Targeting angiogenesis in myocardial infarction: Novel therapeutics (Review)

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Received August 25, 2021; Accepted November 1, 2021

DOI: 10.3892/etm.2021.10986

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.

Contents

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).

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Key words: angiogenesis, acute myocardial infarction, vascular endothelial cells, exosomes, mesenchymal stem cells

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 (o-HA; <10 disaccharides units) is a partially degraded fragment of high molecular weight HA. Cardiac o-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 (Dll)4 signaling is related to angiogenesis (23). VEGFA 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 angiotensin II, thereby preventing fibrosis. HGF/M*et al*so 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 are stromal 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 provascular factors to promote angiogenesis. These cytokines include VEGF, basic fibroblast growth factor, IL-6, IL-8, HGF, insulin-like growth factor (IGF) binding protein (IGFBP)2, IGFBP3 and IGFBP6. These factors generate blood vessels by activating key provascular-related signaling pathways (39).

MSCs from fat and bone marrow promote angiogenesis via unique 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).

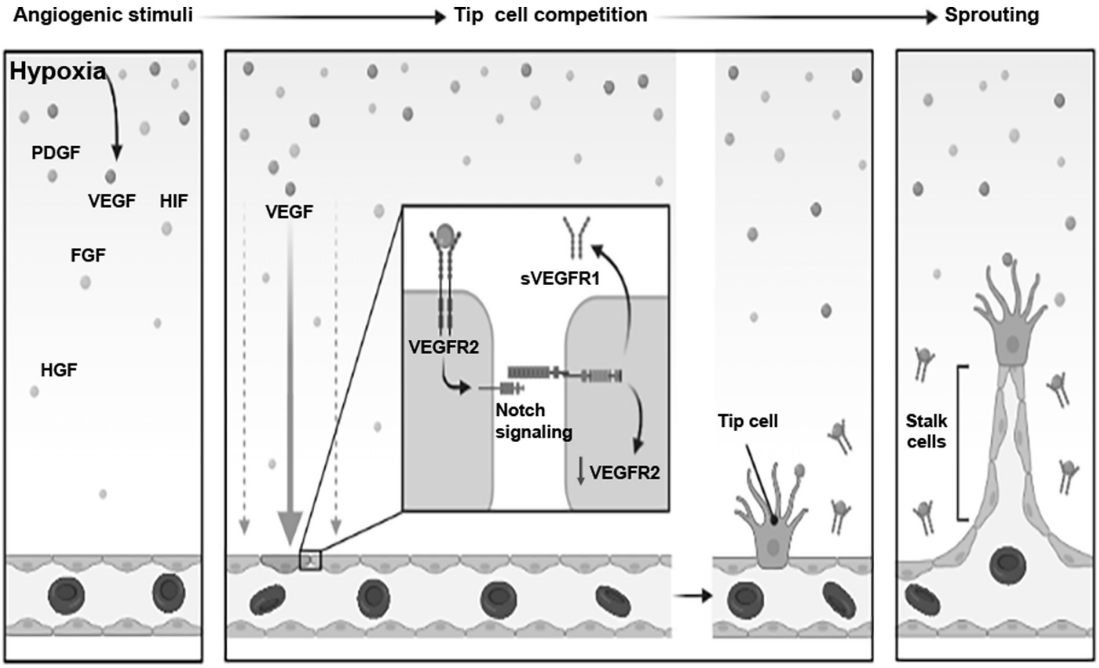

Figure 1. Hypoxia stimulation can produce a variety of pro-angiogenic factors. Among them, VEGF can bind to VEGFR2 of endothelial cells via the Notch signaling pathway to downregulate VEGFR2 and secrete sVEGFR1. Moreover, endothelial cells preferentially transform into Tip cells and combine with Stalk cells to form endothelial cells sprouting process. sVEGFR1, soluble VEGFR1; HIF, hypoxia-inducible factor; FGF, fibroblast growth factor receptors; HGF, hepatocyte growth factor.

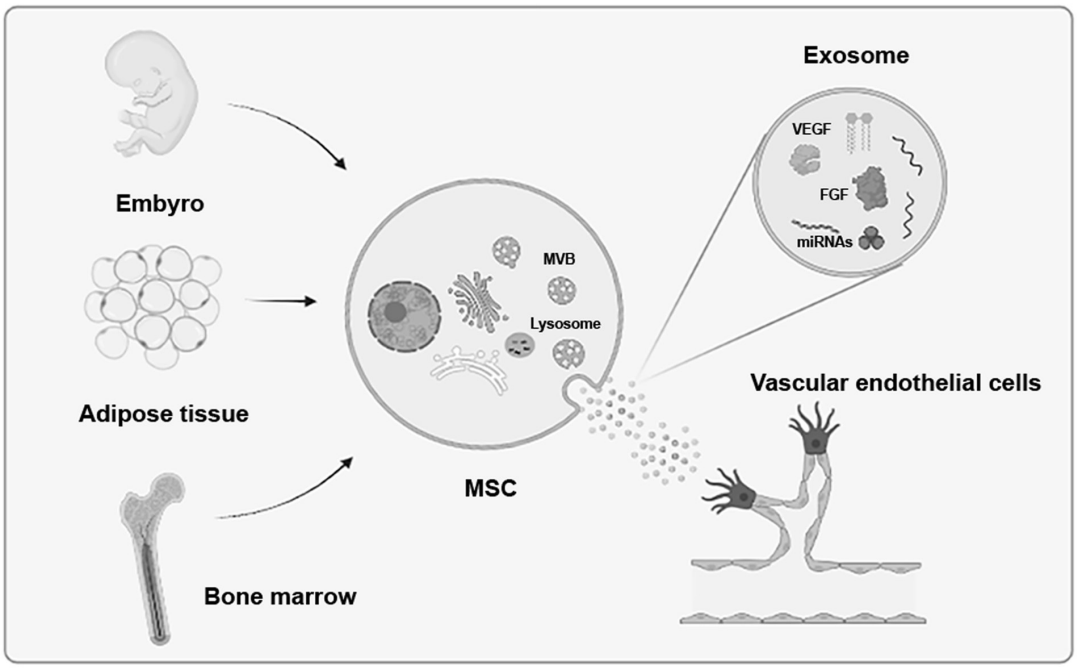

Figure 2. Main sources and packaging release process of exosomes. Exosomes are mainly derived from MSCs isolated from embryos, adipose tissue and bone marrow. The cell membrane invades to form MVB. Some of the multivesicular bodies are degraded by lysosomes through the Golgi apparatus, and some are fused with the plasma membrane and released outside the cell. Exosomes contain several angiogenic molecules, including miRNAs and proteins, such as VEGF and FGF. MSC, mesenchymal stem cell; miRNA, microRNA; FGF, fibroblast growth factor receptors; MVB, multivesicular bodies.

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 ultra-centrifugation, immunoprecipitation, size-based isolation

techniques and commercial rapid extraction reagents. The most widely used methods are ultracentrifugation and rapid extraction reagents (48). These methods have both advantages and disadvantages, and thus the appropriate method to extract exosomes should be selected according to the research needs. Another important point is the identification of exosomes, and the quality of exosomes plays a crucial role in research (49). As early as 2014, the International Association of Extracellular Vesicles proposed that the identification of exosomes can be divided into three levels: Transmission electron microscopy (TEM), nanosight particle size and protein markers (50). In general identification, there must be ≥3 vesicle-positive protein makers, including ≥1 transmembrane or lipid-binding protein and one cytoplasmic protein, ≥1 vesicle-negative protein maker. The identification of a single vesicle requires two different but complementary methods, such as TEM or atomic force microscopy plus nanoparticle tracking analysis (50).

Endothelial progenitor cells (EPCs) were first discovered in peripheral blood (51). Some studies have found that EPCs also participate in the process of angiogenesis by releasing exosomes (52-54). EPC-derived exosomes promote the proliferation and angiogenesis of cardiac fibroblasts by inhibiting mesenchymal-endothelial transition and decreasing the expression of high mobility group protein 1 (55). Furthermore, EPC-derived exosomes are newly found players in the beneficial effects of exercise on vascular diseases. For instance, moderate exercise enhances the function of circulating EPC-derived exosomes in protecting ECs against hypoxic injury, and which may enrich EPC-derived exosomes via the release of miR-126 (56).

Circular RNA (circRNA/circ) in exosomes also plays an important role in tissue repair. Cardiomyocytes subjected to hypoxia release circ_homeodomain-interacting protein kinase 3 (circHIPK3)-rich exosomes to regulate oxidative stress damage in cardiac ECs, and circHIPK3 increases the expression of VEGFA by inhibiting the activity of miR-29a, thereby promoting the acceleration and proliferation of cardiac ECs (57). It has been confirmed that exosomal circHIPK3 released from hypoxia-pretreated cardiomyocytes regulates oxidative damage in cardiac microvascular ECs via the miR-29a/IGF-1 pathway (58). circHIPK3 downregulates miR-421, resulting in increased Forkhead box (FOX)O3a expression, thereby inhibiting apoptosis and inhibiting release of IL-1 antioxidant protein and IL-18, ultimately repairing ischemic injury (59).

Previous research has shown that exosomes from patients with myocardial ischemia promote angiogenesis via the miR-939/inducible nitric oxide (NO) synthase/NO pathway (60). There have been similar studies in skin repair (61-63). Moreover, it has been shown that exosomes from the serum of patients with type 2 diabetes can hinder the process of injury repair, and this effect is related to the miR-20b-5p and Wnt9b/β-catenin pathways (64).

Some researchers have taken on a new approach and focused on exosomes themselves. This approach can achieve targeted repair of injury sites through exosome modification. It was found that tissue inhibitor of metalloproteinase-2-modified human umbilical cord MSC-derived exosomes enhanced the repair of myocardial infarction in a rat model via the Akt/secreted frizzled related protein 2 pathway (65). Moreover, overexpression of HIF-1α in MSC-derived exosomes can enhance angiogenesis after AMI (66). Stromal cell derived factor (SDF)-1 overexpression in MSC-derived exosomes inhibited autophagy of ischemic myocardial cells and promoted microvascular production of ECs (67).

At present, the application of engineered exosomes in injury repair is still the mainstream direction. Exosomes engineered by ischemic myocardium-targeting peptide (IMTP) CSTSMLKAC can specifically target ischemic myocardium, and MSC-derived-IMTP-exosomes exert enhanced therapeutic effects on AMI (68). CSTSMLKAC is a new peptide sequence that can preferentially target the ischemic area of the heart (68). miRNA can also be used to modify exosomes. 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 EXOsomal 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

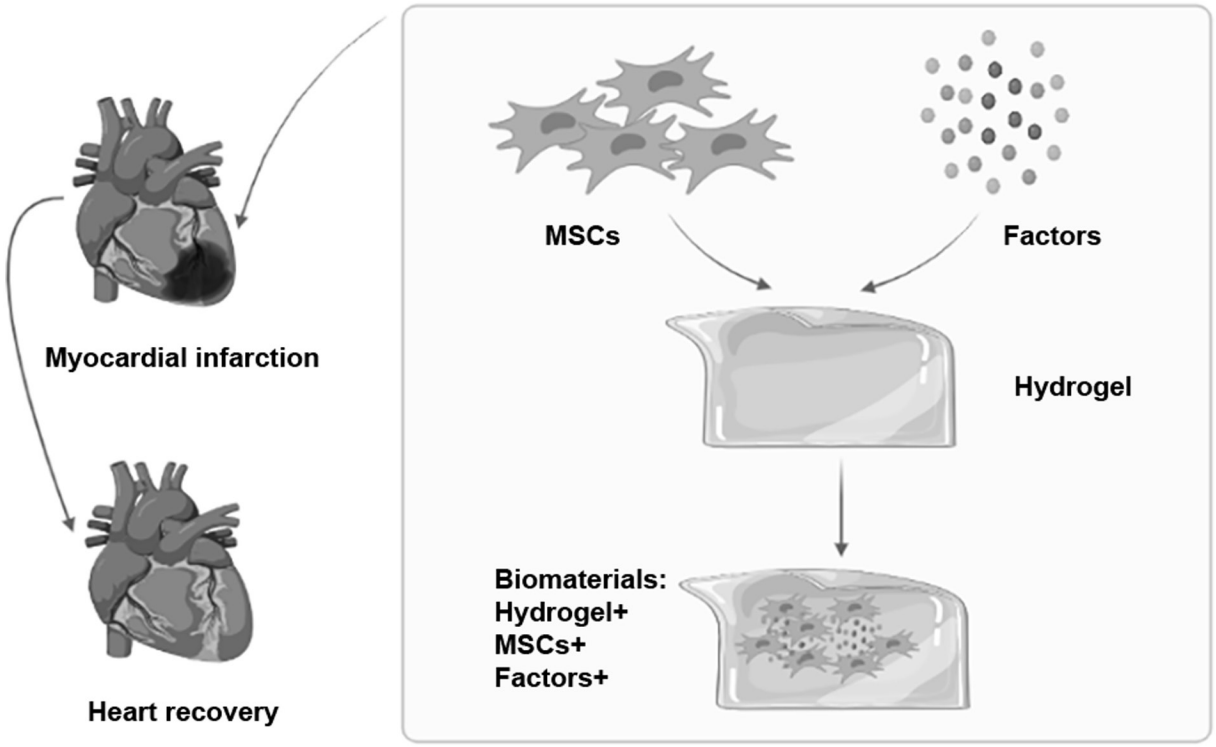

Figure 3. Application of biomaterials for cardiac repair. MSCs or pro-angiogenic factors can be combined with hydrogels to form biomaterials with improved repair performance, and can be targeted to the site of heart injury by injection, implantation and other ways to form new blood vessels. MSC, mesenchymal stem cell.

angiogenesis, reduce fibrosis and generate functional cardiac tissue (78). For example, the encapsulation of VEGF in polylactic 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 cardiopatch 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 RGDfK (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* 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 been 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 crosstalk (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

Table I. Application of angiogenesis for cardiac repair.

Therapy	Source	Mechanism	(Ref.)
MSCs	Umbilical cord, bone marrow, adipose tissue, menses blood, other tissues	Secret pro-angiogenic factors Regulate endothelial cells Regulate MMP expression Regulate cardiac fibroblasts	(39) (40) (42) (55)
Exosomes	Embryos, ADSC BM-MSC, EPC, Serum Engineered exosomes Other tissues	Protect ECs against hypoxia injury Deliver and regulate circRNAs/miRNAs to target cells Involve in miR-939/iNOS/NO pathway Protein modification, overexpressed protein and miRNA	(56) (57) (60) (65-72,74)
Biomaterials	Natural materials: Collagen, fibrinogen, Matrigel, gelatin, etc. Artificial synthetic	Ameliorate inflammation, reduce fibrosis, and generate functional cardiac tissue Promote angiogenesis	(78,80,83) (81,82,84-86)
Biological factors	Artificial synthesis Animal or plant extraction	Reduce apoptosis, increase angiogenesis, reduce infarcted area Induce angiogenic factors	(90-98)
Gene therapy	Genetic engineering technology	Construct angiogenic fusion plasmid Angiogenic gene modified cells	(101) (103,105,107)

MSCs, mesenchymal stem cells; ADSC, adipose-derived MSC; BM-MSC, bone marrow MSC; ECs, endothelial cells; iNOS, inducible nitric oxide synthase; NO, nitric oxide; circRNA, circular RNA; miRNA/miR, microRNA.

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* extracted 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-3 x Flag/ELA-32 fusion expression 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

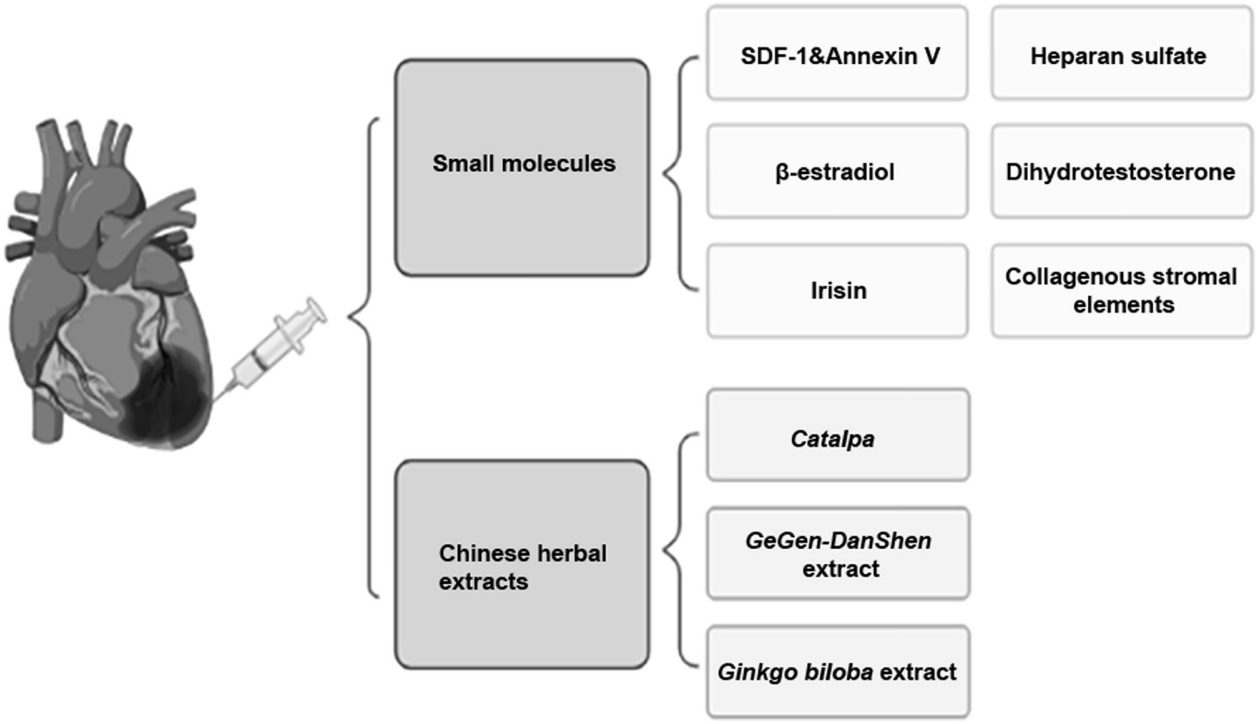

Figure 4. Biological factors for the treatment of myocardial infarction. The figure mainly shows two types of biological factors for cardiac repair. The small molecules listed are SDF-1, Annexin V, β-estradiol, irisin, heparan sulfate, dihydrotestosterone and collagenous stromal elements. *Catalpa*, *GeGen-DanShen* extract and *Ginkgo biloba* extract are all Chinese herbal extracts. SDF-1, stromal cell derived factor.

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.

Acknowledgements

Not applicable.

Funding

This review was supported by the National Natural Science Foundation of China (grant no. 81800270).

Availability of data and materials

Not applicable.

Authors' contributions

JL contributed to the design and conception of the manuscript. YZ and WZ added contributions by revising and editing the final manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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