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Angiogenesis and Microcirculation in Ischemic Heart Disease

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Abstract

Angiogenesis among the functional organ systems, the cardiovascular system is the paramount appearing system in the development of vertebrate embryo. However, different epigenetic and genetic mechanisms play important role in the development of vascular organ system. During embryonic life, the blood capillaries from endothelial tissues differentiate from mesodermal cells in the form of vasculo-genesis. Alteration of primary blood vessels into supplementary vascular system is believed to happen through a process known as angiogenesis. The process of angiogenesis happens naturally during pregnancy, wound healing, female menstrual cycle and important in tissue growth and repair. Different pathological conditions like diabetes, chronic kidney disease, cutaneous complications, cancer, neurodegenerative disorders, rheumatoid arthritis and age-related macular degeneration are considered by excessive angiogenesis in which vessels grow in unmannered and unrestricted pattern.

Keywords: Angiogenesis; Microcirculation; Ischemic heart disease

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Introduction

Angiogenesis among the functional organ systems, the cardiovascular system is the paramount appearing system in the development of vertebrate embryo.Different epigenetic and genetic mechanisms play important role in the development of vascular organ system.During embryonic life, the blood capillaries from endothelial tissues differentiate from mesodermal cells in the form of vasculo-genesis.Thevasculo-genesis involves the differentiation of angioblasts into blood islets which further go into the formation of nascent capillary plexus.Thus the embryonic heart and embryonic vascular plexus are made in this way[1]. Different observations have specified that vasculo-genesis not limited to prompt embryogenesis, but may have a physiological role.The foremost proof supporting this opinion comes from:

- Newly evaluated mechanisms of vasculo-genesis in tumor growth
- Existence of endothelial precursors and endothelial cells [2].

With the commencement of embryonic circulation, the primary blood vessels modified into arteries and veins so as to improve functional vascular loop. Alteration of primary blood vessels into supplementary vascular system is believed to happen through a process known as angiogenesis[3]. During the whole embryonic life, vessel formation matures through transformation, pruning with vessel strips appearing and vanishing and relinking in new patterns throughout development. During the embryonic life, local perfusional modifications crop melodramatic variations in vascular pattern[4]. The process of angiogenesis happens naturally during pregnancy, wound healing, female menstrual cycle and important in tissue growth and repair.The angiogenesis being controlled process is dependent on an intricate equilibrium of both anti-antigenic and pro-angiogenic.The process of angiogenesis completed in arranged series which involves in interactions between vascular components, growth factors and extracellular matrix[5]. Angiogenesis is regulated by various 'classic' and 'non-classic' factors.Basic classic factors generally include cytokines and different growth factors like angiopoietins (Angs), fibroblast growth factor-2 (FGF-2), placental growth factor (PlGF), transforming growth factors (TGFs), platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF).The various endogenous peptides fall in non-classic factors which are adiponectin, adrenomedullin (AM), angiotensin II (Ang II), endothelins (ETs), erythropoietin (Epo), granulocyte-macrophage colony stimulating factor (GM-CSF), granulocyte-colony stimulating factor

(G-CSF), interleukins, leptin, neuropeptide-Y, pituitary adenylatecyclase-activating polypeptide (PACAP), pro-adrenomedullin N-terminal 20 peptide (PAMP)[6]. Different pathological conditions like diabetes, chronic kidney disease, cutaneous complications, cancer, neurodegenerative disorders, rheumatoid arthritis and age-related macular degeneration (Figure1) are considered by excessive angiogenesis in which vessels grow in unmannered and unrestricted pattern.Furthermore, in different pathological situations growth factors also play significance role in the modulation of cellular differentiation, glucose metabolism, lipid metabolism and immune system[7-57].

Basically angiogenesis is of two types: splitting and sprouting. The longitudinal splitting of capillaries is supposed to a reaction to augmented sheer stress to capillaries lumen because of hyperanemia[59]. While the sprouting is the development of capillaries from bud capillaries happens due to stretch on capillaries due to overload[60]. The augmented blood flow during chronic stimulation causes vasodilation due to adenosine, ATP, nitric oxide (NO) and prostacyclin. The NO consecutively boosts expression of VEGF, the most prime angiogenic factor, responsible for differentiation of endothelial cells as well as smooth muscle cells, stimulation and proliferation [61, 62]. Sprouting angiogenesis is appreciated by rise in matrix metallo-proteinases(MMPs), essential for prominent VEGF levels and remodeling of extracellular matrix(59). Certainly, stress exercise encourages VEGF receptor 2 and VEGF production. It has been shown that after two week of overloaded rat muscles the elevated VEGF level return to normal at twenty-eight days in unload condition. Although endothelial NOS has no role on angiogenesis in overloaded rat model, the stress exercise augments angiogenesis in association with raised endothelial NOS and hypoxia induced factor-α (HIF1-α) protein levels[63]. The importance of VEGF is reflected by observation that VEGF catching obliterated angiogenesis in overloaded and stressed conditions[64]. The VEGF derived from myofiber is not mandatory for maintaining capillary bed as perceived in mice in association with myofiber related conditional VEGF[65].

Ischemic Diseases

In cardiovascular system, a group of diseases has known as ischemic diseases that originate mostly from insufficient oxygenation of cells like heart, peripheral muscles and brain.The chief pathophysiological course involved in the progression of ischemic diseases is

atherosclerosis[66]. Generally, the atherosclerosis is a progressive disease in which commonly large arteries are affected by buildup of lipids, fibrous material and inflammatory cells in the inner arterial walls results in the development of stenosis.The symptoms appear in case of significant stenosis are ischemic pain during exercise which represent as stable angina pectoris while pain at rest represent as unstable angina pectoris or chronic limb ischemia[67]. An insufficient blood supply to myocardium describes ischemic heart disease resulting in disturbance of oxygen supply and demand[68]. The main causes of ischemic heart diseases are atherosclerosis, thrombus or embolus. The coronary artery disease residue the primary reason of mortality globally[69]. Along with coronary artery disease aortic stenosis and hypertrophic cardiomyopathy can lead to ischemic myocardium damage(68). In Past era, different combinations like ACE inhibitors, antiplatelets agents and β-blockers provide optimal cure and prevention for coronary artery disease. Moreover, for the restoration of blood flow and relief to patients from ischemicepisodes' coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) adopted[70-72].

Conventional Treatment Strategies

The main purpose of treatment of ischemic diseases is the prevention of progression of diseases.Primary prevention include life style changes like sedentary lifestyle, overweigh, poor diet and smoking[67].Secondary prevention includes pharmacologically management of risk factors like hyperlipidemia, hyperglycemia and hypertension[73]. Though it has been reported that statins are helpful in decreasing the plaque size and improving the vascular endothelium function[74, 75]. Usually anticoagulants, exercise training and vasodilators can be used for relieving recurrent ischemic symptoms.Revascularization procedures like intravascular catheter-mediated thrombolysis, bypass surgery orthromboendarterectomy and percutaneous transluminal angioplasty are performed for improving blood circulation in ischemic patients[76, 77]. Yet, several patients cannot be managed with conservative revascularization plans due to poor health status. Furthermore, a considerable percentage of patients experiencing revascularization trials do not get benefits from therapy or sometimes. These trials have reinvigorated the researchers for new therapeutic approaches for treating ischemic diseases[67].

Angiogenic Factors for IHD

In an ischemic myocardium a lot of proangiogenic factors provoked. But the VEGF as well as FGF families are better studied growth factors in the development of angiogenesis subsequent MI (Table1).

Table 1. Different Growth factors with their effects on angiogenesis

Growth Factor	Mode of Action	References
Vascular Endothelial Growth Factor (VEGF)	- Promotes cardiac vascularization and function. - Triggers vasculogenesis by stimulating endothelial cell proliferation and vascular permeability. - Has antiapoptotic, antioxidative, cardioprotective, and cytoprotective effects.	[78–80]
Placental Growth Factor (PGF)	Overexpression linked to increased cardiac hypertrophy and capillary density.	[81]
Platelet-Derived Growth Factor (PDGF)	- Plays a role in cardiac fibrosis progression. - Important in heart and vessel development.	[82]
Basic Fibroblast Growth Factor (bFGF)	Has pro-angiogenic effects in ischemic heart conditions in both humans and animals (e.g., dogs, mice, pigs, rabbits).	[83–86]
Epidermal Growth Factor (EGF)	Stimulates endothelial cell growth and promotes angiogenic activities.	[87]
Hepatocyte Growth Factor (HGF)	- Prevents apoptosis and stimulates endothelial cell proliferation, supporting vasculogenesis in heart and skeletal muscle. - Upregulates VEGF expression in the heart.	[88–91]

Concept of Angiogenic Therapy

The importance of angiogenesis in tissue regeneration and growth clearly elaborate the angiogenic therapy that is encouraging growth of blood vessel as therapeutically for dealing ischemic heart diseases[67]. The main purpose of angiogenic therapy is to promote blood vessel growth in deprived areas of vascularization and encourage tissue function and recovery. Blood vessel growth prompted by three ways: angiogenesis, arterio-genesis and vasculo-genesis.Angiogenesis by definition is the progression of capillary vessel growth and proceed by:

- Sprouting angiogenesis;
- Extension of preexisting capillaries; or through
- Splitting angiogenesis[92-94].

Arterio-genesis by definition is the phenomenon of collateral arteries growth through which pre-existing arterioles expand and modify into larger vessels that sidestep the arterial occlusion[95, 96]. Arterio-genesis is commenced by shear-stress-mediated mechanisms and blood pressure, while angiogenesis is generated through hypoxia results in fabrication of vascular growth factors in the ischemic areas.The angiogenesis and arterio-genesis both occur endogenously on almost all types of diseases.According to Rissanen et al., (2005), both angiogenesis and arterio-genesis might be valuable throughout the process of angiogenictherapies[92]. The pre angiogenic agents are responsible for the stimulation of vascular growth and can be administered exogenously. The pro angiogenic agents are members of vascular endothelial growth factor (VEGF-A165 and VEGF-D), fibroblast growth factor family (FGF2 and FGF-4), platelet-derived growth factor family (PDGF-BB), angiopoetins (notably ANG-1), hepatocyte growth factor (HGF), hypoxiainducible factor family (HIF-1α), insulin-like growth factors (IGFs) and nitric oxide synthase (NOS)[97-107].

Conclusion

The process of angiogenesis happens naturally during pregnancy, wound healing, female menstrual cycle and important in tissue growth and repair.Vasculo-genesis is not limited to prompt embryogenesis, but may have a physiological role like vasculo-genesis in tumor growth as well as existence of endothelial precursors and endothelial cells. In an ischemic myocardium a lot of pro-angiogenic factors provoked but the VEGF as well as FGF families are better studied growth factors in the development of angiogenesis subsequent MI. The importance of angiogenesis in tissue regeneration and growth clearly elaborate the angiogenic therapy that is encouraging growth of blood vessel as therapeutically for dealing ischemic heart diseases.

References

1. Rizzi A, Benagiano V, Ribatti D. Angiogenesis versus arteriogenesis. Rom J Morphol Embryol. 2017;58(1):15-9.
2. Ribatti D, Vacca A, Nico B, Roncali L, Dammacco F. Postnatal vasculogenesis. Mechanisms of development. 2001;100(2):157-63.
3. Isogai S, Horiguchi M, Weinstein BM. The vascular anatomy of the developing zebrafish: an atlas of embryonic and early larval development. Developmental biology. 2001;230(2):278-301.
4. Le Noble F, Moyon D, Pardanaud L, Yuan L, Djonov V, Matthijsen R, et al. Flow regulates arterial-venous differentiation in the chick embryo yolk sac. Development. 2004;131(2):361-75.
5. Peirce SM, Skalak TC. Microvascular remodeling: a complex continuum spanning angiogenesis to arteriogenesis. Microcirculation. 2003;10(1):99-111.
6. Ribatti D, Conconi MT, Nussdorfer GG. Nonclassic endogenous novel regulators of angiogenesis. Pharmacological reviews. 2007;59(2):185-205.
7. Chung AS, Lee J, Ferrara N. Targeting the tumour vasculature: insights from physiological angiogenesis. Nature Reviews Cancer. 2010;10(7):505-14.
8. Hoeben A, Landuyt B, Highley MS, Wildiers H, Van Oosterom AT, De Bruijn EA. Vascular endothelial growth factor and angiogenesis. Pharmacological reviews. 2004;56(4):549-80.
9. Shibuya M. Vascular endothelial growth factor receptor-1 (VEGFR-1/Flt-1): a dual regulator for angiogenesis. Angiogenesis. 2006;9(4):225-30.
10. Adams RH, Alitalo K. Molecular regulation of angiogenesis and lymphangiogenesis. Nature reviews Molecular cell biology. 2007;8(6):464-78.
11. Evans IM, Yamaji M, Britton G, Pellet-Many C, Lockie C, Zachary IC, et al. Neuropilin-1 signaling through p130Cas tyrosine phosphorylation is essential for growth factor-dependent migration of glioma and endothelial cells. Molecular and cellular biology. 2011;31(6):1174-85.
12. Pellet-Many C, Frankel P, Evans IM, Herzog B, Jünemann-Ramírez M, Zachary IC. Neuropilin-1 mediates PDGF stimulation of vascular smooth muscle cell migration and signalling via p130Cas. Biochemical Journal. 2011;435(3):609-18.
13. Zampeli E, Vlachoyiannopoulos PG, Tzioufas AG. Treatment of rheumatoid arthritis: unraveling the conundrum. Journal of autoimmunity. 2015;65:1-18.
14. Thijssen E, Van Caam A, Van Der Kraan PM. Obesity and osteoarthritis, more than just wear and tear: pivotal roles for inflamed adipose tissue and dyslipidaemia in obesity-induced osteoarthritis. Rheumatology. 2015;54(4):588-600.
15. Gupta N, Mansoor S, Sharma A, Sapkal A, Sheth J, Falatoonzadeh P, et al. Diabetic retinopathy and VEGF. The open ophthalmology journal. 2013;7:4.
16. N Campbell K, Raij L, Mundel P. Role of angiotensin II in the development of nephropathy and podocytopathy of diabetes. Current diabetes reviews. 2011;7(1):3-7.
17. Tufro A, Veron D, editors. VEGF and podocytes in diabetic nephropathy. Seminars in nephrology; 2012: Elsevier.
18. Yoon Y-s, Uchida S, Masuo O, Cejna M, Park J-S, Gwon H-c, et al. Progressive attenuation of myocardial vascular endothelial growth factor expression is a seminal event in diabetic cardiomyopathy: restoration of microvascular homeostasis and recovery of cardiac function in diabetic cardiomyopathy after replenishment of local vascular endothelial growth factor. Circulation. 2005;111(16):2073-85.

19. Koyama S, Sato E, Haniuda M, Numanami H, Nagai S, Izumi T. Decreased level of vascular endothelial growth factor in bronchoalveolar lavage fluid of normal smokers and patients with pulmonary fibrosis. American journal of respiratory and critical care medicine. 2002;166(3):382-5.
20. Kanazawa H, Yoshikawa J. Elevated oxidative stress and reciprocal reduction of vascular endothelial growth factor levels with severity of COPD. Chest. 2005;128(5):3191-7.
21. Imesch P, Fink D. Endometriose-Update 2016. Praxis (Bern. 2016;105(5):253-7.
22. Phipps E, Prasanna D, Brima W, Jim B. Preeclampsia: updates in pathogenesis, definitions, and guidelines. Clinical Journal of the American Society of Nephrology. 2016;11(6):1102-13.
23. Nouri K, Haslinger P, Szabo L, Sator M, Schreiber M, Schneeberger C, et al. Polymorphisms of VEGF and VEGF receptors are associated with the occurrence of ovarian hyperstimulation syndrome (OHSS)—a retrospective case–control study. Journal of ovarian research. 2014;7(1):1-7.
24. Scotti L, Abramovich D, Pascuali N, Irusta G, Meresman G, Tesone M, et al. Local VEGF inhibition prevents ovarian alterations associated with ovarian hyperstimulation syndrome. The Journal of steroid biochemistry and molecular biology. 2014;144:392-401.
25. Kunstfeld R, Hirakawa S, Hong Y-K, Schacht V, Lange-Asschenfeldt B, Velasco P, et al. Induction of cutaneous delayed-type hypersensitivity reactions in VEGF-A transgenic mice results in chronic skin inflammation associated with persistent lymphatic hyperplasia. Blood. 2004;104(4):1048-57.
26. Canavese M, Altruda F, Ruzicka T, Schauber J. Vascular endothelial growth factor (VEGF) in the pathogenesis of psoriasis—a possible target for novel therapies? Journal of dermatological science. 2010;58(3):171-6.
27. Storkebaum E, Carmeliet P. VEGF: a critical player in neurodegeneration. The Journal of clinical investigation. 2004;113(1):14-8.
28. Storkebaum E, Lambrechts D, Dewerchin M, Moreno-Murciano M-P, Appelmans S, Oh H, et al. Treatment of motoneuron degeneration by intracerebroventricular delivery of VEGF in a rat model of ALS. Nature neuroscience. 2005;8(1):85-92.
29. Svensson B, Peters M, König H-G, Poppe M, Levkau B, Rothermundt M, et al. Vascular endothelial growth factor protects cultured rat hippocampal neurons against hypoxic injury via an antiexcitotoxic, caspase-independent mechanism. Journal of Cerebral Blood Flow & Metabolism. 2002;22(10):1170-5.
30. Zeisberg EM, Potenta S, Xie L, Zeisberg M, Kalluri R. Discovery of endothelial to mesenchymal transition as a source for carcinoma-associated fibroblasts. Cancer research. 2007;67(21):10123-8.
31. Sopova K, Gatsiou K, Stellos K, Laske C. Dysregulation of neurotrophic and haematopoietic growth factors in Alzheimer's disease: from pathophysiology to novel treatment strategies. Current Alzheimer Research. 2014;11(1):27-39.
32. Guo H, Zhou H, Lu J, Qu Y, Yu D, Tong Y. Vascular endothelial growth factor: an attractive target in the treatment of hypoxic/ischemic brain injury. Neural regeneration research. 2016;11(1):174.
33. Rasmussen HS, Rasmussen CS, Macko J. VEGF gene therapy for coronary artery disease and peripheral vascular disease. Cardiovascular radiation medicine. 2002;3(2):114-7.
34. Teven CM, Farina EM, Rivas J, Reid RR. Fibroblast growth factor (FGF) signaling in development and skeletal diseases. Genes & diseases. 2014;1(2):199-213.

35. Ahmed A, Wong RJ, Harrison SA. Nonalcoholic fatty liver disease review: diagnosis, treatment, and outcomes. Clinical Gastroenterology and Hepatology. 2015;13(12):2062-70.
36. Yan H, Xia M, Chang X, Xu Q, Bian H, Zeng M, et al. Circulating fibroblast growth factor 21 levels are closely associated with hepatic fat content: a cross-sectional study. PloS one. 2011;6(9):e24895.
37. Shibata K, Fujita S-i, Morita H, Okamoto Y, Sohmiya K, Hoshiga M, et al. Association between circulating fibroblast growth factor 23, α-Klotho, and the left ventricular ejection fraction and left ventricular mass in cardiology inpatients. PLoS One. 2013;8(9):e73184.
38. Wyatt CM, Drüeke TB. Fibroblast growth factor receptor 4: the missing link between chronic kidney disease and FGF23-induced left ventricular hypertrophy? Kidney international. 2016;89(1):7-9.
39. Ding H-Y, Ma H-X. Significant roles of anti-aging protein klotho and fibroblast growth factor23 in cardiovascular disease. Journal of Geriatric Cardiology: JGC. 2015;12(4):439.
40. Chow WS, Xu A, Woo YC, Tso AW, Cheung SC, Fong CH, et al. Serum fibroblast growth factor-21 levels are associated with carotid atherosclerosis independent of established cardiovascular risk factors. Arteriosclerosis, thrombosis, and vascular biology. 2013;33(10):2454-9.
41. Llauradó G, Megia A, Cano A, Giménez-Palop O, Simón I, González-Sastre M, et al. FGF-23/vitamin D axis in type 1 diabetes: the potential role of mineral metabolism in arterial stiffness. PloS one. 2015;10(10):e0140222.
42. Akin F, Celik O, Altun I, Ayca B, Diker VO, Satılmıs S, et al. Relationship of fibroblast growth factor 23 and fetuin-A to coronary atherosclerosis. Journal of Diabetes and its Complications. 2015;29(4):550-5.
43. Fliser D, Kollerits B, Neyer U, Ankerst DP, Lhotta K, Lingenhel A, et al. Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) Study. Journal of the American Society of Nephrology. 2007;18(9):2600-8.
44. Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, et al. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. Jama. 2011;305(23):2432-9.
45. Rossini M, Cheunsuchon B, Donnert E, Ma L-J, Thomas JW, Neilson EG, et al. Immunolocalization of fibroblast growth factor-1 (FGF-1), its receptor (FGFR-1), and fibroblast-specific protein-1 (FSP-1) in inflammatory renal disease. Kidney international. 2005;68(6):2621-8.
46. Pavik I, Jaeger P, Ebner L, Wagner CA, Petzold K, Spichtig D, et al. Secreted Klotho and FGF23 in chronic kidney disease Stage 1 to 5: a sequence suggested from a cross-sectional study. Nephrology Dialysis Transplantation. 2013;28(2):352-9.
47. Hindricks J, Ebert T, Bachmann A, Kralisch S, Lössner U, Kratzsch J, et al. Serum levels of fibroblast growth factor-21 are increased in chronic and acute renal dysfunction. Clinical endocrinology. 2014;80(6):918-24.
48. Guzy RD, Stoilov I, Elton TJ, Mecham RP, Ornitz DM. Fibroblast growth factor 2 is required for epithelial recovery, but not for pulmonary fibrosis, in response to bleomycin. American journal of respiratory cell and molecular biology. 2015;52(1):116-28.

49. Yang J, Meyer M, Müller A-K, Böhm F, Grose R, Dauwalder T, et al. Fibroblast growth factor receptors 1 and 2 in keratinocytes control the epidermal barrier and cutaneous homeostasis. Journal of Cell Biology. 2010;188(6):935-52.
50. Gay D, Kwon O, Zhang Z, Spata M, Plikus MV, Holler PD, et al. Fgf9 from dermal γδ T cells induces hair follicle neogenesis after wounding. Nature medicine. 2013;19(7):916-23.
51. Gong C-X, Lidsky T, Wegiel J, Zuck L, Grundke-Iqbal I, Iqbal K. Phosphorylation of microtubule-associated protein tau is regulated by protein phosphatase 2A in mammalian brain: Implications for neurofibrillary degeneration in Alzheimer's disease. Journal of Biological Chemistry. 2000;275(8):5535-44.
52. Iqbal K, Liu F, Gong C-X, Grundke-Iqbal I. Tau in Alzheimer disease and related tauopathies. Current Alzheimer Research. 2010;7(8):656-64.
53. Butt AM, Dinsdale J. Fibroblast growth factor 2 mediated disruption of myelin-forming oligodendrocytes in vivo is associated with increased tau immunoreactivity. Neuroscience letters. 2005;375(1):28-32.
54. Ogino R, Murayama N, Noshita T, Takemoto N, Toba T, Oka T, et al. SUN11602 has basic fibroblast growth factor-like activity and attenuates neuronal damage and cognitive deficits in a rat model of Alzheimer′ s disease induced by amyloid β and excitatory amino acids. Brain research. 2014;1585:159-66.
55. Song J-S, Lee JG, Kay EP. Induction of FGF-2 synthesis by IL-1β in aqueous humor through P13-kinase and p38 in rabbit corneal endothelium. Investigative ophthalmology & visual science. 2010;51(2):822-9.
56. Wang X, Zhou X, Ma J, Tian H, Jiao Y, Zhang R, et al. Effects of keratinocyte growth factor-2 on corneal epithelial wound healing in a rabbit model of carbon dioxide laser injury. Biological and pharmaceutical bulletin. 2010;33(6):971-6.
57. Dessapt-Baradez C, Woolf AS, White KE, Pan J, Huang JL, Hayward AA, et al. Targeted glomerular angiopoietin-1 therapy for early diabetic kidney disease. Journal of the American Society of Nephrology. 2014;25(1):33-42.
58. Matkar PN, Ariyagunarajah R, Leong-Poi H, Singh KK. Friends turned foes: angiogenic growth factors beyond angiogenesis. Biomolecules. 2017;7(4):74.
59. Olfert IM, Baum O, Hellsten Y, Egginton S. Advances and challenges in skeletal muscle angiogenesis. American journal of physiology-heart and circulatory physiology. 2016;310(3):H326-H36.
60. Hendrickse P, Degens H. The role of the microcirculation in muscle function and plasticity. Journal of muscle research and cell motility. 2019;40(2):127-40.
61. Wagner PD. The critical role of VEGF in skeletal muscle angiogenesis and blood flow. Biochemical Society Transactions. 2011;39(6):1556-9.
62. Egginton S. Invited review: activity-induced angiogenesis. Pflügers Archiv-European Journal of Physiology. 2009;457(5):963-77.
63. Holloway TM, Snijders T, LJC VL, Verdijk L. Temporal response of angiogenesis and hypertrophy to resistance training in young men. Medicine and science in sports and exercise. 2018;50(1):36-45.
64. Williams JL, Cartland D, Rudge JS, Egginton S. VEGF trap abolishes shear stress- and overload-dependent angiogenesis in skeletal muscle. Microcirculation. 2006;13(6):499-509.
65. Knapp AE, Goldberg D, Delavar H, Trisko BM, Tang K, Hogan MC, et al. Skeletal myofiber VEGF regulates contraction-induced perfusion and exercise capacity but not muscle capillarity in adult mice. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2016;311(1):R192-R9.

66. Lusis AJ. Genetics of atherosclerosis. Trends in Genetics. 2012;28(6):267-75.
67. Dragneva G, Korpisalo P, Ylä-Herttuala S. Promoting blood vessel growth in ischemic diseases: challenges in translating preclinical potential into clinical success. Disease models & mechanisms. 2013;6(2):312-22.
68. Zhang H, van Olden C, Sweeney D, Martin-Rendon E. Blood vessel repair and regeneration in the ischaemic heart. Open heart. 2014;1(1).
69. Allender S, Peto V, Scarborough P, Boxer A, Rayner M. Coronary heart disease statistics. 2007.
70. Abbate A, Biondi-Zoccai GG, Appleton DL, Erne P, Schoenenberger AW, Lipinski MJ, et al. Survival and cardiac remodeling benefits in patients undergoing late percutaneous coronary intervention of the infarct-related artery: evidence from a meta-analysis of randomized controlled trials. Journal of the American College of Cardiology. 2008;51(9):956-64.
71. Gaszewska-Zurek E, Zurek P, Olszówka P, Kargul T, Woś S, Tendera M. Effect of coronary artery bypass graft in patients with unstable angina on left ventricular remodelling in medium-term follow-up. Kardiologia polska. 2005;63(2):115-23.
72. Zellweger MJ, Tabacek G, Zutter AW, Weinbacher M, Cron TA, Müller-Brand J, et al. Evidence for left ventricular remodeling after percutaneous coronary intervention: effect of percutaneous coronary intervention on left ventricular ejection fraction and volumes. International journal of cardiology. 2004;96(2):197-201.
73. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Inter-society consensus for the management of peripheral arterial disease (TASC II). Journal of vascular surgery. 2007;45(1):S5-S67.
74. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. Circulation. 2004;109(23_suppl_1):III-39-III-43.
75. Ylä-Herttuala S, Bentzon JF, Daemen M, Falk E, Garcia-Garcia HM, Herrmann J, et al. Stabilisation of atherosclerotic plaques. Thrombosis and haemostasis. 2011;106(07):1-19.
76. Members C, Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). Journal of the American College of Cardiology. 2003;41(1):159-68.
77. Members WC, Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Journal of the American College of Cardiology. 2004;44(3):671-719.
78. Gd Y, Davis S, Nw G, Js R, Sj W, Holash J. Vascular-specific growth factors and blood vessel formation. Nature. 2000;407:242-8.
79. Tafuro S, Ayuso E, Zacchigna S, Zentilin L, Moimas S, Dore F, et al. Inducible adeno-associated virus vectors promote functional angiogenesis in adult organisms via regulated vascular endothelial growth factor expression. Cardiovascular research. 2009;83(4):663-71.
80. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular considerations for patients, health care workers, and health systems

during the COVID-19 pandemic. Journal of the American College of Cardiology. 2020;75(18):2352-71.
81. Accornero F, Van Berlo JH, Benard MJ, Lorenz JN, Carmeliet P, Molkentin JD. Placental growth factor regulates cardiac adaptation and hypertrophy through a paracrine mechanism. Circulation research. 2011;109(3):272-80.
82. Andrae J, Gallini R, Betsholtz C. Role of platelet-derived growth factors in physiology and medicine. Genes & development. 2008;22(10):1276-312.
83. Laham RJ, Rezaee M, Post M, Novicki D, Sellke FW, Pearlman JD, et al. Intrapericardial delivery of fibroblast growth factor-2 induces neovascularization in a porcine model of chronic myocardial ischemia. Journal of Pharmacology and Experimental Therapeutics. 2000;292(2):795-802.
84. Rajanayagam MS, Shou M, Thirumurti V, Lazarous DF, Quyyumi AA, Goncalves L, et al. Intracoronary basic fibroblast growth factor enhances myocardial collateral perfusion in dogs. Journal of the American College of Cardiology. 2000;35(2):519-26.
85. Vickers NJ. Animal communication: when i'm calling you, will you answer too? Current biology. 2017;27(14):R713-R5.
86. Laham RJ, Chronos NA, Pike M, Leimbach ME, Udelson JE, Pearlman JD, et al. Intracoronary basic fibroblast growth factor (FGF-2) in patients with severe ischemic heart disease: results of a phase I open-label dose escalation study. Journal of the American College of Cardiology. 2000;36(7):2132-9.
87. Gogiraju R, Bochenek ML, Schäfer K. Angiogenic endothelial cell signaling in cardiac hypertrophy and heart failure. Frontiers in cardiovascular medicine. 2019;6:20.
88. Ding S, Merkulova-Rainon T, Han ZC, Tobelem G. HGF receptor up-regulation contributes to the angiogenic phenotype of human endothelial cells and promotes angiogenesis in vitro. Blood. 2003;101(12):4816-22.
89. Li F, Qu H, Cao HC, Li MH, Chen C, Chen XF, et al. Both FOXO3a and FOXO1 are involved in the HGF-protective pathway against apoptosis in endothelial cells. Cell biology international. 2015;39(10):1131-7.
90. Wang Y. Ahmad N, Wani MA, Ashraf M. Hepatocyte growth factor prevents ventricular remodeling and dysfunction in mice via Akt pathway and angiogenesis J Mol Cell Cardiol. 2004;37:1041-52.
91. Taniyama Y, Morishita R, Hiraoka K, Aoki M, Nakagami H, Yamasaki K, et al. Therapeutic angiogenesis induced by human hepatocyte growth factor gene in rat diabetic hind limb ischemia model: molecular mechanisms of delayed angiogenesis in diabetes. Circulation. 2001;104(19):2344-50.
92. Rissanen TT, Korpisalo P, Markkanen JE, Liimatainen T, Ordén M-R, Kholová I, et al. CLINICAL PERSPECTIVE. Circulation. 2005;112(25):3937-46.
93. Makanya AN, Hlushchuk R, Djonov VG. Intussusceptive angiogenesis and its role in vascular morphogenesis, patterning, and remodeling. Angiogenesis. 2009;12(2):113.
94. Carmeliet P, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. Nature. 2011;473(7347):298-307.
95. Simons M. Angiogenesis: where do we stand now? Circulation. 2005;111(12):1556-66.
96. Schaper W. Collateral circulation. Basic research in cardiology. 2009;104(1):5-21.
97. Kowanetz M, Ferrara N. Vascular endothelial growth factor signaling pathways: therapeutic perspective. Clinical Cancer Research. 2006;12(17):5018-22.
98. Rissanen TT, Markkanen JE, Gruchala M, Heikura T, Puranen A, Kettunen MI, et al. VEGF-D is the strongest angiogenic and lymphangiogenic effector among VEGFs

delivered into skeletal muscle via adenoviruses. Circulation research. 2003;92(10):1098-106.
99. Murakami M, Simons M. Fibroblast growth factor regulation of neovascularization. Current opinion in hematology. 2008;15(3):215.
100. Fredriksson L, Li H, Eriksson U. The PDGF family: four gene products form five dimeric isoforms. Cytokine & growth factor reviews. 2004;15(4):197-204.
101. Aoki M, Morishita R, Taniyama Y, Kida I, Moriguchi A, Matsumoto K, et al. Angiogenesis induced by hepatocyte growth factor in non-infarcted myocardium and infarcted myocardium: up-regulation of essential transcription factor for angiogenesis, ets. Gene therapy. 2000;7(5):417-27.
102. Ylä-Herttuala S, Rissanen TT, Vajanto I, Hartikainen J. Vascular endothelial growth factors: biology and current status of clinical applications in cardiovascular medicine. Journal of the american college of cardiology. 2007;49(10):1015-26.
103. Delafontaine P, Song Y-H, Li Y. Expression, regulation, and function of IGF-1, IGF-1R, and IGF-1 binding proteins in blood vessels. Arteriosclerosis, thrombosis, and vascular biology. 2004;24(3):435-44.
104. He Y, Rajantie I, Pajusola K, Jeltsch M, Holopainen T, Yla-Herttuala S, et al. Vascular endothelial cell growth factor receptor 3–mediated activation of lymphatic endothelium is crucial for tumor cell entry and spread via lymphatic vessels. Cancer research. 2005;65(11):4739-46.
105. Patel TH, Kimura H, Weiss CR, Semenza GL, Hofmann LV. Constitutively active HIF-1α improves perfusion and arterial remodeling in an endovascular model of limb ischemia. Cardiovascular research. 2005;68(1):144-54.
106. Brevetti LS, Chang DS, Tang GL, Sarkar R, Messina LM. Overexpression of endothelial nitric oxide synthase increases skeletal muscle blood flow and oxygenation in severe rat hind limb ischemia. Journal of vascular surgery. 2003;38(4):820-6.
107. Cooney R, Hynes SO, Duffy AM, Sharif F, O'Brien T. Adenoviral-mediated gene transfer of nitric oxide synthase isoforms and vascular cell proliferation. Journal of vascular research. 2006;43(5):462-72.