Abstract. Acute myocardial infarction (AMI) remains the main cause of mortality worldwide. Despite surgery and medical treatment, the non-regeneration of dead cardiomyocytes and the limited contractile ability of scar tissue can lead to heart failure. Therefore, restoring blood flow in the infarcted area is important for the repair of myocardial injury. The objective of the present review was to summarize the factors influencing angiogenesis after AMI, and to describe the application of angiogenesis for cardiac repair. Collectively, this review may be helpful for relevant studies and to provide insight into future therapeutic applications in clinical practice.

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1. Introduction

Acute myocardial infarction (AMI) is myocardial necrosis caused by acute and persistent ischemia and hypoxia in the coronary arteries (1). There is an urgent need for improved treatment strategies. The traditional treatment for AMI is mainly surgery or drug therapy, including thrombolytic therapy, percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) (2). These traditional treatment methods can save dying cardiomyocytes, decrease the area of infarction progression and delay myocardial remodeling. However, they do not promote myocardial cell regeneration, and the contractile ability of the scar tissue in the infarcted is limited; therefore, the myocardial contractile force is gradually reduced, causing myocardial fibrosis, arrhythmia and ventricular diastolic dysfunction, leading to advanced congestive heart failure (3). Due to the limits of traditional methods, significant research has been devoted to post-infarction repair. Angiogenesis is essential for correct healing post-infarction. The blood supply of the cells in the infarcted area gradually decreases, which restricts oxygen transfer, nutrient absorption and removal of metabolic waste, and the cardiomyocytes gradually become necrotic; therefore, restoring the blood supply to the infarcted area is a favorable repair method (4). The present review outlines the progress of current research on angiogenesis in myocardial infarction repair, including the main factors affecting angiogenesis and the therapeutic methods.

2. Regulation of angiogenesis after AMI

Angiogenesis is the formation of new blood vessels based on previous vasculature. The formation of blood vessels starts with the sprouting of endothelial cells (ECs), which adhere to each other and are connected to the extracellular matrix (ECM), followed by hydrolytic remodeling of ECM in the presence of various enzymes. Hydrolytic remodeling of ECM refers to the continuous process of decomposition and synthesis of the ECM under the action of various enzymes (5). There are three main types of ECs, namely tip, stalk and phalanx cells (6). Tip and stalk cells are located at the sprouting tip of blood vessels and can secrete a variety of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), fibroblast growth factor and platelet-derived growth factor (PDGF) (7). There are numerous factors that affect the formation of blood vessels.

Factors driving angiogenesis after AMI. After AMI, the repair process of cardiac injury begins with the inflammatory phase. This is characterized by the activation of natural immune pathways and the recruitment of inflammatory leukocytes to remove dead cells from the wound, which involves the complement system, reactive oxygen species and the participation of various chemokines (8). Some other cells are also activated and involved in repair, such as macrophages, fibroblasts, ECs, lymphocytes and other immune cells (9).
Macrophages transfer to a pro-angiogenic phenotype after Annexin A1 treatment (10). Moreover, hyaluronic acid (HA) is a major component of the ECM, and is a non-protein extracellular molecule. HA oligosaccharides (α-HA; <10 saccharides units) is a partially degraded fragment of high molecular weight HA. Cardiac α-HA improves polarization of M2 macrophages, and prevents the inflammatory response caused by neutrophils and accelerates restitution of myocardial function (11).

Fibroblasts are the main cellular component of myocardial injury. They are derived from embryonic mesenchymal cells and can produce collagen and other proteins. Fibroblasts have multiple phenotypes, and some populations express fibroblast-specific protein (FSP)1 and α-smooth muscle actin (α-SMA). FSP1-positive fibroblasts contribute to angiogenesis and repair, and their reparative effect is greater than that of α-SMA-positive fibroblasts (12). Moreover, as infarction progresses, fibroblast function transforms from inflammation to angiogenesis (13).

Vascular ECs are simple squamous epithelial cells that line the inner surface of blood vessels. Hypoxia is a potent angiogenic stimulus during cardiac repair (Fig. 1). Hypoxia transcriptionally upregulates angiogenic integrins in microvascular ECs and promotes the migration and tube formation of HMEC-1 cells (14). Furthermore, hypoxia can induce a large number of vascular-related signaling pathways in ECs to upregulate and promote angiogenesis, such as hypoxia-inducible factor (HIF)-1 (15). HIF-1α binds to the promoter of Twist1 to activate Twist1 transcription and regulate endothelial-mesenchymal transition (16). It has been reported that neutrophils and mast cells promote angiogenesis (17,18). Furthermore, neutrophil extracellular traps produced by dead neutrophils promote inflammatory angiogenesis in vivo and in vitro (19). It has also been shown that mast cells can release some pro-angiogenic cytokines, such as PDGF and VEGF (20).

There are several molecules involved in angiogenesis. Under the conditions of ischemia and hypoxia, numerous cells secrete additional pro-angiogenic factors. For instance, VEGF plays an important role in angiogenesis. VEGF is upregulated by HIF-1α and regulates angiogenesis by binding to a specific receptor, VEGFR, and soluble VEGFR1 (sVEGFR1) is secreted out of the cell to participate in the sprouting process of new blood vessels (21). HIF-1α and VEGF are closely associated with Notch signaling (22). Notch and Notch ligand δ-like (Dll4) signaling is related to angiogenesis (23). VEGF activates the membrane-bound ligand Dll4 of tip cells and transmits Dll4 signals to nearby ECs (24). The angiogenin family and hepatocyte growth factor (HGF) also contribute to angiogenesis. HGF/Met induces the proliferation and migration of ECs via Ras-related C3 botulinum toxin substrate 1 activation. In fibroblasts, HGF/Met antagonizes the actions of TGF-β1 and angiotsensin II, thereby preventing fibrosis. HGF/Met also influences the inflammatory response of macrophages and the immune response of dendritic cells, indicating their protective function against atherosclerotic and autoimmune diseases (25). In addition, recombinant protein has been widely used as a molecule to promote angiogenesis. For instance, the recombinant human PDGF antibody promotes the repair of cardiac wounds after myocardial infarction by changing the mechanical mechanism of infarction scarring, thus improving cardiac function, reducing ventricular arrhythmia and improving survival rate (26).

Factors inhibiting angiogenesis after AMI. There are fewer anti-angiogenic than pro-angiogenic factors, including cells, secreted factors and recombinant proteins. M1-like macrophage-derived exosomes suppress angiogenesis in a myocardial infarction microenvironment, which may be related to microRNA (miRNA/miR)-155 in exosomes (27). Moreover, 11β-hydroxysteroid-1 in macrophages can inhibit inflammatory angiogenesis (28). VEGF-A165b is an anti-angiogenic factor that as has been identified as a regulator of vascularization (29). In addition, the anti-angiogenic pigment epithelium-derived factor suppresses angiogenesis in the human heart by inhibiting VEGF-induced sprouting (30). Similarly, Ly6/Plaur domain-containing 1 is a novel antiangiogenic factor derived from human cardiac fibroblasts, which suppresses EC network formation (31). Furthermore, Wnt/β-catenin signaling plays an important role in angiogenesis. The transcription factor BTB and CNC homology 1 impairs angiogenesis after ischemic injury by suppressing Wnt/β-catenin signaling (32). It has also been shown that recombinant human IL-24 can suppress tumor angiogenesis (33,34). However, to the best of our knowledge, IL-24 has not been studied in the repair of myocardial injury. IL-12 is also an anti-angiogenic factor that is mainly produced by CD11b(+) monocytes in mice after MI. In addition, IL-12 affects the formation of blood vessels in the yolk sac, which can retard embryonic development (35).

3. Application of angiogenesis for cardiac repair

Mesenchymal stem cells (MSCs). MSCs arestromal cells that have self-renewal ability and show multilineage differentiation. MSCs can be isolated from a variety of tissues, such as umbilical cord, endometrial polyps, menses blood, stem cells, bone marrow and adipose tissue (36,37). Due to their powerful function and easy access, MSCs have been widely used by researchers in recent years, especially in the study of ischemic heart disease (38). For example, placenta-derived MSCs can be used to promote therapeutic angiogenesis. Such MSCs can differentiate into vascular-like cells and secrete some pro-angiogenic cytokines and protease expression mechanisms. Adipose-derived stem cells promote utilization of the plasminogen activator/plasmin axis by ECs as the primary means of vessel invasion and elongation in fibrin (40). MMPs serve a purpose in regulating capillary diameter and possibly in stabilizing the nascent vessels (40). MMPs also play an important role in the differentiation of stromal stem cells (41). MSCs can regulate expression of MMP9 (42). Therefore, MSCs and MMPs may have important roles in angiogenesis after AMI. In addition to the role of MSCs, it has been proposed that the functional benefits observed after MSC transplantation in experimental models of tissue injury may be associated with the secretion of soluble factors acting in a paracrine fashion (43,44). Moreover, stem cells also play an important role in the repair of other tissues. MSCs derived from the umbilical cord can relieve limb ischemia via the formation of blood vessels in mice (45).
It has also been shown that human neural stem cells promote the proliferation of endogenous neural stem cells and enhance angiogenesis in the brain of ischemic rats (46).

Exosomes. Exosomes are small extracellular vesicles that are only 50-150 nm in diameter, surrounded by a lipid bilayer membrane and contain components derived from their original cells (47). Exosomes have a relatively rich source, existing in various tissues and cells throughout the body, such as embryos, adipose tissue and bone marrow (Fig. 2). The extraction methods for exosomes include ultracentrifugation, immunoprecipitation, size-based isolation.
enhanced the repair of myocardial infarction in a rat model. It was found that tissue inhibitor of metalloproteinase-2-modified repair of injury sites through exosome modification.

Furthermore, it has been shown that exosomes from the serum of patients with type 2 diabetes can hinder the process of injury repair, and miR-322-modified, cardiac-progenitor-cell-derived exosomes provide protection against MI via Nox2-dependent angiogenesis (69). Moreover, exosomes derived from miR-146a-modified adipose-derived stem cells can downregulate early growth response factor 1 to attenuate AMI-induced myocardial damage (70).

In addition, with controlled-release properties, drug-carrying nanoparticle (NP) systems are expected to enhance cardiac protection in patients with cardiac ischemic events. NPs can provide sustained and precise exposure of the infarcted area through direct intramuscular or intravenous injection with drugs with active targets (71). There are also exosomes from MSCs modified with mononuclear cell mimics, which have a high targeting efficiency for injured myocardium and promote endothelial maturation during angiogenesis (72). In cardiac repair, NPs mainly play a role by modifying exosomes and acting as nano drug delivery systems (73).

Some novel ideas and methods have emerged from research into repair of other organs. By constructing a CD9-HuR protein, a new exosome was designed, which has a strong ability to enrich specific RNAs, effectively delivering RNA into cells, targeting genes in vivo and in vitro, and treating liver disease in a mouse model (74). Researchers from Switzerland have reported a series of synthetic biology-inspired control devices that are known as EXOsmal Transfer Into Cells devices, which serve to enhance these steps, enabling efficient exosomal mRNA delivery without the need to concentrate exosomes. This design of exosomes reduces the neurotoxicity and neuroinflammation of Parkinson's disease via the delivery of therapeutic catalase mRNA (75).

Biomaterials. In recent years, additional research has focused on repair by using biomaterials (76). Compared with traditional cell therapy, biomaterials have more advantages, such as being degradable, easy to obtain and free to regulate the repair process. Biomaterials are mainly divided into natural and artificial synthetic materials. Natural materials mainly refer to the various components of mammalian ECM, such as collagen, fibrinogen, Matrigel and gelatin. Natural materials also include some ingredients extracted from plants or animals, such as chitosan and cellulose. Artificial synthetic materials are easier to obtain and are more plastic (77).

Biomaterials can be combined with cells or factors to promote wound healing (78,79) (Fig. 3). Biomaterials with loaded stem cells and immunomodulating and tissue-regenerating factors can be used to ameliorate inflammation, improve...
angiogenesis, reduce fibrosis and generate functional cardiac tissue (78). For example, the encapsulation of VEGF in poly-lactic acid glycolic acid NPs improves the therapeutic efficacy of VEGF and promotes angiogenesis (79). Liu et al (80) reported that co-transplantation of chitosan thermosensitive hydrogel and bone-marrow-derived MSCs can ameliorate the inflammatory response and promote cardiac functional recovery. Citrate hydrogels can be injected as an angiogenic biomaterial to improve cardiac function after AMI and increase the number of blood vessels in the infarcted area (81). In addition to the injectable biomaterials, some researchers have developed thermal plastic poly (glycolic acid) surgical sutures and mussel-inspired conductive particle adhesion into highly elastic, conductive spring-like coils. The polypyrrole-coated biospring acts as an electrode and is assembled into a solid-state supercapacitor. After being injected through a syringe needle (0.33-mm inner diameter), the tangled coils form an elastically conductive three-dimensional (3D) network to modulate angiogenesis (82). Additionally, a cardio-patch has been created with adipose-tissue-derived progenitor cells seeded into an engineered bioimplant consisting of 3D bioabsorbable polycaprolactone scaffolds filled with a peptide hydrogel. This treatment decreases fibrosis, limits infarct scar expansion and reduces postischemic ventricular deformity (83). Similarly, the use of chitosan/calcium silicate heart patches showed increased angiogenesis in rats after myocardial infarction (84). The alginate scaffold modified with RGDFyK (Arg-Gly-Asp-D-Phe-Lys) peptide can be used for cell transplantation and cardiac neovascularization (85). It is also interesting to note that by changing the stiffness of hydrogel, VEGF secretion of MSCs can be improved, thus further promoting vascular formation (86).

In addition to using biomaterials to generate new blood vessels, artificial blood vessels have already been constructed to treat injuries. The raw materials for manufacturing artificial blood vessels are polyester, polytetrafluoroethylene, polyurethane and natural mulberry silk. Artificial blood vessels supported by spider silk can be constructed in vitro (87). Moreover, small-diameter artificial blood vessels can promote in situ endo-endothelialization (88). Remarkably, artificial blood vessels are rarely used in cardiac injury. Therefore, small-diameter artificial blood vessels are expected to be applied in cardiac repair in the future.

**Biological factors.** Some biological factors play a role in the repair of AMI, and an increasing number were applied in recent years (89). Biological factors are partly obtained from artificial synthesis. SDF-1 is a distinctive cytokine that can protect the heart from ischemic injury. Annexin V can accurately detect dead cells in the body. SDF-1 and Annexin V in combination can reduce apoptosis, increase angiogenesis, reduce infarcted area and improve heart function in mice after AMI (90).

Some small-molecule hormones also play an important role in injury repair. For instance, β-estradiol promotes recovery after AMI by enhancing the homing and angiogenesis of bone-marrow-derived EPCs by enhancing estrogen receptor/SDF-1/C-X-C motif chemokine receptor 4 cross-talk (91). Hormones also promote myocardial repair after infarction. Dihydrotestosterone induces angiogenic factors and helps to nest MSCs into heart tissue (92). Furthermore, irisin plays an anti-MI role by promoting angiogenesis (93).

A number of other small molecules have restorative and therapeutic effects. New collagenous stromal elements reduce left ventricular dilatation after MI by promoting scar formation and angiogenesis (94). Enhanced extracellular sulfatase with

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**Figure 3.** Application of biomaterials for cardiac repair. MSCs or pro-angiogenic factors can be combined with hydrogels to form biomaterials with improved repair performance, and can be targeted to the site of heart injury by injection, implantation and other ways to form new blood vessels. MSC, mesenchymal stem cell.
heparan sulfate enhances the bioavailability of VEGF during ischemic heart repair, thereby promoting angiogenesis (95). circRNAs are also involved in myocardial repair. After AMI, adeno‑associated‑virus‑9‑mediated circ_fibronectin type III domain containing 3B overexpression in the heart can reduce myocardial apoptosis, enhance the formation of new blood vessels and improve left ventricular function (96).

Some Chinese herbal extracts also play an important role in injury repair. For example, Catalpa extract from traditional Chinese medicine has been proven to promote angiogenesis and VEGF expression in ischemic myocardium (97). Chinese medicine GeGen‑DanShen extract protects against myocardial ischemic injury by promoting angiogenesis via the upregulation of the VEGF/VEGFR2 signaling pathway (98). Moreover, the Ginkgo biloba extract can suppress the inflammation- and apoptosis-regulating p38 MAPKs, NF‑κB and Bcl‑2 signaling pathways to prevent AMI (Fig. 4) (99).

### Gene therapy
Gene therapy is an emerging technology. Elabela (ELA) is a newly discovered hormone peptide containing 32 amino acids, which is known to regulate endodermal differentiation and cardiovascular development (100). Jin et al (101) successfully constructed a p‑adeno‑associated‑virus‑9‑mediated circ_fibronectin type III domain containing 3B overexpression plasmid using molecular cloning technology. Their results showed that this fusion plasmid can promote angiogenesis after MI (101). Gene and stem cell therapies also hold promise for the treatment of ischemic cardiovascular disease. The combination of human cord blood CD34(+) cells and Ang1 and VEGF genes promotes angiogenesis and reduces infarct size (102). Genetic engineering technology is also widely used to modify cells. FOXO transcription factors can modulate endothelial gene expression and function (103). Human vascular ECs can be functionally enhanced by engineering them to express an activated form of FOXO3 (104). Heme oxygenase (HO)‑1 is a cytoprotective, pro‑angiogenic and anti-inflammatory enzyme. Human placental MSCs modified with HO‑1 can promote placental angiogenesis by improving the balance of angiogenic factors (105). In ischemic skeletal muscle, human adipose‑derived stromal cells expressing VEGF165 can promote angiogenesis (106). Clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 has become a powerful technology to modify cells. Several studies have used CRISPR/Cas9 to edit cells to promote injury of tissues or organs. Deletion of enhancers and long non‑coding RNAs by CRISPR/Cas9 promotes significant changes in VEGFA and VEGFC expression in ECs (107). Moreover, CRISPR/Cas9 gene therapy based on TGF‑β1 alleviates radiation‑induced lung injury (108). Although CRISPR/Cas9 is rarely used in cardiac repair, it can be expected in the future. The application of MSCs, exosomes, biomaterials, biological factors and gene therapy in angiogenesis for cardiac repair was summarized in Table I.

### 4. Discussion
Promoting angiogenesis in the infarcted area is the key to the treatment of sequelae of AMI. Restoring the blood supply...
to this area can effectively reduce the area of cardiac tissue necrosis, which in turn can improve cardiac function and quality of life (109). Although traditional treatments such as PCI and CABG have numerous advantages, there are also several complications that are difficult to overcome (110). The common complications of CABG include postoperative bleeding and acute coronary artery occlusion, which can lead to severe or even critical conditions (111).

By contrast, the new therapeutic methods mentioned in this review have greater repair potential. MSCs have superior therapeutic effects, low antigenicity, wide application and rich sources. Furthermore, the safety of MSCs has been demonstrated in clinical trials (112). Nevertheless, some of the problems with treatment with MSCs also need to be resolved. For example, MSCs are easily differentiated, heterogeneous and diverse in large-scale production. Furthermore, MSCs easily die when transplanted into the body and, in cases, cannot adapt to the microenvironment (113). In response to these problems, further research and development of new technologies and methods are required to achieve precise and efficient repairs.

Exosomes have the advantages of being more stable, capable of mass production, controllable and easy to store. Unlike MSCs, exosomes can maintain biological activity for a long time in vitro, thereby overcoming the short-term apoptotic characteristics of MSCs. In addition, exosomes carry more diversified information, which can be used for early diagnosis, relapse monitoring, and drug resistance monitoring (114). Even so, numerous problems still need to be resolved. For instance, the separation and purification technology of exosomes is not yet mature, and there is no unified standard for separation and analysis, to the best of our knowledge. Otherwise, the identification of exosomes as disease markers still depends on a large number of clinical trials (115).

Biomaterials have been applied clinically for a long time. He et al (116) were the first to achieve a major breakthrough in the clinical study of injectable scaffold materials combined with stem cell transplantation for the treatment of ischemic heart disease, and proved its clinical safety and feasibility. Although biomaterials have benefits, there are still several problems, such as toxicity, cost and effectiveness. The application prospects for biological factors should not be underestimated. Several biological agents have already been applied clinically but there are also some drawbacks, such as adverse effects, easy inactivation and cost (117).

Biological factors and gene therapy also play an important role in cardiac repair. Biological factors are more effective, but at the same time, they have the problems of short half-life and easy inactivation. Therefore, new technology is required to resolve these problems. After >10 years of development, research on gene therapy has made significant progress. However, it is still in the early stage of clinical trials, and cannot guarantee stable efficacy and safety. Despite the numerous obstacles, the trend towards gene therapy is encouraging.

In view of all previous studies on angiogenesis in AMI, it remains necessary to explore the therapeutic mechanisms mediated by these novel methods, especially when the molecules that play an effective role in the disease have not yet been identified. Although MSCs and exosomes face several challenges in industrialization, their functional research, diagnosis and treatment applications in some diseases, such as AMI, have shown potential. Furthermore, there is still much to explore in relation to drug carriers and regenerative medicine and treatment, with broad growth potential in the future.

Figure 4. Biological factors for the treatment of myocardial infarction. The figure mainly shows two types of biological factors for cardiac repair. The small molecules listed are SDF-1, Annexin V, β-estradiol, irisin, heparan sulfate, dihydrotestosterone and collagenous stromal elements. Catalpa, GeGen-DanShen extract and Ginkgo biloba extract are all Chinese herbal extracts.
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The authors declare that they have no competing interests.

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