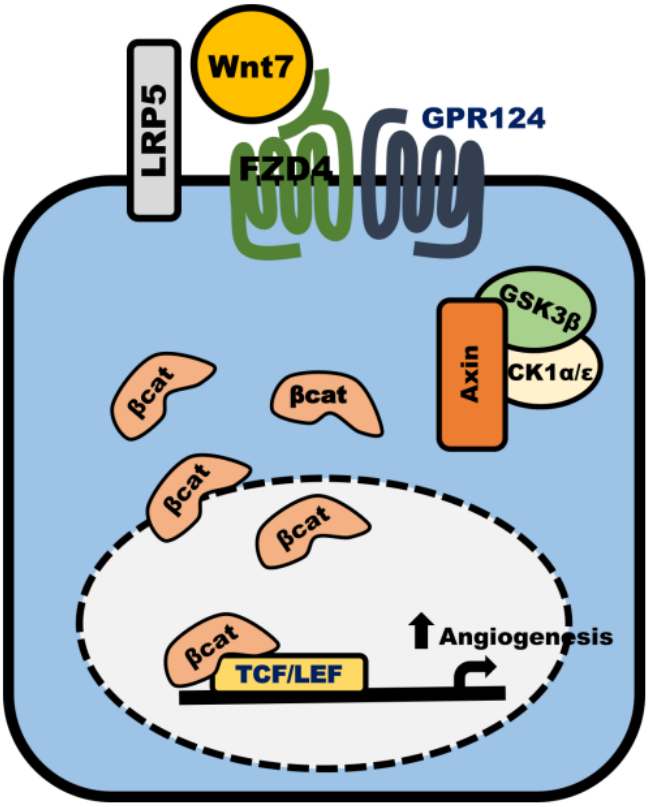

Figure 3. The Wnt7/FZD4/GPR124/LRP5 signaling cascade begins with the binding of Wnt7a/b to Fzd4, activating canonical Wnt/β-catenin signaling. GPR124 and LRP5 function as co-receptors, facilitating signal transduction that destabilizes the destruction complex (Axin, GSK3β, CK1α/ε). This stabilization of β-catenin permits its translocation to the nucleus, where it binds to TCF/LEF transcription factors, promoting vascularization and angiogenesis. (Source data: Jun Jun Olsen *et al.*) [102].

Biological function of troponin

Troponins, integral components of the contractile apparatus in skeletal and cardiac muscles, are composed of three subunits:

Troponin T (TnT): Attaches tropomyosin to the troponin complex.

Troponin I (TnI): Blocks the activity of actomyosin ATPase.

Troponin C (TnC): Binds calcium ions, facilitating muscle contraction.

Cardiac-specific troponins, cTnI and cTnT, are unique to the heart muscle and released into the bloodstream during myocardial injury, making them specific markers for cardiac damage.

Diagnostic role of troponin in myocardial infarction

The measurement of cardiac troponins is a cornerstone in the diagnosis of MI. Elevated levels of cTnI and cTnT indicate myocardial cell injury and necrosis. Key points include:

Early detection: After myocardial damage starts, troponins can be seen as early as two to four hours later, peaking between twelve and twenty-four hours later.

Sensitivity and specificity: When it comes to myocardial damage, troponins are more responsive and specific than other biomarkers like creatine kinase-MB (CK-MB).

Diagnostic criteria: According to current guidelines, a higher-than-99th percentile troponin level exceeding the maximum standard level, coupled with clinical evidence of ischemia, confirms the diagnosis of MI [105].

Challenges and future perspectives

Angiogenesis is an essential process in pathophysiological circumstances like tumour growth, diabetes, endometriosis, and ischemic heart disease, as well as physiological conditions like ovulation and wound healing [106]. Several attempts have been undertaken to determine the mechanics and contributing factors of angiogenesis. Determining the connection between the imbalance between pro- and anti-angiogenic factors and the pathophysiology of different diseases is a major challenge. Comprehending this correlation can facilitate the creation of therapies aimed at these detrimental pathways [107]. Another method for studying angiogenesis ex vivo is to culture aortic ring grafts in biological gels [108].

Conclusion

In the process of remodeling the heart, angiogenesis within the infarcted tissue has a vital role by assisting in the restoration of blood flow to the heart tissue. The heart must go through this process in order to recover and resume normal function. The modulation of intracellular Ca^{2+} content through ion channels and a number of well-orchestrated transduction pathways, including Notch, Wnt, and PI3K, control angiogenesis from preexisting endothelial cells (ECs) and endothelial progenitor cells (EPCs) based on strong data from conventional in vitro angiogenic techniques and experimental animals. Moreover, angiogenic pathways and the infarcted heart are significantly impacted by variables such hypoxia, VEGF and FGF family growth factors, nitric oxide synthase, inflammation, and miRNAs. This study provides an overview of the main angiogenic pathways and how they affect post-infarction myocardial angiogenesis, paying particular attention to the functions that growth factors like VEGF and FGF and endothelial nitric

oxide synthase play in angiogenesis. Furthermore, it offers insight into the signaling pathways that MI initiates, paying special emphasis to the functions of ROS control, Ca2+ influx, and miRNAs in endothelial cell activation and subsequent angiogenesis. This review emphasizes the dual role of troponin in both diagnosing myocardial infarction and inhibiting angiogenesis, underscoring its importance in cardiovascular pathology and potential therapeutic implications.

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Data availability
All data generated or analyzed during this study are included in this published article.

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