MicroRNA-132 may play a role in coexistence of depression and cardiovascular disease: A hypothesis

Different individuals have different degrees of neuroplasticity due to their different experiences. Neuroplasticity may play a role in individual differences among neuropsychiatric disease treatment efficacy. Since the nervous system monitors and coordinates internal organ function, neuroplasticity may be associated with other diseases. Cardiovascular disease (CVD) is associated with depression, which is a disorder of disrupted neuroplasticity. MicroRNA-132 (miR-132) has a role in neuroplasticity and cardiovascular function. Thus, we hypothesize that miR-132 may play a role in coexistence of depression and CVD.

Key words: microRNA-132 • neuroplasticity • depression • cardiovascular disease

Full-text PDF: http://www.medscimonit.com/download/index/idArt/883935
**Background**

Neuroplasticity is the ability of the nervous system to respond to intrinsic or extrinsic stimuli by reorganizing its structure, function, and connections [1]. Individuals show different degrees of neuroplasticity due to their different courses of growth [2]. It has been documented that even monozygotic twins may develop differing neural structure and function despite having an identical genetic background [2]. For instance, some monozygotic twins are discordant for many diseases, such as bulimia nervosa, schizophrenia, and bipolar disorders, and even in sexual orientation [3–6]. Experiences prior to a cerebral injury may influence not only spontaneous recovery but also the efficacy of post-injury treatment [7]. Thus, we propose that neuroplasticity may play a role in individual differences in the treatment response of neuropsychiatric diseases [2]. Since the nervous system monitors and coordinates internal organ function, neuroplasticity may be associated with other diseases. Cardiovascular disease (CVD) is associated with depression, and depression is closely related to neuroplasticity. MicroRNA (miR) is receiving intense research interest at present and microRNA-132 (miR-132) has roles in neuroplasticity and cardiovascular function. Here, we focus on miR-132 as a common component to discuss the mechanism of coexistence of depression and CVD.

**CVD is Associated with Depression**

Depression significantly increases the risk of incident CVD. Many prospective and retrospective studies have investigated the association of depression and incident CVD. These studies showed that depression is independently associated with CVD and mortality due to causes such as coronary heart disease, heart failure, myocardial infarction, ischemic heart disease, and stroke [8–13]. Lifetime association between major depression (MD) and coronary artery disease (CAD) was modest (odds ratio, approximately 1.3). The effect of MD on CAD is largely acute, and the longer-term effects are apparently mediated via recurrence of depression [14]. Some studies have demonstrated a significant positive correlation with a moderate effect size of 1.5–2.7 between depression and CVD [15]. Similarly, several studies have investigated the role of depression status as a prognostic factor in patients with CVD. Meta-analysis of these studies suggests that depressed patients have a 1.6–2.7-fold increased risk for further cardiovascular events within 24 months [16,17].

**Depression is a Disorder of Disrupted Neuroplasticity**

It is broadly accepted that stress triggers the activation of the HPA axis and causes the brain to be exposed to corticosteroids, affecting neurobehavioral functions with a strong down-regulation of hippocampal neurogenesis, and is a major risk factor for depression [18–20]. Chronic or severe stress and high-dose treatment with glucocorticoids decrease hippocampal synaptic plasticity and morphological neuroplasticity. Prolonged stress can negatively affect hippocampal function and its capacity for neuroplasticity. Additionally, chronic restraint stress leads to significant regression of the apical dendrites of pyramidal cells in the medial prefrontal cortex (mPFC) and negatively affects mPFC function. Glial loss and neuronal abnormalities have been observed in the prefrontal cortex in MD. Noradrenergic axons have been found with decreased axonal arborization and density after exposure to stress. Increasing evidence demonstrates that depression is a disorder of disrupted neuroplasticity [21]. Accumulating evidence shows that antidepressant treatment may reverse the atrophy of hippocampal neurons, increase cell survival, and increase monoamine axonal sprouting [22].

Brain-derived neurotrophic factor (BDNF) signaling, through its tyrosine kinase B (TrkB) receptor, plays an important role in neuroplasticity. BDNF has also been shown to be expressed at high levels in the hippocampus and to play an important role in synaptic transmission and in the plasticity of the hippocampus [23,24]. BDNF also mediates some of the injurious effects of glucocorticoids on the hippocampus [25,26]. BDNF expression is regulated by stress-responsive corticosteroids, and increased glucocorticoid exposure induces a reduction in BDNF level [27]. Chronic stress has been shown to result in alterations in BDNF/TrkB signaling and changes in neuronal functions [28]. Serotonergic axon sprouting appears to be dependent on BDNF, which appears to be decreased after stress exposure. Thus, stress and depression may increase neuronal atrophy degeneration. Furthermore, hippocampal neurons continue to proliferate well into adulthood. This continued neurogenesis depends on the presence of BDNF and serotonin, both of which are altered in depression, and are inhibited by glucocorticoids [29,30]. Most circulating BDNF is produced in the brain and passes through the blood–brain barrier [31], so serum BDNF level can be a biomarker for depression [32].

**MiR-132 is an Activity-Regulated MiR Controlling Neuroplasticity**

MiRs are short, non-coding, single-stranded RNA molecules approximately 19–23 nucleotides in length that regulate gene expression by binding to complementary elements in the untranslated regions of target mRNAs and inhibiting protein synthesis [33–35]. Based on sequence homology, each miR has the potential to regulate the translation of hundreds of different genes [36], and greater than 30% of all mammalian genes may be regulated by miRs [37].
MiR-132, a highly conserved miR transcribed from an intergenic region on human chromosome 17 by the transcription factor cAMP response element-binding protein (CREB), is a key coordinator of the intracellular pathways that mediate experience-dependent changes in the brain [38–40]. Using an unbiased genome-wide screen for CREB-bound transcripts in vitro, Impey et al. [41] identified 16 non-coding miR that are induced by CREB-mediated transcription. Further characterization of 1 of these, miR-132, has recently revealed that it is induced by BDNF and neuronal activity, being demonstrated to affect neuronal characteristics such as neurite outgrowth and cell excitability [40,42,43]. miR-132 is able to modulate dendritic morphology via suppression of a specific target, p250 GTPase-activating protein, and regulate cellular excitability via regulation of ion channels [40,42,43].

Interestingly, the CREB-dependent miR-132 has been shown to control the development of dendrites and spines, and synaptic integration in cultured hippocampal neurons and newborn hippocampal neurons [40,42,44–48]. For example, it was reported that knockout of the miR-212/132 locus reduces conditional transgenic mice or knockdown of miR-132 using viral vectors induced reduced dendritic complexity and spine density, respectively, in newborn neurons of the adult hippocampal neurogenic zone [47,48]. The dendritic effect was shown to be preferentially due to miR-132 loss. A recent study has demonstrated that miR-132 is rapidly transcribed in the hippocampus in vivo following enhanced neuronal activity and contextual fear conditioning [39]. Based on the documented ability of miR-132 to regulate cellular characteristics in an activity-dependent manner, Lambert et al. [49] has provided evidence that overexpression of miR-132 in cultured hippocampal neurons leads to selective changes in short-term synaptic plasticity.

BDNF is essential for a variety of neuronal aspects, including cell differentiation, survival, and synaptic plasticity in the central nervous system (CNS). Intriguingly, a recent study suggests that BDNF exerts its beneficial effects on CNS neurons via up-regulation of miR-132 [50]. BDNF increases CREB activation; the CREB pathways are among the most critical and are the pathways on which BDNF exerts its effects [51]. Therefore, it is concluded that BDNF affects CNS by CREB-miR-132 pathway. Additionally, increased blood levels of glucocorticoids cause suppression in BDNF-dependent neuronal function via reducing miR-132 expression [52].

The dysfunction of adult hippocampal neurogenesis is proposed to be an essential mechanism explaining the etiology of depression. BDNF, CREB, and glucocorticoids are the key components for hippocampal neurogenesis, all of which are directly related to miR-132. Thus, it is suggested that miR-132 plays an important role in the etiology of depression.

### MiR-132 has Functions in the Cardiovascular System

There is scant literature on the function of miR-132 in the cardiovascular system. However, the existing literature suggests that miR-132 has functions in the cardiovascular system.

The cardiovascular system is controlled by the nervous system, mainly by the autonomic nervous system; therefore, BDNF can influence the cardiovascular system via the autonomic nervous system. BDNF is important for autonomic nervous system function. BDNF is known to play an important role in regulating the survival of neurons in the autonomic nervous system and the formation of their synaptic connectivity with their peripheral targets in the cardiovascular, digestive, and other organ systems. Emerging evidence suggests that BDNF may also affect the function of the autonomic nervous system during adult life and may, in part, mediate the effects of environmental factors, such as exercise and dietary energy intake, on autonomic nervous system neurons and target cells [53]. BDNF has also been shown to be a modulator of visceral sensory transmission, suggesting that BDNF is involved in maturation and/or plasticity in the arterial baroreceptor pathway [54]. As noted above, BDNF influences CNS via the CREB-miR-132 pathway, and most of circulating BDNF is produced in the brain and passes through the blood-brain barrier. Thus, it is suggested that miR-132 may play an important role in cardiovascular function via the autonomic nervous system. Additionally, BDNF may also influence energy homeostasis through its role in neurogenesis and in the neuroplasticity of the HPA axis [55–57], and is involved in the maintenance of cardiometabolic homeostasis [58]. Therefore, it is suggested that miR-132 may also influence cardiovascular function via the HPA axis.

Endothelial dysfunction is a critical step in development of CVD pathology, such as hypertension, atherosclerosis, and thrombosis [59–61]. The action of vascular endothelial growth factor (VEGF) is essential to maintain proper endothelial and vascular function [62]. The major function of VEGF is angiogenesis [63]. VEGF stimulates virtually all aspects of endothelial function: proliferation, migration, permeability, and nitric oxide production and release. In addition, the action of VEGF makes the endothelium anti-apoptotic. In turn, the inhibition of VEGF action is associated with endothelial dysfunction [62].

The effect of VEGF on the endothelium is related to miR. Research on effects of miR on the endothelium has been conducted, showing that miR-132 is an angiogenic growth factor inducible miR in the endothelium [64,65]. VEGF triggers phosphorylation of CREB and subsequent transcription of miR-132. MiR-132 downregulates p120 Ras GTPase-activating protein, thereby removing the endogenous brake on Ras activity and activating quiescent endothelium [65].
MiR-132 mediates the deleterious effect of angiotensin II in vascular smooth muscle cells [66]. However, endothelial dysfunction is the first step to CVD and plays a central role in its pathogenesis [67]. Additionally, miR-132 may have an important role in cardiovascular function via the autonomic nervous system and the HPA axis. BDNF also maintains vessel stability in the heart through direct angiogenic actions on endothelial cells [68]. Although at present there is no literature on the role of miR-132 in BDNF-induced angiogenesis, it is likely that CREB and miR-132, which are the common components in BDNF-induced neuroplasticity and VEGF-induced angiogenesis, are involved in the mechanism. Thus, the positive effect of miR-132 on the cardiovascular system may be greater than the negative one. For example, Katare et al. [69] investigated the therapeutic activity and mechanistic targets of saphenous vein-derived pericyte progenitor cells (SVPs) in a mouse myocardial infarction model and concluded that SVP transplantation produces long-term improvement of cardiac function by a novel paracrine mechanism involving the secretion of miR-132 and inhibition of its target genes. Furthermore, a study of long-term β-adrenergic administration on the expression levels of the cardiac L-type Ca channel β2 subunit, which regulates channel trafficking and function, showed that cardiac L-type Ca channel β2 subunit protein expression may be down-regulated by miRs, including miR-132, in response to long-term activation of β-adrenergic signaling, possibly as an adaptive response in cardiac hypertrophy and sustained β-adrenergic states [70].

Hypothesis

MiR-132 has functions in both the nervous and cardiovascular system. Stress decreases BDNF level. Low BDNF level reduces CREB activation, resulting in down-regulation of miR-132, and then disrupts neuroplasticity and leads to depression. Stress also increases the level of glucocorticoid, and increased glucocorticoid level also down-regulates miR-132. MiR-132 may affect cardiovascular function by the autonomic nervous system and the HPA axis. Circulating BDNF, most of which is produced in the brain and passes through the blood–brain barrier [31], may also influence cardiovascular function involving miR-132. In addition, miRs are also found in microvesicles, which are plasma membrane fragments shed from virtually all cells [71]. Microvesicles circulate in peripheral blood, where they transport mRNA and proteins between cells and play a pivotal role in cell-to-cell communication. They are also implicated in the process of angiogenesis [72]. Recent studies also raise the possibility that CNS-derived vesicles may enter the bloodstream and interact with endothelial cells in the peripheral circulation [73], suggesting that the synthesis of miR-132 in the brain may be related to miR-132 level in the cardiovascular system. Thus, we hypothesize that miR-132 may play a role in coexistence of depression and CVD. Figure 1 presents an integrative model that shows the possible role of miR-132 in coexistence between depression and CVD. This model is not intended to be complete or all-encompassing, but rather to highlight and connect certain interesting evidence pointing to this miR-132 role.

Based on this hypothesis, miR-132 may be a potential target for treating depression and CVD. Both depression and CVD may benefit from up-regulated miR-132, and more research should be conducted in this field.

Conflicts of interest statement

None declared.

Statement

The work was done in Guangdong Province Pharmaceutical Association.
References:

1. Cramer SC, Sur M, Dobkin BH et al: Harnessing neuroplasticity for clinical applications. Brain, 2011; 134: 1591–609
2. Zheng Z, Xu F: Neuroplasticity may play a role in inter-individual difference among neuropsychiatric disease treatment efficacy. Dev Psychobiol, 2012; 54: 369–71
3. Bulik CM, Wade TD, Kendler KS: Characteristics of monozygotic twins discordant for bulimia nervosa. Int J Eat Disord, 2001; 29: 1–10
4. Cannon TD, Hutteno MN, Lonnqvist J et al: The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia. Am J Hum Genet, 2000; 67: 369–82
5. Gourovtch ML, Torrey EF, Gold JM et al: Neuropsychological performance of monozygotic twins discordant for bipolar disorder. Biol Psychiatry, 1999; 45: 639–46
6. Hall LS, Love CT: Finger-length ratios in female monozygotic twins discordant for sexual orientation. Arch Sex Behav, 2005; 32: 23–28
7. Kolb B, Teskey GC: Age, experience, injury, and the changing brain. Dev Psychobiol, 2012; 54: 369–71
8. Ariyo AA, Haan M, Tengan CM et al: Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans. Cardiovascular Health Study Collaborative Research Group. Circulation, 2000; 102: 1773–79
9. Abramson J, Berger A, Krumholz HM, Vaccarino V: Depression and risk of heart failure among older persons with isolated systolic hypertension. Arch Intern Med, 2001; 161: 1725–30
10. Williams SA, Kasi SV, Heiat A et al: Depression and risk of heart failure among the elderly: a prospective community–based study. Psychosom Med, 2002; 64: 6–12
11. Gump BB, Matthews KA, Eberly LE, Chang YF: Depressive symptoms and mortality in men: results from the Multiple Risk Factor Intervention Trial. Stroke, 2005; 36: 98–102
12. Altimo A, Isaoa R, Puolijoki H, Vahberg T, Kivela SL: Stronger symptoms of depression predict high coronary heart disease mortality in older men and women. Int J Geriatr Psychiatry, 2007: 22: 757–63
13. Surtees PG, Wainwright NW, Luben RN et al: Depression and ischemic heart disease mortality: evidence from the EPIC-Norfolk United Kingdom prospective cohort study. Am J Psychiatry, 2008; 165: 515–23
14. Kendler KS, Gardner CO, Fiske A, Gilmour A et al: The relationship between subtypes of depression and cardiovascular disease: a systematic review of biological models. Transl Psychiatry, 2012; 2: e92
15. Meijer A, Conradi HI, Bos EH et al: Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis of 25 years of research. Gen Hosp Psychiatry, 2011; 33: 203–16
16. van Melle JP, de Jonge P, Spijkerman TA et al: Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. Psychosom Med, 2004; 66: 814–22
17. Masi G, Brovedani P: The hippocampus, neurotrophic factors and depression: possible implications for the pharmacotherapy of depression. CNS Drugs, 2011; 25: 913–31
18. Llorens-Martín M, Trejo I: Mifepristone Prevents Stress-Induced Apoptosis in Newborn Neurons and Increases AMPA Receptor Expression in the Dentate Gyrus of C57/BL6 Mice. PLoS One, 2011; 6: e28376.
19. O’Sullivan E, Barrett E, Grenham S et al: Sequenced treatment alternatives to BDNF expression in the hippocampus of C57/BL6 Mice. PLoS One, 2011; 6: e28376.
20. Duman RS, Monteggia LM: A neurotrophic model for stress-related mood disorders. Biol Psychiatry, 2006; 59: 1116–27
21. Duman RS, Heninger GR, Nestler EI: A molecular and cellular theory of depression. Arch Gen Psychiatry, 1997; 54: 597–606
22. Numakawa T, Yokomokuda D, Richards M et al: Functional interactions between steroid hormones and neurotrophin BDNF. World J Biol Chem, 2010; 1: 133–43
23. Kuttyanawalla A, Terrera AV Jr, Pillai A: Cysteamine attenuates the decreases in TrkB protein levels and the anxiety/depression-like behaviors in mice induced by corticosterone treatment. PLoS One, 2011; 6: e26153
24. Lee TH, Kato H, Chen ST et al: Expression disparity of brain-derived neurotrophic factor immunoreactivity and mRNA in ischemic hippocampal neurons. Neuroreport, 2002; 13: 2271–75
25. Gould E: Serotonin and hippocampal neurogenesis. Neuropsychopharmacology, 1999; 21: 465–515
26. Fossum JR, Nielsen JP, Sharp PA: MicroRNA sponges: competitive inhibitors of small RNAs in mammalian cells. Nature Methods, 2007; 4: 721–26
27. Herringy H, Cohen SM: MicroRNAs and gene regulatory networks: managing the impact of noise in biological systems. Genes Dev, 2010; 24: 1339–44
28. Yoshinura R, Kishi T, Suzuki A et al: The brain-derived neurotrophic factor (BDNF) polymorphism Val66Met is associated with neither BDNF serum levels nor response to selective serotonin reuptake inhibitors in depressed Japanese patients. Prog Neuropsychopharmacol Biol Psychiatry, 2011; 35: 1022–25
29. Ebert MS, Neilson JR, Sharp PA: MicroRNA sponges: possible implications for the pharmacotherapy of depression. CNS Drugs, 2011; 25: 911–20
30. Lim LP, Lau NC, Garrett-Engele P et al: Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. Nature, 2005; 433: 769–73
31. Lewis BP, Shih IH, Jones-Rhoades MW et al: Prediction of mammalian microRNA targets. Cell, 2003; 115: 787–98
32. Scott HL, Tamagnini F, Narduzzo KE et al: MicroRNA-132 regulates recognition memory and synaptic plasticity in the perirhinal cortex. Eur J Neurosci, 2012; 36: 2941–48
33. Cotton AS, Salic D, Lambert TJ et al: Neuronal activity rapidly induces transcription of the CREB-regulated microRNA-132, in vivo. Hippocampus, 2010; 20: 492–98
34. No N, Klein ME, Varlamova O et al: A CREB-response element binding protein (CREB)-induced microRNA regulates neuronal morphogenesis. Proc Natl Acad Sci USA, 2010; 105: 16246–31
35. Impey S, McCorkle SR, Cha-Molstad H et al: Defining the CREB regulon: a family-wide analysis of transcription factor regulatory regions. Cell, 2009; 110: 1041–54
36. Scott HL, Tamagnini F, Narduzzo KE et al: MicroRNA-132 regulates recognition memory and synaptic plasticity in the perirhinal cortex. Eur J Neurosci, 2010; 34: 1022–25
37. Lewis BP, Shih IH, Jones-Rhoades MW et al: Prediction of mammalian microRNA targets. Cell, 2003; 115: 787–98
38. Scott HL, Tamagnini F, Narduzzo KE et al: MicroRNA-132 regulates recognition memory and synaptic plasticity in the perirhinal cortex. Eur J Neurosci, 2012; 36: 2941–48
39. Nudelman AS, DiRocco DP, Lambert TJ et al: Neuronal activity rapidly induces the transcription of the CREB-regulated microRNA-132, in vivo. Hippocampus, 2010; 20: 492–98
40. Vo N, Klein ME, Varlamova O et al: A CREB-response element binding protein (CREB)-induced microRNA regulates neuronal morphogenesis. Proc Natl Acad Sci USA, 2010; 105: 16246–31
41. Impey S, McCorkle SR, Cha-Molstad H et al: Defining the CREB regulon: a family-wide analysis of transcription factor regulatory regions. Cell, 2009; 110: 1041–54
42. Wayman GA, Davare M, Ando H et al: An activity-regulated microRNA controls dendritic plasticity by down-regulating p250GAP. Proc Natl Acad Sci USA, 2010; 2008: 105: 9093–98
43. Cheng HY, Papp JW, Varlamova O et al: microRNA modulation of circadian-clock period and entrainment. Neuron, 2007; 54: 813–29
44. Luihart BW, Bensen AL, Washburn EK et al: mir-132 mediates the integration of newborn neurons into the adult dentate gyrus. PLoS One, 2011; 6: e19077
45. Edsbauer D, Neilson JR, Foster KA et al: Regulation of synaptic structure and function by fMRP-associated microRNAs miR-125b and miR-132. Neuron, 2010; 65: 373–84
46. Hansen KF, Sakamoto K, Wayman GA et al: Transgenic miR-132 alters neuronal spine density and impairs novel object recognition memory. Control Clin Trials, 2004; 25: 119–42
47. Pettenger C, Duman RS: Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology, 2008; 33: 89–109
48. Rush AL, Fava M, Wisniewski SR et al: Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Control Clin Trials, 2004; 25: 119–42
49. Bengtsson B, Schinder AF, Poo MM: Synaptic reliability correlates with reduced susceptibility to synaptic potentiation by brain-derived neurotrophic factor. Learn Mem, 1999; 6: 212–42
50. Thoenen H: Neurotrophins and neuronal plasticity. Science, 1995; 270: 593–98
50. Numakawa T, Richards M, Adachi N et al: MicroRNA function and neurotrophin BDNF. Neurochem Int, 2011; 59: 551–58
51. Numakawa T, Suzuki S, Kumamaru E et al: BDNF function and intracellular signaling in neurons. Histol Histopathol, 2010; 25: 237–58
52. Kawashima H, Numakawa T, Kumamaru E et al: Glucocorticoid attenuates brain-derived neurotrophic factor-dependent upregulation of glutamate receptors via the suppression of microRNA-132 expression. Neuroscience, 2010; 165: 1301–11
53. Mattson MP, Wan R: Neurotrophic factors in autonomic nervous system plasticity and dysfunction. Neuromolecular Med, 2008; 10: 157–68
54. Martin JL, Jenkins VK, Hsieh HY, Balkowiec A: Brain-derived neurotrophic factor in arterial baroreceptor pathways: implications for activity-dependent plasticity at baroafferent synapses. J Neurochem, 2009; 108: 450–64
55. Noble EE, Billington CJ, Kolz CM, Wang C: The lighter side of BDNF. Am J Physiol Regul Integr Comp Physiol, 2011; 300: R1053–69
56. Taliaz D, Loya A, Gersner R et al: Resilience to chronic stress is mediated by hippocampal brain-derived neurotrophic factor. J Neurosci, 2011; 31: 4475–83
57. Jeanneteau FD, Lambert WM, Ismaili N et al: BDNF and glucocorticoids regulate corticotrophin-releasing hormone (CRH) homeostasis in the hypothalamus. Proc Natl Acad Sci USA, 2012; 109: 1305–10
58. Chaldakov G: The metabotrophic NGF and BDNF: an emerging concept. Arch Ital Biol, 2012; 149: 257–63
59. Speer T, Rohrer L, Bliszczuk P et al: Abnormal High-Density Lipoprotein Induces Endothelial Dysfunction via Activation of Toll-Like Receptor-2. Immunity, 2013; 38(4): 754–68
60. Liu W, Peng Y, Wu B et al: A Meta-Analysis of the Impact of EPC Capture Stent on the Clinical Outcomes in Patients with Coronary Artery Disease. J Interv Cardiol, 2013; [Epub ahead of print]
61. Lerman A, Zelmer AM: Endothelial function: cardiac events. Circulation, 2005; 111: 363–68
62. Waltenberger J: VEGF resistance as a molecular basis to explain the angiogenesis paradox in diabetes mellitus. Biochem Soc Trans, 2009; 37: 1167–70
63. Holmes DI, Zachary I: The vascular endothelial growth factor (VEGF) family: angiogenic factors in health and disease. Genome Biol, 2005; 6: 209
64. Xu S, Jin C, Shen X et al: MicroRNAs as potential novel therapeutic targets and tools for regulating paracrine function of endothelial progenitor cells. Med Sci Monit, 2012; 18(7): HV27–31
65. Anand S, Cheres DA: MicroRNA-mediated regulation of the angiogenic switch. Curr Opin Hematol, 2011; 18: 171–76
66. Jin W, Reddy MA, Chen Z et al: Small RNA sequencing reveals microRNAs that modulate angiotensin II effects in vascular smooth muscle cells. J Biol Chem, 2012; 287: 15672–83
67. Hanson M, Gluckman P: Endothelial dysfunction and cardiovascular disease: the role of predictive adaptive responses. Heart, 2005; 91: 864–66
68. Donovan MI, Lin MI, Wiegr P et al: Brain derived neurotrophic factor is an endothelial cell survival factor required for intramyocardial vessel stabilization. Development, 2005; 127: 4531–40
69. Katare R, Riu F, Mitchell K et al: Transplantation of human pericyte progenitor cells improves the repair of infarcted heart through activation of an angiogenic program involving micro-RNA-132. Circ Res, 2011; 109: 894–906
70. Carrillo ED, Escobar Y, Gonzalez G et al: Posttranscriptional regulation of the beta2-subunit of cardiac L-type Ca2+ channels by MicroRNAs during long-term exposure to isoproterenol in rats. J Cardiovasc Pharmacol, 2011; 58: 470–78
71. Deregibus MC, Tetta C, Camussi G: The dynamic stem cell microenvironment is orchestrated by microvesicle-mediated transfer of genetic information. Histol Histopathol, 2010; 25: 397–404
72. Ceman S, Saugstad J: MicroRNAs: Meta-controllers of gene expression in synaptic activity emerge as genetic and diagnostic markers of human disease. Pharmacol Ther, 2011; 130: 26–37
73. Smallheiser NR: Do Neural Cells Communicate with Endothelial Cells via Secretory Exosomes and Microvesicles? Cardiovasc Psychiatry Neurol, 2009; 2009: 383086.