





Review

# VEGF-A in Cardiomyocytes and Heart Diseases

Mariantonia Braile <sup>1,2,†</sup>, Simone Marcella <sup>1,2,†</sup>, Leonardo Cristinziano <sup>1,2</sup>,  
Maria Rosaria Galdiero <sup>1,2,3</sup>, Luca Modestino <sup>1,2</sup>, Anne Lise Ferrara <sup>1,2,3</sup>, Gilda Varricchi <sup>1,2,3</sup> ,  
Giancarlo Marone <sup>4,5</sup> and Stefania Loffredo <sup>1,2,3,\*</sup> 

<sup>1</sup> Department of Translational Medical Sciences and Center for Basic and Clinical Immunology Research (CISI), University of Naples Federico II, 80131 Naples, Italy; brailemariantonia@gmail.com (M.B.); s.marcella92@gmail.com (S.M.); l.cristinziano@gmail.com (L.C.); mrgaldiero@libero.it (M.R.G.); modestino.luca@gmail.com (L.M.); annelisefferrara@gmail.com (A.L.F.); gildanet@gmail.com (G.V.)

<sup>2</sup> WAO Center of Excellence, 80131 Naples, Italy

<sup>3</sup> CNR Institute of Experimental Endocrinology and Oncology “G. Salvatore”, 80131 Naples, Italy

<sup>4</sup> Department of Public Health, University of Naples Federico II, 80131 Naples, Italy; gcmarone@hotmail.it

<sup>5</sup> Azienda Ospedaliera Ospedali dei Colli – Monaldi Hospital Pharmacy, 80131 Naples, Italy

\* Correspondence: stefanialoffredo@hotmail.com

† These authors contributed equally to this work.

Received: 8 June 2020; Accepted: 22 July 2020; Published: 26 July 2020



**Abstract:** The vascular endothelial growth factor (VEGF), a homodimeric vasoactive glycoprotein, is the key mediator of angiogenesis. Angiogenesis, the formation of new blood vessels, is responsible for a wide variety of physio/pathological processes, including cardiovascular diseases (CVD). Cardiomyocytes (CM), the main cell type present in the heart, are the source and target of VEGF-A and express its receptors, VEGFR1 and VEGFR2, on their cell surface. The relationship between VEGF-A and the heart is double-sided. On the one hand, VEGF-A activates CM, inducing morphogenesis, contractility and wound healing. On the other hand, VEGF-A is produced by CM during inflammation, mechanical stress and cytokine stimulation. Moreover, high concentrations of VEGF-A have been found in patients affected by different CVD, and are often correlated with an unfavorable prognosis and disease severity. In this review, we summarized the current knowledge about the expression and effects of VEGF-A on CM and the role of VEGF-A in CVD, which are the most important cause of disability and premature death worldwide. Based on clinical studies on angiogenesis therapy conducted to date, it is possible to think that the control of angiogenesis and VEGF-A can lead to better quality and span of life of patients with heart disease.

**Keywords:** angiogenesis; atherosclerosis; cardiovascular disease; inflammation; ischemic heart disease; myocardial infarction

## 1. Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) has been discovered to be a permeability-enhancing agent leading to the disruption of intercellular contacts and the increase of permeability [1]. VEGF family, in humans, consists of five separate gene products: VEGF-A, VEGF-B and Placental growth factor, which are key regulators of blood vessel growth; and VEGF-C and VEGF-D, which modulate lymphangiogenesis [2]. VEGF-A, a homodimeric glycoprotein of approximately 45 kDa [3], is the key to vasculogenesis (the *de novo* formation of vessels) and angiogenesis (the formation of new vessels from preformed vasculature) [4,5]. VEGF-A induces cellular chemotaxis [6] and the expression of plasminogen activators [7] and collagenases [8] in endothelial cells (EC). VEGF-A promotes blood vessel growth and remodeling processes, and it also provides survival and mitogenic stimuli for EC [9–11]. During inflammation and tumorigenesis, sequestered VEGF can be released by proteases including

matrix metalloproteinases [12,13], plasmin, urokinase-type plasminogen activator, elastase and tissue kallikrein. These proteases, affecting VEGF-A activity through VEGF-A cleavage, activation and degradation, can both promote angiogenesis, for example as a key step in carcinogenesis, and suppress VEGF's angiogenic effects [14].

In humans, VEGF-A gene locus is on chromosome 6p21.1 and contains eight exons and seven introns. Through alternative splicing, human VEGF-A is represented by multiple isoforms [15,16]. The four major expressed variants are 121, 165, 189 and 206 amino acids long, with the VEGF-A<sub>165</sub> representing the predominant species of VEGF-A [2,17–20]. The larger isoforms, VEGF-A<sub>165</sub>, VEGF-A<sub>189</sub> and VEGF-A<sub>206</sub>, are basic and bind to isolated heparin and heparin proteoglycans distributed on cellular surfaces and extracellular matrices [21,22]. The VEGF short form, VEGF-A<sub>121</sub>, is acidic and is more freely diffusible [20,21]. VEGF gene expression is upregulated by a variety of factors, such as growth factors (i.e., fibroblast growth factors, epidermal growth factor, tumor necrosis factor (TNF) [23–28].

VEGF isoforms, with their differences in biotransport, sequestration and receptor binding, induce a spectrum of vascular phenotypes [20] from the malformed, edematous, hypovascular networks of VEGF-A<sub>120</sub> (VEGF-A<sub>121</sub> in human) due to dilated and poorly branched vessel generation [29] to the stable, thin and branching vessels of VEGF-A<sub>188</sub> (VEGF-A<sub>189</sub> in human) [30]. These vascular phenotypes are related to the ability of VEGF-A isoforms to induce the sprouting, migratory phenotype. VEGF-A<sub>165</sub> (VEGF-A<sub>164</sub> in mouse) is the first isoform characterized and as a potent stimulator of angiogenesis [20]. Its expression is adequate neonatal growth and has been well documented in tissues during physiological and/or pathological conditions [2,17].

The physiological effects of VEGF-A are driven by the binding to two homologous VEGF-A receptors. These receptors are known as VEGFR1 (Flt-1 in mice) and VEGFR2 (Flk-1; KDR) [31,32]. They are encoded by separate genes and are members of the class IV receptor tyrosine kinase family [33]. The expression of VEGFR has been demonstrated on EC, macrophages, mast cells and smooth muscle cells [34–37]. Although VEGFR1 binds VEGF-A with high affinity, it is believed to act primarily by modulating the availability of VEGF-A for binding to VEGFR2 [38–41]. Receptors for the VEGF-A, apart from those bound to cellular membranes, also occur in soluble form [42]. The soluble VEGFR1 (sVEGFR1) and sVEGFR2 receptors, binding VEGF-A before it reaches membrane-bound receptors on surface cells, are regarded as physiological inhibitors of the processes of angiogenesis and neoangiogenesis [43].

## 2. Cardiomyocytes

Cardiomyocytes (CM), also known as myocardiocytes or cardiac myocytes, are the muscle cells that belong to the heart muscle [44]. CM are contractile cells that, through their autorhythmicity and coordinated action with other CM, enable the heart to function as a pump [45]. This mechanism ensures that sufficient oxygenated blood and metabolites reach the tissues to meet the body's needs, whether at rest or during exercise [46]. To fulfill these functions, the CM are equipped with highly specialized subcellular machinery [44,47]. The first one of this system is the basement membrane, whose functions are to separate the intracellular structure from the extracellular environment, promote the exchange of macromolecules and catch ions, such as calcium [48–50].

A specialized structure of the CM is the sarcolemma. The sarcolemma controls the type of molecules that enters the cell [51,52] and guarantees the contraction and relaxation of the cells [53,54]. The CM cytoskeleton forms an important structural link between the extracellular environment and the contractile apparatus, and it can influence CM geometry and function through the phosphorylation of some of its proteins [55]. Myofilaments, contractile proteins formed from myosin and actin, are additional important subcellular structures. The interaction of these motor proteins guarantees the contraction of the muscle that allows blood to be pumped throughout the body [56–58]. Finally, CM contain a large number of mitochondria, which maintain high levels of ATP required by the cells to promote the contraction and relaxation of the heart muscle [59,60].

CM produce and secrete several mediators such as adiponectin [61], regenerating islet-derived protein 3- $\beta$  [62], TNF- $\alpha$ , interleukin-1 $\beta$  (IL-1 $\beta$ ), interferon  $\gamma$  [63], transforming growth factor  $\beta$  (TGF- $\beta$ ) [64], IL-6 and IL-11 [65,66]. It has been shown that CM are also a source of angiogenic factors, such as angiopoietin 1 (ANGPT1), ANGPT2 [67,68] and mainly VEGF-A [69].

### 3. Cardiomyocytes as Producers of VEGF-A

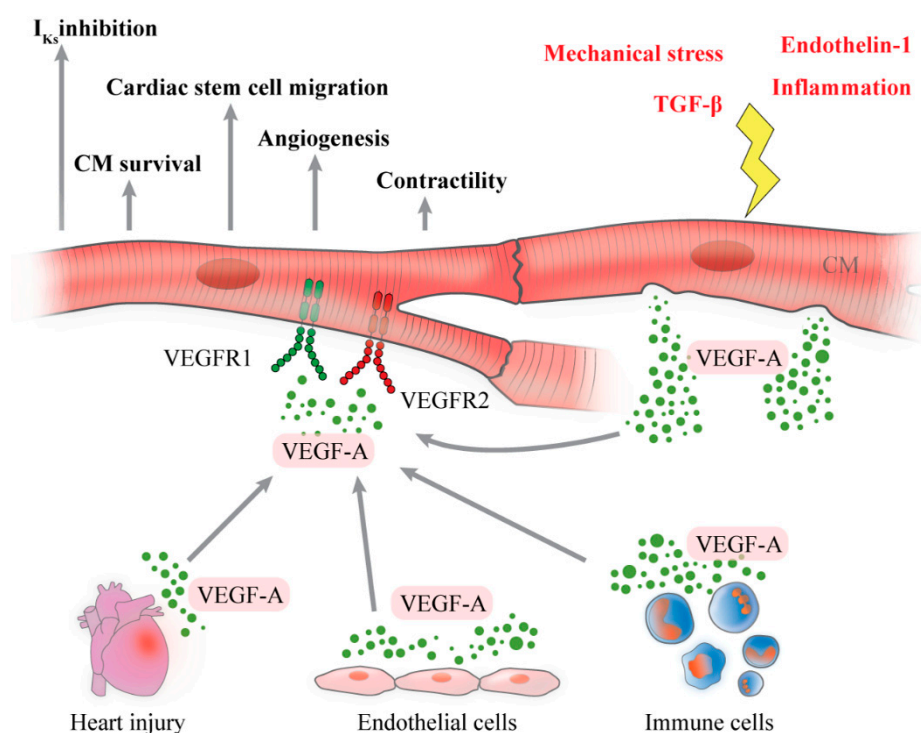
CM are a source of VEGF-A, which performs several functions in the heart. VEGF-A is the main regulator of vascular permeability and of angiogenesis [70]. In the mouse model, CM-specific deletion of VEGF-A alters negatively vasculogenesis/angiogenesis and causes a thinner ventricular wall [71], confirming mutual signaling from the CM to the EC during heart development. Interestingly, in mice lacking the VEGF-A the myocardial microvasculature is underdeveloped, but the coronary artery structure is preserved, involving a different signaling pathway for vasculogenesis/angiogenesis in the myocardium and epicardial coronary arteries [72]. Mice with CM-specific deletion of VEGF-A<sub>164</sub> and VEGF-A<sub>188</sub> isoforms show impaired myocardial angiogenesis with subsequent ischemic cardiomyopathy and heart failure [73]. These mice also exhibit heart capillaries that are more irregular, tortuous and dilated, indicating an incomplete vessel remodeling. Therefore, VEGF-A induces myocardial angiogenesis and enhances vascular permeability and EC proliferation [73].

In mouse model, the production of VEGF-A from CM also blocks the transformation of cardiac endocardial into mesenchymal [74]. This mechanism plays an important role in cardiac cushion formation and requires gentle control of VEGF-A concentration [74–76]. In the same animal model, low levels of VEGF-A induce the transformation of cardiac endocardial into mesenchymal, whereas high levels of VEGF-A block this transformation [77]. Interestingly, this signal induced by the production of VEGF-A from CM for endocardial–mesenchymal transformation may be regulated by an endothelial-derived feedback process through the calcineurin/NFAT pathway [78], demonstrating the importance of EC–CM interactions for cardiac morphogenesis [67].

In rat CM, mechanical stress regulates VEGF-A expression, while stretch improves the secretion [79]. Factors involved in the upregulation of VEGF-A expression in mice hypertrophied CM include hypoxia-inducible factor 1- $\alpha$  [80–82], but also NF $\kappa$ B [83], TGF- $\beta$  [84] and endothelin-1 [85]. Mice with CM lacking GATA4, a transcription factor that directly binds the VEGF-A promoter, show a poor capillary density in their hearts, while overexpression of GATA4 markedly improves cardiac vascularization and function following myocardial infarction by promoting angiogenesis (via VEGF-A production), hypertrophy, and inhibiting apoptosis [86,87]. In addition to GATA4, GATA6 and GATA2 also control angiogenesis [88–90]. In CM, the activation p38MAPK induces VEGF-A production, whereas its secretion occurs in an Sp1-dependent manner [91,92]. In this regard, the heart of mice with p38-inactivated CM exhibits compromised compensatory angiogenesis after pressure overload, and it is prone to early onset of heart failure. In summary, p38 $\alpha$ MAPK plays a critical role in the cross dialogue between CM and vascularization by regulating stress-induced VEGF-A expression and secretion in murine CM [93].

To date, there are no data on the expression and release of VEGF in human CM. Further studies are required to define the mechanistic role of VEGF-A in humans and whether this knowledge may be beneficial in specific patient populations.

The release of VEGF-A by CM is schematized in Figure 1.



**Figure 1.** Schematic representation of cardiomyocytes (CM) as source and target of vascular endothelial growth factor-A (VEGF-A). A plethora of stimuli including inflammation, mechanical stress, endothelin-1 and transforming growth factor- $\beta$  (TGF- $\beta$ ) induce CM to produce and release VEGF-A, whose function is to promote angiogenesis in myocardial tissue. CM are also a target of VEGF-A, produced by several cells and during heart injury, through binding with VEGFR1 and VEGFR2, expressed on their surface. CM activation, induced by VEGF-A, enhances CM survival, contractility, cardiac stem cell recruitment, cardiac angiogenesis and reduction of potassium current ( $I_{Ks}$ ).

#### 4. Cardiomyocytes as Target of VEGF-A

CM are both producers and targets of VEGF-A [94–96]. This latter exhibits a plethora of actions in reparative wound healing within the myocardium, including vasculogenesis [97], recruitment and homing of stem cells [98], decreased apoptosis [99,100] and increased vasodilatation [101] and modulation of the autonomic response [102]. As previously described, VEGF-A exerts its biological effects by interacting with two main tyrosine kinase receptors, VEGFR1 and VEGFR2, with an affinity for VEGFR1 higher than VEGFR2 [97,103]. VEGFR1 and VEGFR2 are both expressed on CM surface, but VEGFR1 is upregulated following hypoxia and oxidative stress [104]. VEGFR1 is also important for cardiac contractility; in fact, the heart uses VEGF-A–phospholipase C $\gamma$ 1 signaling to control the strength of the heartbeat [105,106]. VEGFR2 is largely expressed on the surviving mouse CM after acute myocardial infarction, and CM viability is significantly improved with VEGF-A<sub>164</sub> [107].

It has been demonstrated in the rat model that VEGF-A inhibits CM apoptosis and activates the expression of genes involved in myocardial contractility and metabolism [104,108]. VEGF-A involvement in heart repair also encourages cardiac stem cell migration via the PI3K/Akt pathway [98]. The same research group demonstrates that the pathway VEGF-A together with myocardial stromal cell-derived factor-1 (SDF-1) encourages cardiac stem cell mobilization and myocardial repair within infarcted heart [109,110].

VEGF-A plays a pivotal role in triggering the cardiac angiogenic response following acute infarcted myocardium [111]. VEGF-A and VEGFR expression is increased at the border zone only in the first day post rat myocardial infarction, but not in the later stages [112], and then it is suppressed during the first week when angiogenesis is more active [113]. Therefore, the withdrawal of VEGF-A

may be also related to the later vascular stabilization in the infarcted myocardium [114]. Moreover, VEGF-A reduces potassium current ( $I_{Ks}$ ) through a phosphatidylinositol 3-kinase-mediated molecular pathway, increasing the duration of cardiac action potential in guinea pig ventricular CM. In conclusion, we speculate that VEGF-A, after being released by CM, may have autocrine/paracrine effects activating CM by binding to VEGFRs.

The effects of VEGF-A on CM are shown in Figure 1.

## 5. VEGF-A and Angiogenesis in Cardiovascular Diseases

As previously stated, angiogenesis is the process of formation of new blood vessels from pre-existing vessels, involving cell proliferation, migration, differentiation, tube formation and regulation of angiogenic factors [115]. It is responsible for a great variety of physiological and pathological processes, including cardiovascular diseases (CVD) [116].

CVD are pathological processes representing the number one cause of mortality in the world [117]. Among them, the most recognized CVD are ischemic disease and atherosclerosis [118,119], which are the most important cause of disability and premature death worldwide [117]. Therefore, CVD seriously affects the quality of life, increasing the psychological and economic burden [117,120].

### 5.1. Ischemic Heart Disease

Ischemic heart disease (IHD) remains the leading cause of death worldwide [121]. World Health Organization reports that 740 million people die of IHD annually all around the world, accounting for the death of 13.2% of the total population [Organization WH. World Health Organization report. May 2014, <http://www.who.int/mediacentre/factsheets/fs310/zh/>]. Myocardial infarction (MI) is one of the main manifestations of IHD, which induces myocardial necrosis or apoptosis in a short time [122], leading to heart failure with a poor prognosis [123]. It has been classified as the main cause of death in IHD [124]. To date, there are several types of treatments for MI, such as reducing incidence of coronary atherosclerosis [125], antithrombotic therapy including vitamin K antagonists [126], antiplatelet therapy with low-dose aspirin [127] and clopidogrel [128]. In the last years, the therapeutic angiogenesis has been proposed as a new strategy for the treatment of MI. Angiogenesis appears in all vascularized organs [129]. Although ischemia leads to endogenous myocardial angiogenesis, it cannot reach the effect to maintain normal capillary density [130]. Experiments conducted on rat models reveal that serum VEGF-A levels are positively associated with increased microvessel density in the infarcted area, suggesting VEGF-A role in myocardial remodeling and angiogenesis [131–135]. There is compelling evidence that patients with MI have high serum levels of VEGF-A [136]. Moreover, altered levels of VEGF-A are detected also in plasma after MI and are correlated with high inflammation cytokine concentrations [137] suggesting that increased levels of VEGF-A are a part of ongoing inflammatory activity. Since high concentrations of VEGF-A in these patients lead to neovascularization of inflamed plaques and their destabilization, VEGF-A levels are a negative prognostic value [137]. Therefore, therapeutic stimulation of angiogenesis has been regarded as an effective treatment for IHD [138]. Stroke is another main manifestation of IHD. In stroke, the breakdown of the blood–brain barrier leads to the release of reactive oxygen species capable of transforming astrocytes into reactive astrocytes. These reactive astrocytes modify the extracellular matrix (ECM) [139] with a consequent restructuring of the ECM with the formation of ECM traits [140]. EC use these new ECM traits to establish new capillary buds [141]. This mechanism is strictly regulated by a balance between proangiogenic and angiostatic factors [142–145]. At the onset of ischemia, the combined presence of nitric oxide (NO) and VEGF-A leads to vasodilation and an increase in vascular permeability. This condition generates the extravasation of plasma proteins that promote temporary communication for the migration of EC to ensure vascular germination [146], with subsequent dissociation of smooth muscle cells and the loosening of the ECM. ANGPT2, an inhibitor of Tie2 signaling, and matrix metalloproteinases regulate these mechanisms [117]. After the germination path has been established, the EC proliferate and migrate under VEGF-A signaling, and new blood vessels are maintained by ANGPT1 by activating

the Tie2 receptor [147]. To date, understanding the dynamic changes of these angiogenic factors after stroke could be useful for developing effective therapeutic strategies. In this regard, high levels of VEGF-A within hours of a stroke are correlated with angiogenesis in the injured area of the brain. Administration of VEGF-A, after a few minutes of reoxygenation following hypoxic ischemia, exhibits a reduction in brain injury in rats [117].

## 5.2. Atherosclerosis

Atherosclerosis is an alteration characterized by the accumulation of cholesterol and non-resolving inflammation in the vascular wall of the medium and large arteries [148]. Neovascularization in atherosclerotic damage is essential for plaque growth and instability [149]. In atherosclerosis, VEGF-A performs a dual function [150]. On the one hand, it induces beneficial effects, protecting the EC by increasing the expression levels of anti-apoptotic proteins and NO synthesis [2]. On the other hand, VEGF-A induces harmful effects, acting as mitogen by re-endothelialization [151] and prevention or repair of the endothelial lesion that can induce atherogenesis [152]. In addition, VEGF-A promotes monocyte adhesion, transendothelial migration and activation [153,154], improving also endothelium permeability [1], adhesion protein expression [155] and monocyte chemoattractant protein-1 [156]. In human coronaries, VEGF-A and its receptors are not found in normal coronary segments, but their expression increases in EC of microcapillaries, in macrophages and in partially differentiated smooth muscle cells of atherosclerotic lesions [157]. VEGF-A is identified as a marker of atherosclerosis, performing experiments on rabbits [158,159]. Chronic stress reduces atherosclerosis tunica media and induces plaque instability, promoting angiogenesis by release of VEGF-A identified in a great amount in serum [158]. Administration of Resveratrol decreases VEGF-A serum concentration, reducing formation and evolution of atherosclerotic lesions in rabbit model [159]. It has been demonstrated that anti-angiogenic factors reduce atherosclerosis development in various animal models [160]. Therefore, clinical trials with anti-angiogenic drugs such as anti-VEGF/VEGFR, used in anti-cancer therapy, show cardiovascular adverse effects and require additional investigations [161]. Conversely, plasma VEGF-A is weakly associated with cardiovascular risk factors, suggesting circulating VEGF-A has only a little influence on the development of atherosclerosis [162].

As a result of atherosclerosis, there are two other important pathological processes: Atherothrombosis and coronary artery disease.

Atherothrombosis is a complex inflammatory pathological process that involves lipid deposition in the arterial wall with recruitment of circulating leukocytes [163]. This continuous accumulation leads to the growth of a plaque that could become unstable and break, triggering the formation of a thrombus [164]. An occlusive thrombus may possibly be responsible for an ischemic event [165]. In this process, inflammation plays an important role in all phases, especially the reactive protein C, which is one of the main ones responsible for the cascade of events that induces thrombosis [166].

The VEGF-A signaling pathway (VSP) plays an important role in EC, and its inhibition has huge effects on thrombosis [114,167]. Generalized endothelial dysfunction predisposes to both arterial and venous thrombosis [168]. VSP blockade induces vascular toxicity, including arterial thromboembolic events (ATE) [169–171]. VSP inhibitors are antibodies, acting directly on VEGF-A, such as bevacizumab [172] and tyrosine kinases inhibitors [173], binding to the kinase domain of VEGF-A receptors, such as sunintib [174] and sorafenib [161]. Age over 65 years, previous thromboembolic events, history of atherosclerotic disease and duration of VSP inhibitor therapy are possible risk factors for ATE during VSP inhibitor therapy [175].

Coronary artery disease (CAD) is a pathological process, generally caused by atherosclerosis, in which the coronary arteries are constricted or blocked. The relationship between angiogenesis and CAD is complex. Angiogenesis promotes growth [176] and vulnerability of plaques [177,178], causing intraplaque hemorrhage [179] and the influx of inflammatory cells and erythrocytes [180]. The growth of this accumulation could break the plaque, worsening the pathological condition. In this

regard, the blockade of intraplaque angiogenesis is considered as a potential therapeutic target for CAD [160,181,182].

Moreover, patients with CAD have increased serum and plasma levels of VEGF-A [183,184] that correlate with IL-18 concentrations [185], a cytokine that induces VEGF-A expression [183]. This increase may indicate that VEGF-A can be considered as a marker for revascularization when coronary artery injury is critical [186]. Therefore, therapeutic angiogenesis is used to improve the ischemic myocardial reperfusion in patients with CAD and to expand the myocardial microvascular network. To date, there are several therapies. The first one is the administration of angiogenic growth factors directly (protein therapy) [187–189]; the second strategy is promoting angiogenic genes expression in vivo (gene therapy) [190–192]. Finally, there are other strategies, such as delivering stem cells (cell therapy) [193–196] or exosomes (cell-free therapy) [143,197–200].

The effects of VEGF-A in CVD are summarized in Table 1.

**Table 1.** Schematic representation of VEGF-A expression in cardiovascular diseases.

Cardiovascular Diseases	VEGF-A	Effects	References
Ischemic heart disease: →Myocardial infarction	↑	microvessel density in the infarcted area, myocardial remodeling angiogenesis, neovascularization, destabilization of inflamed plaques.	[131–137]
→Stroke	↑	vasodilation, vascular permeability, endothelial cells migration, dissociation of smooth muscle cells, loosening of the extracellular matrix.	[146]
Atherosclerosis: →Atherothrombosis	↓	vascular toxicity, arterial thrombosis.	[169–171]
→Coronary artery disease	↑	angiogenesis, growth and vulnerability of plaques, intraplaque hemorrhage, inflammatory cell and erythrocyte recruitment, coronary artery revascularization.	[176–180]

## 6. Conclusions

Angiogenesis is a process responsible for a great variety of physiological and pathological mechanisms, including heart diseases. VEGF-A is the key regulator of angiogenesis. In this review, we discussed present knowledge on the expression and effects on VEGF-A on cardiomyocytes and on the role of VEGF-A in CVD that are the most important cause of disability and premature death worldwide.

CM, the main cell type found in the heart, produce and release VEGF-A and express its receptors, VEGFR1 and VEGFR2, on their cell surface. The lack of VEGF-A expression in CM affects myocardial angiogenesis, resulting in conditions that impair heart functions. Moreover, CM is also a target of VEGF-A because it influences CM biology such as mobilization.

VEGF-A plays an important role in cardiac morphogenesis, cardiac contractility and wound healing within the myocardium. At the same time, high concentrations of VEGF-A are detected in several CVD and are often associated with poor prognosis and disease severity. Further scientific advances have led to the discovery of a broad range of therapeutical targets and novel biomarkers associated with cardiovascular risks. In addition to protein therapy, gene therapy, cell therapy and cell-less therapy, other concepts have been applied to this field with a large amount of energy. As our understanding of pathophysiological mechanisms of CVD becomes more refined, therapeutic angiogenesis is increasingly interesting in the resolution of these pathologies. Based on clinical trials of angiogenesis therapy conducted to date, some of the approaches appear to have modest effects and continue to be investigated, while some of them have affirmed strong evidence of its success.

In this review, we summarized interesting and thought-provoking studies implicating the role of VEGF-A in various cardiovascular diseases. We suggest that with properly designed and conducted clinical trials, it is possible to think that therapeutic angiogenesis could lead to better quality and life span of patients affected by heart diseases.

**Funding:** This research received no external funding.

**Acknowledgments:** The authors thank Gjada Criscuolo for critical reading of the review and the administrative staff (Roberto Bifulco and Anna Ferraro), without whom it would not be possible to work as a team.

**Conflicts of Interest:** The authors have no relevant affiliation or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, patents received or pending, or royalties.

## Abbreviations

ANGPT	angiopoietin
ATE	arterial thromboembolic events
CM	cardiomyocytes
CVD	cardiovascular disease
CAD	coronary artery disease
EC	endothelial cells
ECM	extracellular matrix
IL-	interleukin
IHD	ischemic heart disease
MI	myocardial infarction
NO	nitric oxide
sVEGF-A	soluble vascular endothelial growth factor receptor
TGF- $\beta$	transforming growth factor $\beta$
TNF	tumor necrosis factor
VEGF	vascular endothelial growth
VSP	VEGF-A signaling pathway
VEGFR	vascular endothelial growth factor receptor

## References

1. Senger, D.R.; Galli, S.J.; Dvorak, A.M.; Perruzzi, C.A.; Harvey, V.S.; Dvorak, H.F. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science* **1983**, *219*, 983–985. [[CrossRef](#)]
2. Ferrara, N.; Gerber, H.-P.; LeCouter, J. The biology of VEGF and its receptors. *Nat. Med.* **2003**, *9*, 669–676. [[CrossRef](#)]
3. Ferrara, N.; Davis-Smyth, T. The Biology of Vascular Endothelial Growth Factor. *Endocr. Rev.* **1997**, *18*, 4–25. [[CrossRef](#)]
4. Moens, S.; Goveia, J.; Stapor, P.C.; Cantelmo, A.R.; Carmeliet, P. The multifaceted activity of VEGF in angiogenesis—Implications for therapy responses. *Cytokine Growth Factor Rev.* **2014**, *25*, 473–482. [[CrossRef](#)]
5. Varricchi, G.; Loffredo, S.; Galdiero, M.R.; Marone, G.; Cristinziano, L.; Granata, F.; Marone, G. Innate effector cells in angiogenesis and lymphangiogenesis. *Curr. Opin. Immunol.* **2018**, *53*, 152–160. [[CrossRef](#)] [[PubMed](#)]
6. Koch, A.E.; Harlow, L.A.; Haines, G.K.; Amento, E.P.; Unemori, E.N.; Wong, W.L.; Pope, R.M.; Ferrara, N. Vascular endothelial growth factor. A cytokine modulating endothelial function in rheumatoid arthritis. *J. Immunol. Baltim. Md 1950* **1994**, *152*, 4149–4156.
7. Mandriota, S.J.; Seghezzi, G.; Vassalli, J.-D.; Ferrara, N.; Wasi, S.; Mazzieri, R.; Mignatti, P.; Pepper, M.S. Vascular Endothelial Growth Factor Increases Urokinase Receptor Expression in Vascular Endothelial Cells. *J. Biol. Chem.* **1995**, *270*, 9709–9716. [[CrossRef](#)] [[PubMed](#)]
8. Unemori, E.N.; Ferrara, N.; Bauer, E.A.; Amento, E.P. Vascular endothelial growth factor induces interstitial collagenase expression in human endothelial cells. *J. Cell. Physiol.* **1992**, *153*, 557–562. [[CrossRef](#)]



9. Hu, G.-J.; Feng, Y.-G.; Lu, W.-P.; Li, H.-T.; Xie, H.-W.; Li, S.-F. Effect of combined VEGF165/ SDF-1 gene therapy on vascular remodeling and blood perfusion in cerebral ischemia. *J. Neurosurg.* **2017**, *127*, 670–678. [[CrossRef](#)]
10. Kazi, A.S.; Lotfi, S.; Goncharova, E.A.; Tliba, O.; Amrani, Y.; Krymskaya, V.P.; Lazaar, A.L. Vascular endothelial growth factor-induced secretion of fibronectin is ERK dependent. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2004**, *286*, L539–L545. [[CrossRef](#)]
11. Morales-Ruiz, M.; Fulton, D.; Sowa, G.; Languino, L.R.; Fujio, Y.; Walsh, K.; Sessa, W.C. Vascular endothelial growth factor-stimulated actin reorganization and migration of endothelial cells is regulated via the serine/threonine kinase Akt. *Circ. Res.* **2000**, *86*, 892–896. [[CrossRef](#)] [[PubMed](#)]
12. Lundkvist, A.; Lee, S.; Iruela-Arispe, L.; Betsholtz, C.; Gerhardt, H. Growth factor gradients in vascular patterning. *Novartis Found. Symp.* **2007**, *283*, 194–201; discussion 201. [[CrossRef](#)] [[PubMed](#)]
13. Lee, S.; Jilani, S.M.; Nikolova, G.V.; Carpizo, D.; Iruela-Arispe, M.L. Processing of VEGF-A by matrix metalloproteinases regulates bioavailability and vascular patterning in tumors. *J. Cell Biol.* **2005**, *169*, 681–691. [[CrossRef](#)] [[PubMed](#)]
14. Vempati, P.; Popel, A.S.; Mac Gabhann, F. Extracellular regulation of VEGF: Isoforms, proteolysis, and vascular patterning. *Cytokine Growth Factor Rev.* **2014**, *25*, 1–19. [[CrossRef](#)] [[PubMed](#)]
15. Tischer, E.; Mitchell, R.; Hartman, T.; Silva, M.; Gospodarowicz, D.; Fiddes, J.C.; Abraham, J.A. The human gene for vascular endothelial growth factor. Multiple protein forms are encoded through alternative exon splicing. *J. Biol. Chem.* **1991**, *266*, 11947–11954.
16. Venables, J.P. Unbalanced alternative splicing and its significance in cancer. *BioEssays News Rev. Mol. Cell. Dev. Biol.* **2006**, *28*, 378–386. [[CrossRef](#)]
17. Azimi-Nezhad, M. Vascular endothelial growth factor from embryonic status to cardiovascular pathology. *Rep. Biochem. Mol. Biol.* **2014**, *2*, 59–69.
18. Ferrara, N. Role of vascular endothelial growth factor in regulation of physiological angiogenesis. *Am. J. Physiol. Cell Physiol.* **2001**, *280*, C1358–C1366. [[CrossRef](#)]
19. Gorenjak, V.; Vance, D.R.; Petrelis, A.M.; Stathopoulou, M.G.; Dadé, S.; El Shamieh, S.; Murray, H.; Masson, C.; Lamont, J.; Fitzgerald, P.; et al. Peripheral blood mononuclear cells extracts VEGF protein levels and VEGF mRNA: Associations with inflammatory molecules in a healthy population. *PLoS ONE* **2019**, *14*, e0220902. [[CrossRef](#)]
20. Peach, C.J.; Mignone, V.W.; Arruda, M.A.; Alcobia, D.C.; Hill, S.J.; Kilpatrick, L.E.; Woolard, J. Molecular Pharmacology of VEGF-A Isoforms: Binding and Signalling at VEGFR2. *Int. J. Mol. Sci.* **2018**, *19*, 1264. [[CrossRef](#)]
21. Houck, K.A.; Leung, D.W.; Rowland, A.M.; Winer, J.; Ferrara, N. Dual regulation of vascular endothelial growth factor bioavailability by genetic and proteolytic mechanisms. *J. Biol. Chem.* **1992**, *267*, 26031–26037. [[PubMed](#)]
22. Park, J.E.; Keller, G.A.; Ferrara, N. The vascular endothelial growth factor (VEGF) isoforms: Differential deposition into the subepithelial extracellular matrix and bioactivity of extracellular matrix-bound VEGF. *Mol. Biol. Cell* **1993**, *4*, 1317–1326. [[CrossRef](#)] [[PubMed](#)]
23. Chen, M.; Bao, L.; Zhao, M.; Cao, J.; Zheng, H. Progress in Research on the Role of FGF in the Formation and Treatment of Corneal Neovascularization. *Front. Pharmacol.* **2020**, *11*, 111. [[CrossRef](#)] [[PubMed](#)]
24. Ferrara, N. Vascular endothelial growth factor as a target for anticancer therapy. *Oncologist* **2004**, *9* (Suppl. 1), 2–10. [[CrossRef](#)]
25. Nicolas, S.; Abdellatef, S.; Haddad, M.A.; Fakhoury, I.; El-Sibai, M. Hypoxia and EGF Stimulation Regulate VEGF Expression in Human Glioblastoma Multiforme (GBM) Cells by Differential Regulation of the PI3K/Rho-GTPase and MAPK Pathways. *Cells* **2019**, *8*, 1397. [[CrossRef](#)] [[PubMed](#)]
26. Saryeddine, L.; Zibara, K.; Kassem, N.; Badran, B.; El-Zein, N. EGF-Induced VEGF Exerts a PI3K-Dependent Positive Feedback on ERK and AKT through VEGFR2 in Hematological In Vitro Models. *PLoS ONE* **2016**, *11*, e0165876. [[CrossRef](#)] [[PubMed](#)]
27. Seghezzi, G.; Patel, S.; Ren, C.J.; Gualandris, A.; Pintucci, G.; Robbins, E.S.; Shapiro, R.L.; Galloway, A.C.; Rifkin, D.B.; Mignatti, P. Fibroblast growth factor-2 (FGF-2) induces vascular endothelial growth factor (VEGF) expression in the endothelial cells of forming capillaries: An autocrine mechanism contributing to angiogenesis. *J. Cell Biol.* **1998**, *141*, 1659–1673. [[CrossRef](#)]

28. Wang, H.; Han, X.; Wittchen, E.S.; Hartnett, M.E. TNF- $\alpha$  mediates choroidal neovascularization by upregulating VEGF expression in RPE through ROS-dependent  $\beta$ -catenin activation. *Mol. Vis.* **2016**, *22*, 116–128.
29. Ruhrberg, C.; Gerhardt, H.; Golding, M.; Watson, R.; Ioannidou, S.; Fujisawa, H.; Betsholtz, C.; Shima, D.T. Spatially restricted patterning cues provided by heparin-binding VEGF-A control blood vessel branching morphogenesis. *Genes Dev.* **2002**, *16*, 2684–2698. [[CrossRef](#)]
30. Stalmans, I.; Ng, Y.-S.; Rohan, R.; Fruttiger, M.; Bouché, A.; Yuce, A.; Fujisawa, H.; Hermans, B.; Shani, M.; Jansen, S.; et al. Arteriolar and venular patterning in retinas of mice selectively expressing VEGF isoforms. *J. Clin. Investig.* **2002**, *109*, 327–336. [[CrossRef](#)]
31. Koch, S.; Tugues, S.; Li, X.; Gualandi, L.; Claesson-Welsh, L. Signal transduction by vascular endothelial growth factor receptors. *Biochem. J.* **2011**, *437*, 169–183. [[CrossRef](#)] [[PubMed](#)]
32. Smith, G.A.; Fearnley, G.W.; Tomlinson, D.C.; Harrison, M.A.; Ponnambalam, S. The cellular response to vascular endothelial growth factors requires co-ordinated signal transduction, trafficking and proteolysis. *Biosci. Rep.* **2015**, *35*. [[CrossRef](#)] [[PubMed](#)]
33. Alexander, S.P.; Fabbro, D.; Kelly, E.; Marrion, N.; Peters, J.A.; Benson, H.E.; Faccenda, E.; Pawson, A.J.; Sharman, J.L.; Southan, C.; et al. The Concise Guide to PHARMACOLOGY 2015/16: Catalytic receptors. *Br. J. Pharmacol.* **2015**, *172*, 5979–6023. [[CrossRef](#)] [[PubMed](#)]
34. Detoraki, A.; Staiano, R.I.; Granata, F.; Giannattasio, G.; Prevete, N.; de Paulis, A.; Ribatti, D.; Genovese, A.; Triggiani, M.; Marone, G. Vascular endothelial growth factors synthesized by human lung mast cells exert angiogenic effects. *J. Allergy Clin. Immunol.* **2009**, *123*, 1142–1149.e5. [[CrossRef](#)] [[PubMed](#)]
35. Ishida, A.; Murray, J.; Saito, Y.; Kanthou, C.; Benzakour, O.; Shibuya, M.; Wijelath, E.S. Expression of vascular endothelial growth factor receptors in smooth muscle cells. *J. Cell. Physiol.* **2001**, *188*, 359–368. [[CrossRef](#)] [[PubMed](#)]
36. Kabrun, N.; Bühring, H.J.; Choi, K.; Ullrich, A.; Risau, W.; Keller, G. Flk-1 expression defines a population of early embryonic hematopoietic precursors. *Dev. Camb. Engl.* **1997**, *124*, 2039–2048.
37. Witmer, A.N.; Dai, J.; Weich, H.A.; Vrensen, G.F.J.M.; Schlingemann, R.O. Expression of vascular endothelial growth factor receptors 1, 2, and 3 in quiescent endothelia. *J. Histochem. Cytochem. Off. J. Histochem. Soc.* **2002**, *50*, 767–777. [[CrossRef](#)]
38. Meyer, R.D.; Mohammadi, M.; Rahimi, N. A single amino acid substitution in the activation loop defines the decoy characteristic of VEGFR-1/FLT-1. *J. Biol. Chem.* **2006**, *281*, 867–875. [[CrossRef](#)]
39. Terman, B.I.; Dougher-Vermazen, M.; Carrion, M.E.; Dimitrov, D.; Armellino, D.C.; Gospodarowicz, D.; Böhlen, P. Identification of the KDR tyrosine kinase as a receptor for vascular endothelial cell growth factor. *Biochem. Biophys. Res. Commun.* **1992**, *187*, 1579–1586. [[CrossRef](#)]
40. De Vries, C.; Escobedo, J.A.; Ueno, H.; Houck, K.; Ferrara, N.; Williams, L.T. The fms-like tyrosine kinase, a receptor for vascular endothelial growth factor. *Science* **1992**, *255*, 989–991. [[CrossRef](#)]
41. Waltenberger, J.; Claesson-Welsh, L.; Siegbahn, A.; Shibuya, M.; Heldin, C.H. Different signal transduction properties of KDR and Flt1, two receptors for vascular endothelial growth factor. *J. Biol. Chem.* **1994**, *269*, 26988–26995. [[PubMed](#)]
42. Hornig, C.; Weich, H.A. Soluble VEGF receptors. *Angiogenesis* **1999**, *3*, 33–39. [[CrossRef](#)]
43. Shibuya, M.; Claesson-Welsh, L. Signal transduction by VEGF receptors in regulation of angiogenesis and lymphangiogenesis. *Exp. Cell Res.* **2006**, *312*, 549–560. [[CrossRef](#)] [[PubMed](#)]
44. Woodcock, E.A.; Matkovich, S.J. Cardiomyocytes structure, function and associated pathologies. *Int. J. Biochem. Cell Biol.* **2005**, *37*, 1746–1751. [[CrossRef](#)] [[PubMed](#)]
45. Ribeiro, A.J.S.; Ang, Y.-S.; Fu, J.-D.; Rivas, R.N.; Mohamed, T.M.A.; Higgs, G.C.; Srivastava, D.; Pruitt, B.L. Contractility of single cardiomyocytes differentiated from pluripotent stem cells depends on physiological shape and substrate stiffness. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 12705–12710. [[CrossRef](#)] [[PubMed](#)]
46. Pittman, R.N. *Regulation of Tissue Oxygenation*; Integrated Systems Physiology: From Molecule to Function to Disease; Morgan & Claypool Life Sciences: San Rafael, CA, USA, 2011.
47. Walker, C.A.; Spinale, F.G. The structure and function of the cardiac myocyte: A review of fundamental concepts. *J. Thorac. Cardiovasc. Surg.* **1999**, *118*, 375–382. [[CrossRef](#)]
48. Frank, J.S.; Langer, G.A.; Nudd, L.M.; Seraydarian, K. The myocardial cell surface, its histochemistry, and the effect of sialic acid and calcium removal on its structure and cellular ionic exchange. *Circ. Res.* **1977**, *41*, 702–714. [[CrossRef](#)]

49. Frank, J.S.; Langer, G.A. The myocardial interstitium: Its structure and its role in ionic exchange. *J. Cell Biol.* **1974**, *60*, 586–601. [[CrossRef](#)]
50. Yang, H.; Borg, T.K.; Wang, Z.; Ma, Z.; Gao, B.Z. Role of the Basement Membrane in Regulation of Cardiac Electrical Properties. *Ann. Biomed. Eng.* **2014**, *42*, 1148–1157. [[CrossRef](#)]
51. Langer, G.A.; Frank, J.S.; Rich, T.L.; Orner, F.B. Calcium exchange, structure, and function in cultured adult myocardial cells. *Am. J. Physiol.* **1987**, *252*, H314–H324. [[CrossRef](#)]
52. Langer, G.A.; Frank, J.S.; Philipson, K.D. Ultrastructure and calcium exchange of the sarcolemma, sarcoplasmic reticulum and mitochondria of the myocardium. *Pharmacol. Ther.* **1982**, *16*, 331–376. [[CrossRef](#)]
53. Hong, T.; Shaw, R.M. Cardiac T-Tubule Microanatomy and Function. *Physiol. Rev.* **2017**, *97*, 227–252. [[CrossRef](#)] [[PubMed](#)]
54. Zhao, G.; Qiu, Y.; Zhang, H.M.; Yang, D. Intercalated discs: Cellular adhesion and signaling in heart health and diseases. *Heart Fail. Rev.* **2019**, *24*, 115–132. [[CrossRef](#)] [[PubMed](#)]
55. McCain, M.L.; Parker, K.K. Mechanotransduction: The role of mechanical stress, myocyte shape, and cytoskeletal architecture on cardiac function. *Pflüg. Arch.-Eur. J. Physiol.* **2011**, *462*, 89–104. [[CrossRef](#)]
56. Guhathakurta, P.; Prochniewicz, E.; Thomas, D.D. Actin-Myosin Interaction: Structure, Function and Drug Discovery. *Int. J. Mol. Sci.* **2018**, *19*, 2628. [[CrossRef](#)]
57. Powers, J.D.; Yuan, C.-C.; McCabe, K.J.; Murray, J.D.; Childers, M.C.; Flint, G.V.; Moussavi-Harami, F.; Mohran, S.; Castillo, R.; Zuzek, C.; et al. Cardiac myosin activation with 2-deoxy-ATP via increased electrostatic interactions with actin. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 11502–11507. [[CrossRef](#)]
58. Yamada, Y.; Namba, K.; Fujii, T. Cardiac muscle thin filament structures reveal calcium regulatory mechanism. *Nat. Commun.* **2020**, *11*, 153. [[CrossRef](#)]
59. Kuznetsov, A.V.; Javadov, S.; Grimm, M.; Margreiter, R.; Ausserlechner, M.J.; Hagenbuchner, J. Crosstalk between Mitochondria and Cytoskeleton in Cardiac Cells. *Cells* **2020**, *9*, 222. [[CrossRef](#)]
60. Pohjoismäki, J.L.; Goffart, S. The role of mitochondria in cardiac development and protection. *Free Radic. Biol. Med.* **2017**, *106*, 345–354. [[CrossRef](#)]
61. Solarewicz, J.; Manly, A.; Kokoszka, S.; Sleiman, N.; Leff, T.; Cala, S. Adiponectin secretion from cardiomyocytes produces canonical multimers and partial co-localization with calsequestrin in junctional SR. *Mol. Cell. Biochem.* **2019**, *457*, 201–214. [[CrossRef](#)]
62. Frangogiannis, N.G. The Reparative Function of Cardiomyocytes in the Infarcted Myocardium. *Cell Metab.* **2015**, *21*, 797–798. [[CrossRef](#)] [[PubMed](#)]
63. Estrada, D.; Specker, G.; Martínez, A.; Dias, P.P.; Hissa, B.; Andrade, L.O.; Radi, R.; Piacenza, L. Cardiomyocyte diffusible redox mediators control Trypanosoma cruzi infection: Role of parasite mitochondrial iron superoxide dismutase. *Biochem. J.* **2018**, *475*, 1235–1251. [[CrossRef](#)] [[PubMed](#)]
64. Shi, H.; Zhang, X.; He, Z.; Wu, Z.; Rao, L.; Li, Y. Metabolites of Hypoxic Cardiomyocytes Induce the Migration of Cardiac Fibroblasts. *Cell. Physiol. Biochem.* **2017**, *41*, 413–421. [[CrossRef](#)] [[PubMed](#)]
65. Ancy, C.; Corbi, P.; Froger, J.; Delwail, A.; Wijdenes, J.; Gascan, H.; Potreau, D.; Lecron, J.-C. Secretion of IL-6, IL-11 and lif by human cardiomyocytes in primary culture. *Cytokine* **2002**, *18*, 199–205. [[CrossRef](#)] [[PubMed](#)]
66. Aoyagi, T.; Matsui, T. The Cardiomyocyte as a Source of Cytokines in Cardiac Injury. *J. Cell Sci. Ther.* **2011**, *2012*. [[CrossRef](#)]
67. Hsieh, P.C.H.; Davis, M.E.; Lisowski, L.K.; Lee, R.T. Endothelial-cardiomyocyte interactions in cardiac development and repair. *Annu. Rev. Physiol.* **2006**, *68*, 51–66. [[CrossRef](#)]
68. Ziegler, T.; Horstkotte, J.; Schwab, C.; Pfetsch, V.; Weinmann, K.; Dietzel, S.; Rohwedder, I.; Hinkel, R.; Gross, L.; Lee, S.; et al. Angiopoietin 2 mediates microvascular and hemodynamic alterations in sepsis. *J. Clin. Investig.* **2013**. [[CrossRef](#)]
69. Kuwabara, M.; Kakinuma, Y.; Ando, M.; Katare, R.G.; Yamasaki, F.; Doi, Y.; Sato, T. Nitric Oxide Stimulates Vascular Endothelial Growth Factor Production in Cardiomyocytes Involved in Angiogenesis. *J. Physiol. Sci.* **2006**, *56*, 95–101. [[CrossRef](#)]
70. Abhinand, C.S.; Raju, R.; Soumya, S.J.; Arya, P.S.; Sudhakaran, P.R. VEGF-A/VEGFR2 signaling network in endothelial cells relevant to angiogenesis. *J. Cell Commun. Signal.* **2016**, *10*, 347–354. [[CrossRef](#)]
71. Giordano, F.J.; Gerber, H.P.; Williams, S.P.; VanBruggen, N.; Bunting, S.; Ruiz-Lozano, P.; Gu, Y.; Nath, A.K.; Huang, Y.; Hickey, R.; et al. A cardiac myocyte vascular endothelial growth factor paracrine pathway is required to maintain cardiac function. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 5780–5785. [[CrossRef](#)]

72. Smart, N.; Dubé, K.N.; Riley, P.R. Coronary vessel development and insight towards neovascular therapy. *Int. J. Exp. Pathol.* **2009**, *90*, 262–283. [[CrossRef](#)] [[PubMed](#)]
73. Carmeliet, P.; Ng, Y.S.; Nuyens, D.; Theilmeier, G.; Brusselmans, K.; Cornelissen, I.; Ehler, E.; Kakkar, V.V.; Stalmans, I.; Mattot, V.; et al. Impaired myocardial angiogenesis and ischemic cardiomyopathy in mice lacking the vascular endothelial growth factor isoforms VEGF164 and VEGF188. *Nat. Med.* **1999**, *5*, 495–502. [[CrossRef](#)] [[PubMed](#)]
74. Dor, Y.; Camenisch, T.D.; Itin, A.; Fishman, G.I.; McDonald, J.A.; Carmeliet, P.; Keshet, E. A novel role for VEGF in endocardial cushion formation and its potential contribution to congenital heart defects. *Dev. Camb. Engl.* **2001**, *128*, 1531–1538.
75. Dor, Y.; Klewer, S.E.; McDonald, J.A.; Keshet, E.; Camenisch, T.D. VEGF modulates early heart valve formation. *Anat. Rec. A. Discov. Mol. Cell. Evol. Biol.* **2003**, *271*, 202–208. [[CrossRef](#)] [[PubMed](#)]
76. Miquerol, L.; Langille, B.L.; Nagy, A. Embryonic development is disrupted by modest increases in vascular endothelial growth factor gene expression. *Dev. Camb. Engl.* **2000**, *127*, 3941–3946.
77. Lambrechts, D.; Carmeliet, P. Sculpting heart valves with NFATc and VEGF. *Cell* **2004**, *118*, 532–534. [[CrossRef](#)]
78. Chang, C.-P.; Neilson, J.R.; Bayle, J.H.; Gestwicki, J.E.; Kuo, A.; Stankunas, K.; Graef, I.A.; Crabtree, G.R. A field of myocardial-endocardial NFAT signaling underlies heart valve morphogenesis. *Cell* **2004**, *118*, 649–663. [[CrossRef](#)]
79. Seko, Y.; Seko, Y.; Takahashi, N.; Shibuya, M.; Yazaki, Y. Pulsatile stretch stimulates vascular endothelial growth factor (VEGF) secretion by cultured rat cardiac myocytes. *Biochem. Biophys. Res. Commun.* **1999**, *254*, 462–465. [[CrossRef](#)]
80. Semenza, G.L. Hypoxia-inducible factor 1 and cardiovascular disease. *Annu. Rev. Physiol.* **2014**, *76*, 39–56. [[CrossRef](#)]
81. Shen, J.; Xie, Y.; Liu, Z.; Zhang, S.; Wang, Y.; Jia, L.; Wang, Y.; Cai, Z.; Ma, H.; Xiang, M. Increased myocardial stiffness activates cardiac microvascular endothelial cell via VEGF paracrine signaling in cardiac hypertrophy. *J. Mol. Cell. Cardiol.* **2018**, *122*, 140–151. [[CrossRef](#)]
82. Zhang, J.; Liu, A.; Hou, R.; Zhang, J.; Jia, X.; Jiang, W.; Chen, J. Salidroside protects cardiomyocyte against hypoxia-induced death: A HIF-1 $\alpha$ -activated and VEGF-mediated pathway. *Eur. J. Pharmacol.* **2009**, *607*, 6–14. [[CrossRef](#)] [[PubMed](#)]
83. Leychenko, A.; Konorev, E.; Jijiwa, M.; Matter, M.L. Stretch-induced hypertrophy activates NFkB-mediated VEGF secretion in adult cardiomyocytes. *PLoS ONE* **2011**, *6*, e29055. [[CrossRef](#)] [[PubMed](#)]
84. Li, J.; Hampton, T.; Morgan, J.P.; Simons, M. Stretch-induced VEGF expression in the heart. *J. Clin. Investig.* **1997**, *100*, 18–24. [[CrossRef](#)] [[PubMed](#)]
85. Shimojo, N.; Jesmin, S.; Zaedi, S.; Otsuki, T.; Maeda, S.; Yamaguchi, N.; Aonuma, K.; Hattori, Y.; Miyauchi, T. Contributory role of VEGF overexpression in endothelin-1-induced cardiomyocyte hypertrophy. *Am. J. Physiol. Heart Circ. Physiol.* **2007**, *293*, H474–H481. [[CrossRef](#)] [[PubMed](#)]
86. Rysä, J.; Tenhunen, O.; Serpi, R.; Soini, Y.; Nemer, M.; Leskinen, H.; Ruskoaho, H. GATA-4 is an angiogenic survival factor of the infarcted heart. *Circ. Heart Fail.* **2010**, *3*, 440–450. [[CrossRef](#)]
87. Heineke, J.; Auger-Messier, M.; Xu, J.; Oka, T.; Sargent, M.A.; York, A.; Klevitsky, R.; Vaikunth, S.; Duncan, S.A.; Aronow, B.J.; et al. Cardiomyocyte GATA4 functions as a stress-responsive regulator of angiogenesis in the murine heart. *J. Clin. Investig.* **2007**, *117*, 3198–3210. [[CrossRef](#)]
88. Van Berlo, J.H.; Elrod, J.W.; van den Hoogenhof, M.M.G.; York, A.J.; Aronow, B.J.; Duncan, S.A.; Molkenin, J.D. The transcription factor GATA-6 regulates pathological cardiac hypertrophy. *Circ. Res.* **2010**, *107*, 1032–1040. [[CrossRef](#)]
89. Nam, Y.S.; Kim, Y.; Joung, H.; Kwon, D.-H.; Choe, N.; Min, H.-K.; Kim, Y.S.; Kim, H.-S.; Kim, D.-K.; Cho, Y.K.; et al. Small heterodimer partner blocks cardiac hypertrophy by interfering with GATA6 signaling. *Circ. Res.* **2014**, *115*, 493–503. [[CrossRef](#)]
90. Van Berlo, J.H.; Aronow, B.J.; Molkenin, J.D. Parsing the roles of the transcription factors GATA-4 and GATA-6 in the adult cardiac hypertrophic response. *PLoS ONE* **2013**, *8*, e84591. [[CrossRef](#)] [[PubMed](#)]
91. Curry, J.M.; Eubank, T.D.; Roberts, R.D.; Wang, Y.; Pore, N.; Maity, A.; Marsh, C.B. M-CSF signals through the MAPK/ERK pathway via Sp1 to induce VEGF production and induces angiogenesis in vivo. *PLoS ONE* **2008**, *3*, e3405. [[CrossRef](#)]
92. Lin, H.-H.; Lai, S.-C.; Chau, L.-Y. Heme oxygenase-1/carbon monoxide induces vascular endothelial growth factor expression via p38 kinase-dependent activation of Sp1. *J. Biol. Chem.* **2011**, *286*, 3829–3838. [[CrossRef](#)]

93. Rose, B.A.; Yokota, T.; Chintalgattu, V.; Ren, S.; Iruela-Arispe, L.; Khakoo, A.Y.; Minamisawa, S.; Wang, Y. Cardiac myocyte p38 $\alpha$  kinase regulates angiogenesis via myocyte-endothelial cell cross-talk during stress-induced remodeling in the heart. *J. Biol. Chem.* **2017**, *292*, 12787–12800. [[CrossRef](#)]
94. Chen, Y.; Amende, I.; Hampton, T.G.; Yang, Y.; Ke, Q.; Min, J.-Y.; Xiao, Y.-F.; Morgan, J.P. Vascular endothelial growth factor promotes cardiomyocyte differentiation of embryonic stem cells. *Am. J. Physiol.-Heart Circ. Physiol.* **2006**, *291*, H1653–H1658. [[CrossRef](#)]
95. Neufeld, G.; Cohen, T.; Gengrinovitch, S.; Poltorak, Z. Vascular endothelial growth factor (VEGF) and its receptors. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* **1999**, *13*, 9–22. [[CrossRef](#)]
96. Pearlman, J.D.; Hibberd, M.G.; Chuang, M.L.; Harada, K.; Lopez, J.J.; Gladstone, S.R.; Friedman, M.; Sellke, F.W.; Simons, M. Magnetic resonance mapping demonstrates benefits of VEGF-induced myocardial angiogenesis. *Nat. Med.* **1995**, *1*, 1085–1089. [[CrossRef](#)]
97. Taimeh, Z.; Loughran, J.; Birks, E.J.; Bolli, R. Vascular endothelial growth factor in heart failure. *Nat. Rev. Cardiol.* **2013**, *10*, 519–530. [[CrossRef](#)]
98. Tang, J.; Wang, J.; Kong, X.; Yang, J.; Guo, L.; Zheng, F.; Zhang, L.; Huang, Y.; Wan, Y. Vascular endothelial growth factor promotes cardiac stem cell migration via the PI3K/Akt pathway. *Exp. Cell Res.* **2009**, *315*, 3521–3531. [[CrossRef](#)]
99. Friehs, I.; Barillas, R.; Vasilyev, N.V.; Roy, N.; McGowan, F.X.; del Nido, P.J. Vascular endothelial growth factor prevents apoptosis and preserves contractile function in hypertrophied infant heart. *Circulation* **2006**, *114*, I290–I295. [[CrossRef](#)]
100. Tao, Z.; Chen, B.; Tan, X.; Zhao, Y.; Wang, L.; Zhu, T.; Cao, K.; Yang, Z.; Kan, Y.W.; Su, H. Coexpression of VEGF and angiopoietin-1 promotes angiogenesis and cardiomyocyte proliferation reduces apoptosis in porcine myocardial infarction (MI) heart. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 2064–2069. [[CrossRef](#)]
101. Conway, E. Molecular mechanisms of blood vessel growth. *Cardiovasc. Res.* **2001**, *49*, 507–521. [[CrossRef](#)]
102. Borgers, M.; Voipio-Pulkki, L.-M.; Izumo, S. Apoptosis. *Cardiovasc. Res.* **2000**, *45*, 525–527. [[CrossRef](#)]
103. Madonna, R.; De Caterina, R. VEGF receptor switching in heart development and disease. *Cardiovasc. Res.* **2009**, *84*, 4–6. [[CrossRef](#)]
104. Zentilin, L.; Puligadda, U.; Lionetti, V.; Zacchigna, S.; Collesi, C.; Pattarini, L.; Ruozi, G.; Camporesi, S.; Sinagra, G.; Pepe, M.; et al. Cardiomyocyte VEGFR-1 activation by VEGF-B induces compensatory hypertrophy and preserves cardiac function after myocardial infarction. *FASEB J.* **2010**, *24*, 1467–1478. [[CrossRef](#)]
105. Guo, H.; Cui, G.; Yang, J.; Wang, C.; Zhu, J.; Zhang, L.; Jiang, J.; Shao, S. Sustained delivery of VEGF from designer self-assembling peptides improves cardiac function after myocardial infarction. *Biochem. Biophys. Res. Commun.* **2012**, *424*, 105–111. [[CrossRef](#)]
106. Rottbauer, W. VEGF-PLC 1 pathway controls cardiac contractility in the embryonic heart. *Genes Dev.* **2005**, *19*, 1624–1634. [[CrossRef](#)]
107. Arsic, N.; Zentilin, L.; Zacchigna, S.; Santoro, D.; Stanta, G.; Salvi, A.; Sinagra, G.; Giacca, M. Induction of functional neovascularization by combined VEGF and angiopoietin-1 gene transfer using AAV vectors. *Mol. Ther. J. Am. Soc. Gene Ther.* **2003**, *7*, 450–459. [[CrossRef](#)]
108. Poltorak, Z.; Cohen, T.; Neufeld, G. The VEGF splice variants: Properties, receptors, and usage for the treatment of ischemic diseases. *Herz* **2000**, *25*, 126–129. [[CrossRef](#)]
109. Ren, G.; Dewald, O.; Frangogiannis, N. Inflammatory Mechanisms in Myocardial Infarction. *Curr. Drug Target -Inflamm. Allergy* **2003**, *2*, 242–256. [[CrossRef](#)]
110. Tang, J.-M.; Wang, J.-N.; Zhang, L.; Zheng, F.; Yang, J.-Y.; Kong, X.; Guo, L.-Y.; Chen, L.; Huang, Y.-Z.; Wan, Y.; et al. VEGF/SDF-1 promotes cardiac stem cell mobilization and myocardial repair in the infarcted heart. *Cardiovasc. Res.* **2011**, *91*, 402–411. [[CrossRef](#)] [[PubMed](#)]
111. Zhao, T.; Zhao, W.; Chen, Y.; Liu, L.; Ahokas, R.A.; Sun, Y. Differential expression of vascular endothelial growth factor isoforms and receptor subtypes in the infarcted heart. *Int. J. Cardiol.* **2013**, *167*, 2638–2645. [[CrossRef](#)] [[PubMed](#)]
112. Li, J.; Brown, L.F.; Hibberd, M.G.; Grossman, J.D.; Morgan, J.P.; Simons, M. VEGF, flk-1, andflt-1 expression in a rat myocardial infarction model of angiogenesis. *Am. J. Physiol.* **1996**, *270*, H1803–H1811. [[CrossRef](#)] [[PubMed](#)]

113. Zhao, T.; Zhao, W.; Chen, Y.; Ahokas, R.A.; Sun, Y. Vascular endothelial growth factor (VEGF)-A: Role on cardiac angiogenesis following myocardial infarction. *Microvasc. Res.* **2010**, *80*, 188–194. [[CrossRef](#)] [[PubMed](#)]
114. Touyz, R.M.; Herrmann, J. Cardiotoxicity with vascular endothelial growth factor inhibitor therapy. *NPJ Precis. Oncol.* **2018**, *2*, 13. [[CrossRef](#)]
115. Ucuzian, A.A.; Gassman, A.A.; East, A.T.; Greisler, H.P. Molecular mediators of angiogenesis. *J. Burn Care Res. Off. Publ. Am. Burn Assoc.* **2010**, *31*, 158–175. [[CrossRef](#)]
116. Carmeliet, P.; Jain, R.K. Angiogenesis in cancer and other diseases. *Nature* **2000**, *407*, 249–257. [[CrossRef](#)]
117. Feng, Y.-M.; Verfaillie, C.; Yu, H. Vascular Diseases and Metabolic Disorders. *Stem Cells Int.* **2016**, *2016*, 5810358. [[CrossRef](#)]
118. Moran, A.; Forouzanfar, M.; Sampson, U.; Chugh, S.; Feigin, V.; Mensah, G. The epidemiology of cardiovascular diseases in sub-Saharan Africa: The Global Burden of Diseases, Injuries and Risk Factors 2010 Study. *Prog. Cardiovasc. Dis.* **2013**, *56*, 234–239. [[CrossRef](#)]
119. Mozaffarian, D.; Benjamin, E.J.; Go, A.S.; Arnett, D.K.; Blaha, M.J.; Cushman, M.; Das, S.R.; de Ferranti, S.; Després, J.-P.; Fullerton, H.J.; et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation* **2016**, *133*, e38–360. [[CrossRef](#)]
120. Semenkovich, C.F. We Know More Than We Can Tell About Diabetes and Vascular Disease: The 2016 Edwin Bierman Award Lecture. *Diabetes* **2017**, *66*, 1735–1741. [[CrossRef](#)]
121. Lauer, M.S. Advancing cardiovascular research. *Chest* **2012**, *141*, 500–505. [[CrossRef](#)]
122. Luo, K.; Long, H.; Xu, B. Reduced apoptosis after acute myocardial infarction by simvastatin. *Cell Biochem. Biophys.* **2015**, *71*, 735–740. [[CrossRef](#)]
123. Hung, J.; Teng, T.-H.K.; Finn, J.; Knuiman, M.; Briffa, T.; Stewart, S.; Sanfilippo, F.M.; Ridout, S.; Hobbs, M. Trends from 1996 to 2007 in incidence and mortality outcomes of heart failure after acute myocardial infarction: A population-based study of 20,812 patients with first acute myocardial infarction in Western Australia. *J. Am. Heart Assoc.* **2013**, *2*, e000172. [[CrossRef](#)] [[PubMed](#)]
124. Mendis, S.; Thygesen, K.; Kuulasmaa, K.; Giampaoli, S.; Mähönen, M.; Ngu Blackett, K.; Lisheng, L. Writing group on behalf of the participating experts of the WHO consultation for revision of WHO definition of myocardial infarction World Health Organization definition of myocardial infarction: 2008–09 revision. *Int. J. Epidemiol.* **2011**, *40*, 139–146. [[CrossRef](#)] [[PubMed](#)]
125. Dalen, J.E.; Alpert, J.S.; Goldberg, R.J.; Weinstein, R.S. The epidemic of the 20(th) century: Coronary heart disease. *Am. J. Med.* **2014**, *127*, 807–812. [[CrossRef](#)] [[PubMed](#)]
126. Patel, N.R.; Patel, D.V.; Murumkar, P.R.; Yadav, M.R. Contemporary developments in the discovery of selective factor Xa inhibitors: A review. *Eur. J. Med. Chem.* **2016**, *121*, 671–698. [[CrossRef](#)]
127. Antithrombotic Trialists' (ATT) Collaboration; Baigent, C.; Blackwell, L.; Collins, R.; Emberson, J.; Godwin, J.; Peto, R.; Buring, J.; Hennekens, C.; Kearney, P.; et al. Aspirin in the primary and secondary prevention of vascular disease: Collaborative meta-analysis of individual participant data from randomised trials. *Lancet Lond. Engl.* **2009**, *373*, 1849–1860. [[CrossRef](#)]
128. Jackson, L.R.; Ju, C.; Zettler, M.; Messenger, J.C.; Cohen, D.J.; Stone, G.W.; Baker, B.A.; Effron, M.; Peterson, E.D.; Wang, T.Y. Outcomes of Patients With Acute Myocardial Infarction Undergoing Percutaneous Coronary Intervention Receiving an Oral Anticoagulant and Dual Antiplatelet Therapy: A Comparison of Clopidogrel Versus Prasugrel From the TRANSLATE-ACS Study. *JACC Cardiovasc. Interv.* **2015**, *8*, 1880–1889. [[CrossRef](#)]
129. Anisimov, A.; Tvorogov, D.; Alitalo, A.; Leppänen, V.-M.; An, Y.; Han, E.C.; Orsenigo, F.; Gaál, E.I.; Holopainen, T.; Koh, Y.J.; et al. Vascular endothelial growth factor-angiopoietin chimera with improved properties for therapeutic angiogenesis. *Circulation* **2013**, *127*, 424–434. [[CrossRef](#)]
130. Albrecht-Schgoer, K.; Schgoer, W.; Holfeld, J.; Theurl, M.; Wiedemann, D.; Steger, C.; Gupta, R.; Semsroth, S.; Fischer-Colbrie, R.; Beer, A.G.E.; et al. The angiogenic factor secretoneurin induces coronary angiogenesis in a model of myocardial infarction by stimulation of vascular endothelial growth factor signaling in endothelial cells. *Circulation* **2012**, *126*, 2491–2501. [[CrossRef](#)]
131. Cheng, C.; Li, P.; Wang, Y.-G.; Bi, M.-H.; Wu, P.-S. Study on the expression of VEGF and HIF-1 $\alpha$  in infarct area of rats with AMI. *Eur. Rev. Med. Pharmacol. Sci.* **2016**, *20*, 115–119.
132. Seko, Y.; Fukuda, S.; Nagai, R. Serum levels of endostatin, vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) in patients with acute myocardial infarction undergoing early reperfusion therapy. *Clin. Sci. Lond. Engl.* 1979 **2004**, *106*, 439–442. [[CrossRef](#)] [[PubMed](#)]

133. Yang, Z.; Wan, J.; Pan, W.; Zou, J. Expression of vascular endothelial growth factor in cardiac repair: Signaling mechanisms mediating vascular protective effects. *Int. J. Biol. Macromol.* **2018**, *113*, 179–185. [[CrossRef](#)]
134. Yu, F.; Lu, J.; Li, Z.; Zhou, X.; Zeng, S.; Zhan, Q.; Yuan, M.; Yang, Q.; Xia, J. Correlation of Plasma Vascular Endothelial Growth Factor and Endostatin Levels with Symptomatic Intra- and Extracranial Atherosclerotic Stenosis in a Chinese Han Population. *J. Stroke Cerebrovasc. Dis. Off. J. Natl. Stroke Assoc.* **2017**, *26*, 1061–1070. [[CrossRef](#)] [[PubMed](#)]
135. Yu, J.-M.; Zhang, X.-B.; Jiang, W.; Wang, H.-D.; Zhang, Y.-N. Astragalosides promote angiogenesis via vascular endothelial growth factor and basic fibroblast growth factor in a rat model of myocardial infarction. *Mol. Med. Rep.* **2015**, *12*, 6718–6726. [[CrossRef](#)] [[PubMed](#)]
136. Shinohara, K. The expression and the role of vascular endothelial growth factor (VEGF) in human normal and myocardial infarcted heart. *Hokkaido Igaku Zasshi* **1994**, *69*, 978–993. [[PubMed](#)]
137. Eržen, B.; Šilar, M.; Šabovič, M. Stable phase post-MI patients have elevated VEGF levels correlated with inflammation markers, but not with atherosclerotic burden. *BMC Cardiovasc. Disord.* **2014**, *14*, 166. [[CrossRef](#)] [[PubMed](#)]
138. Banquet, S.; Gomez, E.; Nicol, L.; Edwards-Lévy, F.; Henry, J.-P.; Cao, R.; Schapman, D.; Dautreux, B.; Lallemand, F.; Bauer, F.; et al. Arteriogenic therapy by intramyocardial sustained delivery of a novel growth factor combination prevents chronic heart failure. *Circulation* **2011**, *124*, 1059–1069. [[CrossRef](#)] [[PubMed](#)]
139. Iadecola, C. The pathobiology of vascular dementia. *Neuron* **2013**, *80*, 844–866. [[CrossRef](#)]
140. Del Zoppo, G.J.; Mabuchi, T. Cerebral microvessel responses to focal ischemia. *J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab.* **2003**, *23*, 879–894. [[CrossRef](#)]
141. Fan, Y.; Yang, G.-Y. Therapeutic angiogenesis for brain ischemia: A brief review. *J. Neuroimmune Pharmacol. Off. J. Soc. NeuroImmune Pharmacol.* **2007**, *2*, 284–289. [[CrossRef](#)]
142. Beck, H.; Plate, K.H. Angiogenesis after cerebral ischemia. *Acta Neuropathol. (Berl.)* **2009**, *117*, 481–496. [[CrossRef](#)] [[PubMed](#)]
143. Li, T.-S.; Cheng, K.; Malliaras, K.; Smith, R.R.; Zhang, Y.; Sun, B.; Matsushita, N.; Blusztajn, A.; Terrovitis, J.; Kusuoka, H.; et al. Direct comparison of different stem cell types and subpopulations reveals superior paracrine potency and myocardial repair efficacy with cardiosphere-derived cells. *J. Am. Coll. Cardiol.* **2012**, *59*, 942–953. [[CrossRef](#)] [[PubMed](#)]
144. Talwar, T.; Srivastava, M.V.P. Role of vascular endothelial growth factor and other growth factors in post-stroke recovery. *Ann. Indian Acad. Neurol.* **2014**, *17*, 1–6. [[CrossRef](#)] [[PubMed](#)]
145. Zhao, B.-Q.; Wang, S.; Kim, H.-Y.; Storrie, H.; Rosen, B.R.; Mooney, D.J.; Wang, X.; Lo, E.H. Role of matrix metalloproteinases in delayed cortical responses after stroke. *Nat. Med.* **2006**, *12*, 441–445. [[CrossRef](#)] [[PubMed](#)]
146. Carmeliet, P.; Collen, D. Molecular basis of angiogenesis. Role of VEGF and VE-cadherin. *Ann. N. Y. Acad. Sci.* **2000**, *902*, 249–262; discussion 262. [[CrossRef](#)] [[PubMed](#)]
147. Lutsenko, S.V.; Kiselev, S.M.; Severin, S.E. Molecular mechanisms of tumor angiogenesis. *Biochem. Biokhimiia* **2003**, *68*, 286–300. [[CrossRef](#)]
148. Kobiyama, K.; Ley, K. Atherosclerosis. *Circ. Res.* **2018**, *123*, 1118–1120. [[CrossRef](#)]
149. Chistiakov, D.A.; Melnichenko, A.A.; Myasoedova, V.A.; Grechko, A.V.; Orekhov, A.N. Role of lipids and intraplaque hypoxia in the formation of neovascularization in atherosclerosis. *Ann. Med.* **2017**, *49*, 661–677. [[CrossRef](#)]
150. Holm, P.W.; Slart, R.H.J.A.; Zeebregts, C.J.; Hillebrands, J.L.; Tio, R.A. Atherosclerotic plaque development and instability: A dual role for VEGF. *Ann. Med.* **2009**, *41*, 257–264. [[CrossRef](#)]
151. Asahara, T.; Chen, D.; Tsurumi, Y.; Kearney, M.; Rossow, S.; Passeri, J.; Symes, J.F.; Isner, J.M. Accelerated restitution of endothelial integrity and endothelium-dependent function after phVEGF165 gene transfer. *Circulation* **1996**, *94*, 3291–3302. [[CrossRef](#)]
152. Camaré, C.; Pucelle, M.; Nègre-Salvayre, A.; Salvayre, R. Angiogenesis in the atherosclerotic plaque. *Redox Biol.* **2017**, *12*, 18–34. [[CrossRef](#)] [[PubMed](#)]
153. Barleon, B.; Sozzani, S.; Zhou, D.; Weich, H.A.; Mantovani, A.; Marmé, D. Migration of human monocytes in response to vascular endothelial growth factor (VEGF) is mediated via the VEGF receptor flt-1. *Blood* **1996**, *87*, 3336–3343. [[CrossRef](#)] [[PubMed](#)]
154. Jaipersad, A.S.; Lip, G.Y.H.; Silverman, S.; Shantsila, E. The Role of Monocytes in Angiogenesis and Atherosclerosis. *J. Am. Coll. Cardiol.* **2014**, *63*, 1–11. [[CrossRef](#)] [[PubMed](#)]

155. Kim, I.; Moon, S.O.; Kim, S.H.; Kim, H.J.; Koh, Y.S.; Koh, G.Y. Vascular endothelial growth factor expression of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin through nuclear factor-kappa B activation in endothelial cells. *J. Biol. Chem.* **2001**, *276*, 7614–7620. [[CrossRef](#)] [[PubMed](#)]
156. Hong, K.H.; Ryu, J.; Han, K.H. Monocyte chemoattractant protein-1-induced angiogenesis is mediated by vascular endothelial growth factor-A. *Blood* **2005**, *105*, 1405–1407. [[CrossRef](#)] [[PubMed](#)]
157. Ylä-Herttuala, S.; Rissanen, T.T.; Vajanto, I.; Hartikainen, J. Vascular Endothelial Growth Factors. *J. Am. Coll. Cardiol.* **2007**, *49*, 1015–1026. [[CrossRef](#)] [[PubMed](#)]
158. Yu, Z.-M.; Deng, X.-T.; Qi, R.-M.; Xiao, L.-Y.; Yang, C.-Q.; Gong, T. Mechanism of Chronic Stress-induced Reduced Atherosclerotic Medial Area and Increased Plaque Instability in Rabbit Models of Chronic Stress. *Chin. Med. J. (Engl.)* **2018**, *131*, 161–170. [[CrossRef](#)]
159. Figueira, L.; González, J.C. Effect of resveratrol on seric vascular endothelial growth factor concentrations during atherosclerosis. *Clin. E Investig. En Arterioscler. Publicacion Soc. Espanola Arterioscler.* **2018**, *30*, 209–216. [[CrossRef](#)]
160. Moulton, K.S.; Heller, E.; Konerding, M.A.; Flynn, E.; Palinski, W.; Folkman, J. Angiogenesis inhibitors endostatin or TNP-470 reduce intimal neovascularization and plaque growth in apolipoprotein E-deficient mice. *Circulation* **1999**, *99*, 1726–1732. [[CrossRef](#)]
161. Choueiri, T.K.; Schutz, F.A.B.; Je, Y.; Rosenberg, J.E.; Bellmunt, J. Risk of arterial thromboembolic events with sunitinib and sorafenib: A systematic review and meta-analysis of clinical trials. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2010**, *28*, 2280–2285. [[CrossRef](#)]
162. Sandhofer, A.; Tatarczyk, T.; Kirchmair, R.; Iglseider, B.; Paulweber, B.; Patsch, J.R.; Schratzberger, P. Are plasma VEGF and its soluble receptor sFlt-1 atherogenic risk factors? Cross-sectional data from the SAPHIR study. *Atherosclerosis* **2009**, *206*, 265–269. [[CrossRef](#)]
163. Libby, P.; Loscalzo, J.; Ridker, P.M.; Farkouh, M.E.; Hsue, P.Y.; Fuster, V.; Hasan, A.A.; Amar, S. Inflammation, Immunity, and Infection in Atherothrombosis: JACC Review Topic of the Week. *J. Am. Coll. Cardiol.* **2018**, *72*, 2071–2081. [[CrossRef](#)] [[PubMed](#)]
164. Döring, Y.; Soehnlein, O.; Weber, C. Neutrophil Extracellular Traps in Atherosclerosis and Atherothrombosis. *Circ. Res.* **2017**, *120*, 736–743. [[CrossRef](#)] [[PubMed](#)]
165. Badimon, L.; Suades, R.; Crespo, J.; Padro, T.; Chiva-Blanch, G. Diet, microparticles and atherothrombosis. *Front. Biosci. Landmark Ed.* **2018**, *23*, 432–457. [[CrossRef](#)] [[PubMed](#)]
166. Daigo, K.; Inforzato, A.; Barajon, I.; Garlanda, C.; Bottazzi, B.; Meri, S.; Mantovani, A. Pentraxins in the activation and regulation of innate immunity. *Immunol. Rev.* **2016**, *274*, 202–217. [[CrossRef](#)] [[PubMed](#)]
167. Arrillaga-Romany, I.; Norden, A.D. Antiangiogenic therapies for glioblastoma. *CNS Oncol.* **2014**, *3*, 349–358. [[CrossRef](#)] [[PubMed](#)]
168. Puranik, R.; Celermajer, D.S. Smoking and endothelial function. *Prog. Cardiovasc. Dis.* **2003**, *45*, 443–458. [[CrossRef](#)]
169. Cooney, M.M.; Tserng, K.-Y.; Makar, V.; McPeak, R.J.; Ingalls, S.T.; Dowlati, A.; Overmoyer, B.; McCrae, K.; Ksenich, P.; Lavertu, P.; et al. A phase IB clinical and pharmacokinetic study of the angiogenesis inhibitor SU5416 and paclitaxel in recurrent or metastatic carcinoma of the head and neck. *Cancer Chemother. Pharmacol.* **2005**, *55*, 295–300. [[CrossRef](#)]
170. Oppelt, P.; Betbadal, A.; Nayak, L. Approach to chemotherapy-associated thrombosis. *Vasc. Med. Lond. Engl.* **2015**, *20*, 153–161. [[CrossRef](#)]
171. Zangari, M.; Fink, L.M.; Elice, F.; Zhan, F.; Adcock, D.M.; Tricot, G.J. Thrombotic events in patients with cancer receiving antiangiogenesis agents. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2009**, *27*, 4865–4873. [[CrossRef](#)]
172. Mir, O.; Coriat, R.; Cabanes, L.; Ropert, S.; Billefont, B.; Alexandre, J.; Durand, J.-P.; Treluyer, J.-M.; Knebelmann, B.; Goldwasser, F. An observational study of bevacizumab-induced hypertension as a clinical biomarker of antitumor activity. *Oncologist* **2011**, *16*, 1325–1332. [[CrossRef](#)] [[PubMed](#)]
173. Semeniuk-Wojtaś, A.; Lubas, A.; Stec, R.; Szczylik, C.; Niemczyk, S. Influence of Tyrosine Kinase Inhibitors on Hypertension and Nephrotoxicity in Metastatic Renal Cell Cancer Patients. *Int. J. Mol. Sci.* **2016**, *17*, 2073. [[CrossRef](#)] [[PubMed](#)]



174. Rini, B.I.; Cohen, D.P.; Lu, D.R.; Chen, I.; Hariharan, S.; Gore, M.E.; Figlin, R.A.; Baum, M.S.; Motzer, R.J. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. *J. Natl. Cancer Inst.* **2011**, *103*, 763–773. [[CrossRef](#)] [[PubMed](#)]
175. Touyz, R.M.; Herrmann, S.M.S.; Herrmann, J. Vascular toxicities with VEGF inhibitor therapies-focus on hypertension and arterial thrombotic events. *J. Am. Soc. Hypertens.* **2018**, *12*, 409–425. [[CrossRef](#)]
176. Van Hinsbergh, V.W.M.; Eringa, E.C.; Daemen, M.J.A.P. Neovascularization of the atherosclerotic plaque: Interplay between atherosclerotic lesion, adventitia-derived microvessels and perivascular fat. *Curr. Opin. Lipidol.* **2015**, *26*, 405–411. [[CrossRef](#)]
177. Pilarczyk, K.; Sattler, K.J.E.; Galili, O.; Versari, D.; Olson, M.L.; Meyer, F.B.; Zhu, X.-Y.; Lerman, L.O.; Lerman, A. Placenta growth factor expression in human atherosclerotic carotid plaques is related to plaque destabilization. *Atherosclerosis* **2008**, *196*, 333–340. [[CrossRef](#)]
178. Sluimer, J.C.; Kolodgie, F.D.; Bijmens, A.P.J.J.; Maxfield, K.; Pacheco, E.; Kutys, B.; Duimel, H.; Frederik, P.M.; van Hinsbergh, V.W.M.; Virmani, R.; et al. Thin-walled microvessels in human coronary atherosclerotic plaques show incomplete endothelial junctions relevance of compromised structural integrity for intraplaque microvascular leakage. *J. Am. Coll. Cardiol.* **2009**, *53*, 1517–1527. [[CrossRef](#)]
179. Michel, J.-B.; Virmani, R.; Arbustini, E.; Pasterkamp, G. Intraplaque haemorrhages as the trigger of plaque vulnerability. *Eur. Heart J.* **2011**, *32*, 1977–1985, 1985a, 1985b, 1985c. [[CrossRef](#)]
180. Tziakas, D.N.; Kaski, J.C.; Chalikias, G.K.; Romero, C.; Fredericks, S.; Tentis, I.K.; Kortsaris, A.X.; Hatseras, D.I.; Holt, D.W. Total cholesterol content of erythrocyte membranes is increased in patients with acute coronary syndrome: A new marker of clinical instability? *J. Am. Coll. Cardiol.* **2007**, *49*, 2081–2089. [[CrossRef](#)]
181. Moulton, K.S.; Vakili, K.; Zurakowski, D.; Soliman, M.; Butterfield, C.; Sylvain, E.; Lo, K.-M.; Gillies, S.; Javaherian, K.; Folkman, J. Inhibition of plaque neovascularization reduces macrophage accumulation and progression of advanced atherosclerosis. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 4736–4741. [[CrossRef](#)]
182. Winnik, S.; Lohmann, C.; Siciliani, G.; von Lukowicz, T.; Kuschnerus, K.; Kraenkel, N.; Brokopp, C.E.; Enseleit, F.; Michels, S.; Ruschitzka, F.; et al. Systemic VEGF inhibition accelerates experimental atherosclerosis and disrupts endothelial homeostasis—implications for cardiovascular safety. *Int. J. Cardiol.* **2013**, *168*, 2453–2461. [[CrossRef](#)] [[PubMed](#)]
183. Cho, M.-L.; Jung, Y.O.; Moon, Y.-M.; Min, S.-Y.; Yoon, C.-H.; Lee, S.-H.; Park, S.-H.; Cho, C.-S.; Jue, D.-M.; Kim, H.-Y. Interleukin-18 induces the production of vascular endothelial growth factor (VEGF) in rheumatoid arthritis synovial fibroblasts via AP-1-dependent pathways. *Immunol. Lett.* **2006**, *103*, 159–166. [[CrossRef](#)] [[PubMed](#)]
184. Meng, R.; Pei, Z.; Chen, B.; Ma, R.; Zhang, C.; Chen, B.; Zhang, A.; Wu, T.; Liu, D.; Dong, Y. Age-related change of serum angiogenic factor levels in patients with coronary artery disease. *Acta Cardiol.* **2009**, *64*, 735–740. [[CrossRef](#)] [[PubMed](#)]
185. Vm, M.; Al, S.; Aa, A.; As, Z.; Av, K.; Rs, O.; Im, M.; Ga, K. Circulating interleukin-18: Association with IL-8, IL-10 and VEGF serum levels in patients with and without heart rhythm disorders. *Int. J. Cardiol.* **2016**, *215*, 105–109. [[CrossRef](#)] [[PubMed](#)]
186. Kucukardali, Y.; Aydogdu, S.; Ozmen, N.; Yonem, A.; Solmazgul, E.; Ozyurt, M.; Cingozbay, Y.; Aydogdu, A. The relationship between severity of coronary artery disease and plasma level of vascular endothelial growth factor. *Cardiovasc. Revasc. Med.* **2008**, *9*, 66–70. [[CrossRef](#)]
187. Henning, R.J. Therapeutic angiogenesis: Angiogenic growth factors for ischemic heart disease. *Future Cardiol.* **2016**, *12*, 585–599. [[CrossRef](#)]
188. Laham, R.J.; Chronos, N.A.; Pike, M.; Leimbach, M.E.; Udelson, J.E.; Pearlman, J.D.; Pettigrew, R.I.; Whitehouse, M.J.; Yoshizawa, C.; Simons, M. Intracoronary basic fibroblast growth factor (FGF-2) in patients with severe ischemic heart disease: Results of a phase I open-label dose escalation study. *J. Am. Coll. Cardiol.* **2000**, *36*, 2132–2139. [[CrossRef](#)]
189. Mitsos, S.; Katsanos, K.; Koletsis, E.; Kagadis, G.C.; Anastasiou, N.; Diamantopoulos, A.; Karnabatidis, D.; Dougenis, D. Therapeutic angiogenesis for myocardial ischemia revisited: Basic biological concepts and focus on latest clinical trials. *Angiogenesis* **2012**, *15*, 1–22. [[CrossRef](#)]
190. Grines, C.L.; Watkins, M.W.; Helmer, G.; Penny, W.; Brinker, J.; Marmur, J.D.; West, A.; Rade, J.J.; Marrott, P.; Hammond, H.K.; et al. Angiogenic Gene Therapy (AGENT) trial in patients with stable angina pectoris. *Circulation* **2002**, *105*, 1291–1297. [[CrossRef](#)]

191. Grines, C.L.; Watkins, M.W.; Mahmarian, J.J.; Iskandrian, A.E.; Rade, J.J.; Marrott, P.; Pratt, C.; Kleiman, N. Angiogene GENE Therapy (AGENT-2) Study Group A randomized, double-blind, placebo-controlled trial of Ad5FGF-4 gene therapy and its effect on myocardial perfusion in patients with stable angina. *J. Am. Coll. Cardiol.* **2003**, *42*, 1339–1347. [[CrossRef](#)]
192. Henry, T.D.; Grines, C.L.; Watkins, M.W.; Dib, N.; Barbeau, G.; Moreadith, R.; Andrasfay, T.; Engler, R.L. Effects of Ad5FGF-4 in patients with angina: An analysis of pooled data from the AGENT-3 and AGENT-4 trials. *J. Am. Coll. Cardiol.* **2007**, *50*, 1038–1046. [[CrossRef](#)] [[PubMed](#)]
193. Afzal, M.R.; Samanta, A.; Shah, Z.I.; Jeevanantham, V.; Abdel-Latif, A.; Zuba-Surma, E.K.; Dawn, B. Adult Bone Marrow Cell Therapy for Ischemic Heart Disease: Evidence and Insights From Randomized Controlled Trials. *Circ. Res.* **2015**, *117*, 558–575. [[CrossRef](#)] [[PubMed](#)]
194. Epelman, S.; Liu, P.P.; Mann, D.L. Role of innate and adaptive immune mechanisms in cardiac injury and repair. *Nat. Rev. Immunol.* **2015**, *15*, 117–129. [[CrossRef](#)] [[PubMed](#)]
195. Sattler, S.; Rosenthal, N. The neonate versus adult mammalian immune system in cardiac repair and regeneration. *Biochim. Biophys. Acta* **2016**, *1863*, 1813–1821. [[CrossRef](#)]
196. Tompkins, B.A.; Natsumeda, M.; Balkan, W.; Hare, J.M. What Is the Future of Cell-Based Therapy for Acute Myocardial Infarction. *Circ. Res.* **2017**, *120*, 252–255. [[CrossRef](#)]
197. Duran, J.M.; Makarewich, C.A.; Sharp, T.E.; Starosta, T.; Zhu, F.; Hoffman, N.E.; Chiba, Y.; Madesh, M.; Berretta, R.M.; Kubo, H.; et al. Bone-derived stem cells repair the heart after myocardial infarction through transdifferentiation and paracrine signaling mechanisms. *Circ. Res.* **2013**, *113*, 539–552. [[CrossRef](#)]
198. Gray, W.D.; French, K.M.; Ghosh-Choudhary, S.; Maxwell, J.T.; Brown, M.E.; Platt, M.O.; Searles, C.D.; Davis, M.E. Identification of therapeutic covariant microRNA clusters in hypoxia-treated cardiac progenitor cell exosomes using systems biology. *Circ. Res.* **2015**, *116*, 255–263. [[CrossRef](#)]
199. Sahoo, S.; Losordo, D.W. Exosomes and cardiac repair after myocardial infarction. *Circ. Res.* **2014**, *114*, 333–344. [[CrossRef](#)]
200. Vicencio, J.M.; Yellon, D.M.; Sivaraman, V.; Das, D.; Boi-Doku, C.; Arjun, S.; Zheng, Y.; Riquelme, J.A.; Kearney, J.; Sharma, V.; et al. Plasma exosomes protect the myocardium from ischemia-reperfusion injury. *J. Am. Coll. Cardiol.* **2015**, *65*, 1525–1536. [[CrossRef](#)]



© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).