Am J Transl Res 2019;11(11):6717-6738
www.ajtr.org /ISSN:1943-8141/AJTR0100089

Review Article

Mechanisms supporting potential use of bone marrow-derived mesenchymal stem cells in psychocardiology

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Received July 25, 2019; Accepted October 25, 2019; Epub November 15, 2019; Published November 30, 2019

Abstract: Despite great efforts made in recent years, globally cardiovascular disease (CVD) remains the most common and devastating disease. Pharmacological, interventional and surgical treatments have proved to be only partly satisfactory for the majority of patients. A major underlying cause of poor prognosis is a high comorbidity rate between CVD and mental illness, which calls for the approaches of psychocardiology. As psychiatric disorders and CVD can influence each other bidirectionally, it is necessary to develop novel therapies targeting both systems simultaneously. Therefore, innovative stem cell (SC) therapy has become the most promising treatment strategy in psychocardiology. Bone marrow-derived mesenchymal stem/stromal cells (BM-MSCs), among all different types of SCs, have drawn the most attention due to unique advantages in terms of ethical considerations, low immunogenicity and simplicity of preparation. In this review, we survey recent publications and clinical trials to summarize the knowledge and progress gained so far. Moreover, we discuss the feasibility of the clinical application of BM-MSCs in the area of psychocardiology.

Keywords: Psychocardiology, bone marrow-derived mesenchymal stem/stromal cells, inflammation, autonomic nervous system, platelet activation

Introduction

Epidemiology and concepts addressed by psychocardiology

Cardiovascular disease (CVD) is the leading global cause of mortality accounting for at least 16 million deaths annually [1]. In the USA alone, the financial burden on hospitals reached 196 billion USD in 2015 and is expected to exceed one trillion USD by 2030 [2]. Although significant advances in pharmacological, interventional and surgical treatments have been made during the last two decades, the population affected and mortality caused by CVD are still increasing with poor long-term prognosis for sufferers [2]. This is mainly caused by the complexity of CVD which involves multiple systemic dysfunctions. Among these, mental illness exhibits exceptionally high comorbidity rates with CVD. The concept of psychocardiology has been proposed as a new medical specialty aiming to unravel the entangled relationships between "heart" and "mind", and so eventually improve the prognosis of those patients suffered from both CVD and psychiatric disorders [3].

Major depressive disorder (MDD), or depression, is one of the mental health disorders which draws particular attention because of its high comorbidity with CVD. It is reported that 15.9% of the patients who had experienced atrial fibrillation (AF) suffered from comorbid depression which resulted in a significantly increased incidence of intracranial bleeding [4]. For patients with unstable angina and ischemic heart disease (IHD), the occurrence rate of depression is as high as 41.4% and 45% respectively [5]. Recent meta-analysis has further revealed that several mental disorders including MDD (OR=2.52, P<0.0001), anxiety (OR=1.41, P<0.001), schizophrenia (OR=1.52, P<0.001) and post-traumatic stress disorder (PTSD) (OR=1.27, P<0.05) significantly increase the incidence of CVD [6].

The consequences of this comorbidity are severe. Mental health disorders not only decrease the quality of life in CVD patients, but also lead to significant increases in both short-term and long-term mortality [7-9]. Therefore, the need to develop novel therapies in psychocardiology is still tremendous and urgent.

Bone marrow-derived mesenchymal stem/stromal cells (BM-MSCs)

The use of Stem Cells (SCs) has drawn much attention in the area of regenerative medicine because of its ability to regenerate damaged cardiac tissues and among all different types of SCs, BM-MSCs have already been well studied in animal and clinical research. In comparison with other SCs such as Embryonic Stem Cells (ESCs) and induced Pluripotent Stem Cells (iPSCs), BM-MSCs have several advantages including fewer ethical considerations, a minor risk of tumorigenicity and lower immunogenicity [10].

BM-MSCs are a subtype of non-hematopoietic stem cells localized in the bone marrow. They were first identified in 1976 and have proven to be capable of differentiating into adipocytes, chondrocytes, osteocytes and cardiomyocytes. Although they occupy only 0.001%-0.01% of the total monocytes in the bone marrow, they can be expanded over a million folds or 6 generations *in vitro* [11]. Since Friedenstein et al established the first method for isolating BM-MSCs, several techniques have been developed including a wholes defined by The International Society for Cellular Therapy (ISCT), all mesenchymal stem cells (MSCs) should be positive for CD105, CD73 and CD90 while being negative for CD34, CD45, CD11b/14 and CD19/79a [12]. Researchers also suggest that MSCs, especially BM-MSCs, also express several other surface markers such as CD13, CD26, CD29, CD105 and Stro-1 [13, 14].

In 2002, Shake et al first observed the beneficial effects of BM-MSC transplantation in a swine Myocardial Infarct (MI) model where they discovered a significant increase in end diastolic/systolic wall thickness after autologous BM-MSCs transplantation [15]. Two years later, the first clinical trial was completed in 69 patients with Acute Myocardial Infarct (AMI). At the end of the 6 months follow-up period, patients receiving BM-MSCs transplantation showed compelling changes in terms of their cardiac functions. The Left Ventricular Ejection Fraction (LVEF) of patients was 67±3% in the BM-MSCs group and 54±5% in the control group [16]. Since then, BM-MSC therapy has been widely discussed in terms of the treatment for a broad range of cardiovascular diseases (see previous reviews for details [17, 18]). However, none ever considered the potential applications of BM-MSC in psychocardiology. In this review, we discuss the feasibility of BM-MSC therapy in patients with both CVD and mental disorders by comprehensively summarizing possible effects of BM-MSC transplantation on underlying mechanisms of psychocardiological disease.

Mechanisms underlying the therapeutic effects of BM-MSCs in psychocardiology

Tissue regeneration

It is widely acknowledged that cell apoptosis and tissue necrosis are associated with the pathology of both CVD and psychiatric illness. Thus, the ability of BM-MSC to regenerate functional cardiomyocytes, endothelial cells, neurons and astrocytes is of great importance for its therapeutic effects in psychocardiological disorders (**Figure 1**).

In 1999, a research team from Keio University successfully generated cardiomyocytes from marrow stromal cells by 5-azacytidine (5-aza) treatment *in vitro* [19]. By now, several methodologies have been established to induce *ex vivo/in vitro* differentiation of BM-MSC into cardiomyocyte-like cells. These methodologies include aggregate co-culture, treatment with demethylating agents, incubation with growth factors and treatments with rehmannia glutinosa oligosaccharide [20-23]. Moreover, several research teams report that they have observed in vivo differentiation of BM-MSC into cardiac cells expressing multiple cardiac markers, such as desmin, β-MHC, β-actin, CTn-T and phospholamban, at almost the same levels seen in endogenous cardiomyocytes [24]. Molecular mechanisms underlying this differentiation involve the up-regulation of nuclear membrane proteins and transcription factors [25, 26] which eventually activate downstream signal pathways such as Notch1 and WNT [27, 28].

Besides cardiomyocytes, BM-MSCs were also shown to be able to differentiate into vessel smooth muscle (SM) cells and vascular endo-

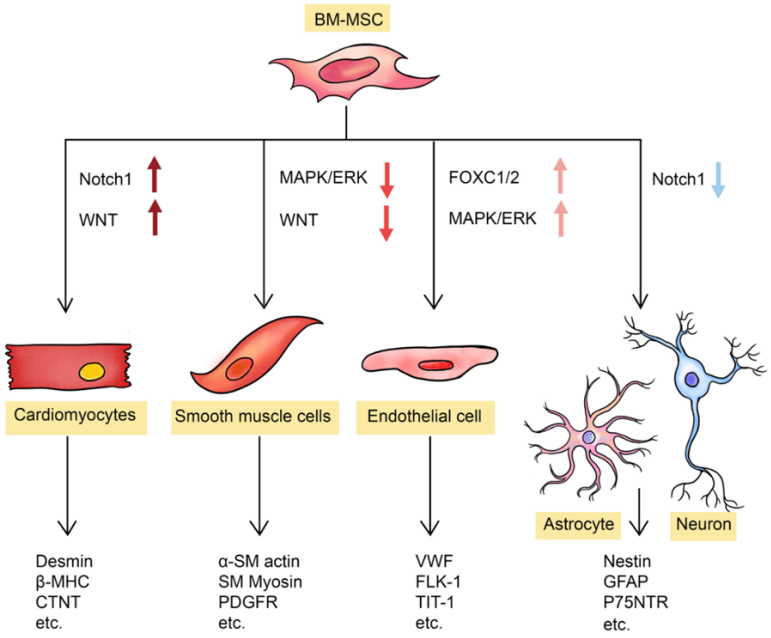

Figure 1. Regenerative abilities contribute to the application of BM-MSC in psychocardiological disease. Under different stimulations, BM-MSC can differentiate into cardiomyocytes *via* activation of Notch-1 and Wnt signaling pathways; into smooth muscle cells *via* inhibition of MAPK and Wnt signaling pathways; into endothelial cells *via* activation of FoxC and ERK signaling pathways; or into neural cells *via* inhibition of Notch-1 signaling pathway. The differentiated cells can express related biomarkers. Abbreviations: BM-MSC, bone marrow-derived mesenchymal stem cell.

thelial cells. SM-like cells induced from BM-MSCs express SM proteins, including α-SM actin, PDGF-β receptor, SM myosin light chain and SM myosin heavy chain, at similar levels to those in freshly isolated SM cells. In addition, SM-like cells also exhibit identical electrophysiological features compared to SM cells [24]. On the other hand, expression of endothelial markers (vWF, Flk-1 and TIT1) can also be detected after, but not before, endothelial induction in BM-MSCs [24]. *In vivo* differentiation of BM-MSC into SM and endothelial cells was also observed, and more recent publications reveal that the inhibition of MAPK and WNT pathways result in differentiation into SM cells [29] while the activation of FOXC1/2 and ERK1/2 pathways contribute to the differentiation into endothelial cells [30, 31].

Finally, BM-MSCs also show potential to differentiate into neuron-like cells which are able to express neural markers (Nestin, GFAP and DCX) and secrete multiple neurotrophic factors (BDNF, IGF-1 and FGF-2) *in vitro* [32]. Recently, different procedures have been established to generate specific subtypes of neural cells, such as Schwann cells and GABAergic neurons. Differentiated Schwann cells not only express neural markers (Nestin, GFAP and p75NTR), but also exhibit myelinating functions *in vitro* [33]. A culture medium consisting of retinoic acid (RA), ciliary neurotrophic factor (CNTF), and creatine was shown to be able to induce in vitro differentiation of GABAergic neurons from BM-MSC with enhanced expression of GAD1/2, VGAT, GABA and synaptophysin [34]. In addition, BM-MSC differentiation into neural cells was also detected *in vivo* both with and without chemical stimulations [35, 36]. The mechanism regulating neural differentiation largely remains unknown, but it is believed to be associated with inhibition of Notch-1 signaling pathway [37].

Although differentiation into cardiomyocytes and neural cells was confirmed both *in vitro* and *in vivo*, whether the differentiation is directly leading the tissue regeneration is still in debate. Dai et al suggested that beneficial effects of BM-MSC transplantation in MI rats are caused by paracrine effects but not direct differentiation of introduced SCs [38]. Similarly, nerve regeneration following BM-MSC transplantation in a gastric denervation rat model was also demonstrated to result from secretion of neurotrophic factors but not direct differentiation of grafted BM-MSC [39]. Therefore, understanding these paracrine effects is of particular importance for the future application of BM-MSC in psychocardiological illness.

BM-MSCs secrete various growth factors and cytokines under certain conditions such as hypoxia, TNF stimulation and formation of cell-cell contacts [39-41]. These cytokines not only participate in angiogenesis and neurogenesis but also contribute to anti-apoptosis properties and endogenous regenerative activities. The

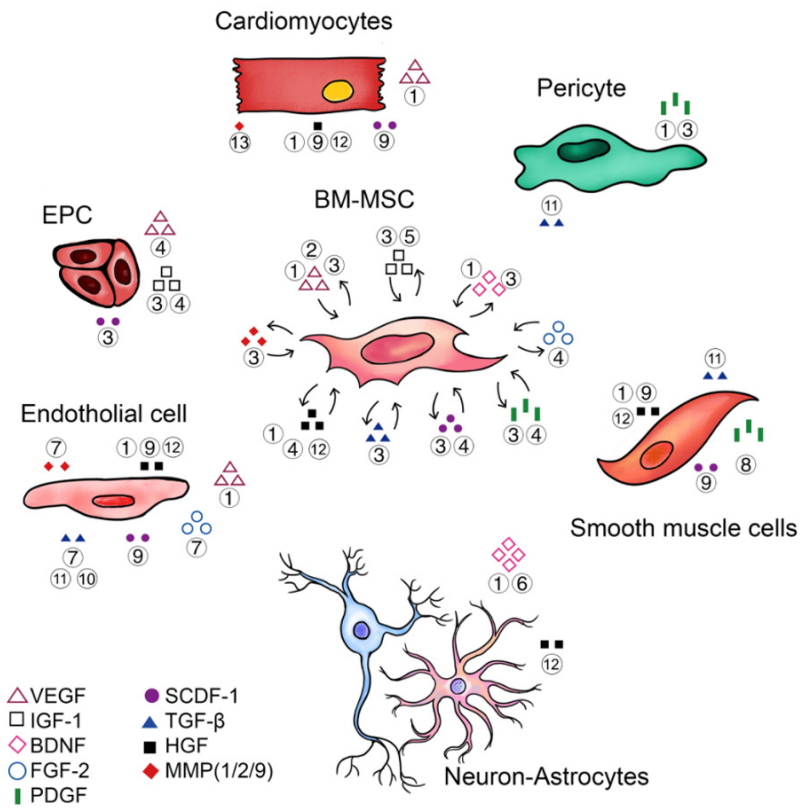

Figure 2. Functions of major cytokines and soluble factors secreted by BM-MSC. The growth factors and cytokines secreted by BM-MSC can act on both BM-MSC itself (autocrine) and other target cells (paracrine) which play essential roles during the development of psychocardiological disease. Figure legends: ① Anti-apoptosis; ② Activate endogenous BM-MSC; ③ Increase homing; ④ Promote proliferation; ⑤ Induce differentiation; ⑥ Increase neural plasticity; ⑦ Increase stability and integrity; ⑧ Inhibit over-proliferation of smooth muscle cells; ⑨ Anti-fibrosis; ⑩ Inhibition of migration; ⑪ Promote cell adherent; ⑫ Anti-oxidation; ⑬ Inhibit ventricular remodeling. Abbreviations: BM-MSC, bone marrow-derived mesenchymal stem cell; VEGF, Vascular Endothelial Growth Factor; EPC, Endothelial Progenitor Cell; IGF-1, Insulin-like Growth Factor 1; BDNF, Brain-Derived Neurotrophic Factor; FGF-2, Fibroblast Growth Factor 2; PDGF, Platelet-Derived Growth Factor; SCDF-1, Stromal Cell-Derived Factor 1; TGF-β, Transforming Growth Factor beta; HGF, Hepatocyte Growth Factor; MMP, Matrix Metalloproteinase.

detailed functions of each cytokine can be found in **Figure 2** [42-67] as well as another review studying SC promoted angiogenesis [68]. Overall, the regenerative activity of BM-MSCs is one of the most fundamental predictors of their future application in psychocardiology.

Immunosuppressive effects

Elevated inflammatory responses are detected in patients with CVD as well as patients with mental illness [69]. A recent meta-analysis indicated that depression is associated with significant increases in levels of multiple cytokines including interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP) [70]. Higher concentrations of such pro-inflammatory markers not only suggest an increased inflammatory state which is known to participate in the development of CVD [71-73], but also foreboode increased risks of major cardiovascular adverse events (MCAE) and even cardiac death. For example, a higher serum level of IL-6 (range from 2.08 pg/mL to 3.9 pg/mL) results in risk ratios (RR) of all-cause mortality and cardiovascular mortality at 1.49 (95% CI 1.33-1.67) and 1.69 (95% CI 1.27-2.25) respectively. On the other hand, higher levels of CRP are associated with a RR of 2.03 (95% CI 1.65-2.50) for cardiovascular mortality, and 1.75 (95% CI 1.55-1.98) for all-cause mortality [74]. Meanwhile, elevated baseline levels of CRP and IL-6 are also positively associated with cognitive symptoms of depression after full adjustments [75]. The importance of inflammation management in psychocardiology can also be corroborated by the fact that several widely used drugs in the treatment of CVD and mental illness exhibit anti-inflammatory properties. Metoprolol, a representative of β-blockers, were shown to inhibit the activation of neutrophils, and thereby rescue cardiac function in MI mice and patients [76]. Similarly, fluoxetine, a selective serotonin reuptake inhibitor (SSRI) commonly used as an antidepressant, has been shown to be able to inhibit the activation of microglia, the innate immune cells of the central nervous system (CNS) [77]. In a recent meta-analysis reduced serum levels of IL-6, TNF-α and IL-1β were also

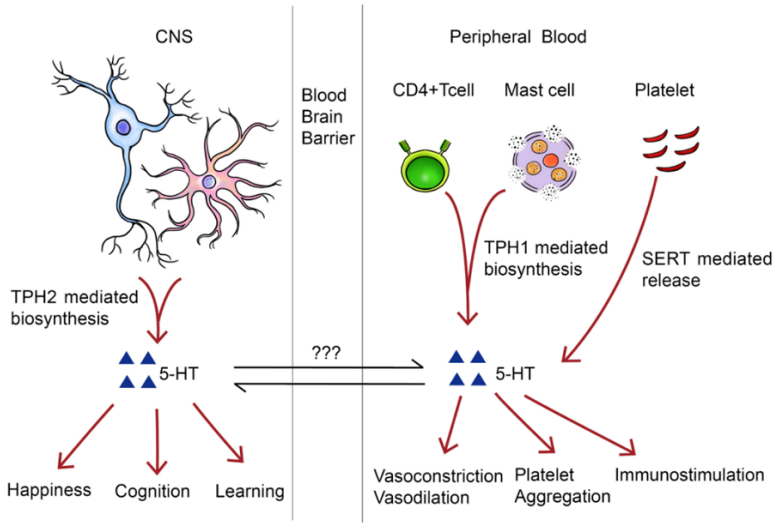

Figure 3. Brief introduction of the importance of 5-HT in the central nerve system (CNS) and peripheral blood system (PBS). The 5-HT is synthesized by Tph2 and Tph1 in the CNS and PBS respectively. In addition, the 5-HT can also be released from platelet. Inside the CNS, 5-HT functions as a neurotransmitter during the physiological process in happiness, cognition and learning. In the circulatory blood, 5-HT is a hormone which can regulate vascular tone, induce platelet aggregation and trigger immunological responses. Abbreviations: BM-MSC, bone marrow-derived mesenchymal stem cell; 5-HT, 5-hydroxytryptamine, TPH, tryptophan hydroxylase; SERT, serotonin transporter.

observed after SSRI treatment in patients with MDD [78]. Although which cytokines are involved in SSRIs induced anti-inflammatory responses are still under debate [79], there seems no doubt that immunoregulation by SSRIs plays an essential role in their modulation of neurobehavioral functions. Nowadays, increasing interest is being focused on developing therapeutics targeting the immune system and related signaling pathways in both cardiology and psychology [80-83].

Although the exact molecular mechanisms underlying the interaction of CVD, mental health disorders and inflammation are not completely understood, it is widely accepted that 5-hydroxytryptamine (5-HT), which is also known as serotonin, is one of the most important mediators (**Figure 3**). As a neurotransmitter in the CNS, 5-HT regulates a wide range of neurological activities including happiness, cognition, learning and memory. Abnormal levels of 5-HT, 5-HT transporter (SERT) and 5-HT receptors are believed to be a major cause of mental health disorders and are considered to be the main targets for the treatment [84-87]. Meanwhile, 5-HT also acts as a vasoconstrictor or a vasodilator under pathological or physiological circumstances in the peripheral circulatory system [88]. In particular, its vasoconstrictive ability is believed to be a major contributor to the development of several cardiovascular diseases including hypertension [89], heart failure (HF) [90] and atherosclerosis [91]. Roles for 5-HT in the immune system have been thoroughly presented in other reviews [92, 93]. Briefly, 5-HT can be synthesized by tryptophan hydroxylase 1 (TPH 1) in multiple immune cells including mast cells [94] and T helper (Th) cells [95]. The release of 5-HT from platelets and other cells can further exert immunostimulatory functions through the activation of various 5-HT receptors while the blockage of such receptors results in immunosuppression [92]. On the other hand, pro-inflammatory cytokines, such as Interferon-γ (IFN-γ) and TNF-α, can induce increased activity of indoleamine 2,3-dioxygenase (IDO), which degrades tryptophan into kynurenine [96]. This inflammation-driven kynurenine metabolism is considered to be a primary pathologic pathway leading to depression. Degradation of tryptophan not only increases the formation of neurotoxic metabolites, but also contributes directly to a decline in the level of 5-HT, which can only be synthesized from tryptophan, and thereby promotes depressive symptoms [97-99].

The immunoregulatory effects of BM-MSCs can't be overemphasized when considering their applications in psychocardiology. Firstly, BM-MSC can inhibit the activation of lymphocytes and B cells through direct cell-cell interaction mainly mediated by integration of programmed cell death protein 1 (PD-1) and Programmed cell death 1 ligand 1 (PD-L1). Transplantation of BM-MSCs results in increased proliferation of Th2 and Treg with a decrease in numbers of Th1 and Th17 cells, which suggests down-regulation of immune responses. Silencing PD-L1 in BM-MSCs significantly attenuated the above immunosuppressive effects [100]. Similarly, the PD1/PDL1

pathway is also important for inhibitory effects on B cells which lead to dramatic reductions in secretion of IgM and IgG [101]. Interestingly, recent studies also show that BM-MSCs are able to secret PDL1 and thereby inhibit CD4+ T cells through the AKT-FOXO3 signaling pathway [102].

Although there is no doubt that PD-1/PD-L1 induced reticence plays essential roles in BM-MSC effects, most research has still been focused on their paracrine activities. Soluble factors from BM-MSCs or BM-MSC extracellular vesicles can act on both innate and adaptive immune cells. Prostaglandin E2 (PGE2), IL-6 and granulocyte macrophage colony stimulating factor (GM-CSF) released by BM-MSCs can suppress the differentiation of macrophage subtype 1 (M1) from immature macrophages and promotes differentiation towards an immunosuppressive phenotype (macrophage subtype 2, M2) [103, 104]. This polarization from M1 to M2 is associated with increased expression of CD206 and decreased expression of CD86 on the cell membrane [105], as well as elevated secretion of anti-inflammatory cytokines (IL-10) and reduced secretion of pro-inflammatory cytokines (TNF-α) [106]. In addition to macrophages, IL-6 also inhibits apoptosis of neutrophils, and prevents the respiratory burst which generates reactive oxygen species (ROS) [107]. Moreover, mast cells, which produce histamine and heparin during infection and allergy, are also under the control of BM-MSC secreted PGE2. Activation of prostanoid receptor EP4 results in decreased levels of degranulation and reduced release of TNF-α from mast cells [108]. Nature killer (NK) cells, as a major element of innate immunity, are targets of BM-MSC secreted factors as well. Evidence suggested that indoleamine 2,3-dioxygenase (IDO) [109], PGE2 [109], TGF-β [110] together with human leucocyte antigen-G5 (HLA-G5) [111] contribute to suppress cytotoxic effects of NK cells. On the other hand, dendritic cells (DCs) can also be regulated by IL-6 and PGE2 [112], finally resulting in down-regulation of DC markers (CD40&CD83), reduced expression levels of pro-inflammatory markers (TNF-α, IFN-γ, IL-12p70 and MIP-1) [113, 114], enhanced expression of immunoregulatory factors (IL-6&IL-10) [115], and the inhibition of migration of DCs [116]. Furthermore, similarly soluble PD-L1, IDO [109], PGE2 [109, 117] and HLA-G5 [111] also exhibit anti-inflammatory functions through the polarization from Th1 and Th17 to Treg. In addition to the proteins and metabolites mentioned above, at least 49 micro-RNAs were identified as being enriched in exosomes secreted from BM-MSC including miR21-5p, miR142-3p, miR223-3p, and miR126-3p [118]. Some of these micro-RNAs work together and regulate target immune cells. For example, miR21-5p down-regulates CCR7 expression on DC cells and limits their migratory ability [118]. MiR146a-5p targets the gene IRAK1 which plays a crucial part in Toll-like Receptors (TLR) mediated inflammatory reactions [119]. Overall, BM-MSCs display remarkable anti-inflammatory effects which give great promise for their future application in psychocardiology (**Figure 4**).

It should also be acknowledged that BM-MSCs also show the potential to regulate levels of 5-HT in the CNS and the peripheral circulatory system, through mechanisms that are not fully recognized. Ali et al have suggested that BM-MSC transplantation increases concentrations of 5-HT in the cortex and midbrain in a rodent brain injury model [120]. An avian model also revealed increased 5-HTR1A expression and decreased TPH-1 expression after the transplantation of BM-MSC [121]. Additionally, IDO released from BM-MSCs may also be involved in the modulation of the 5-HT system *via* altered tryptophan metabolism.

Antiplatelet properties

Thrombogenesis induced by platelet activation and aggregation, as is well-known, is the leading cause of the development of multiple CVD and major adverse cardiovascular events (MACE) [122]. Markers of platelet activation usually include the increased synthesis of the αIIb-β3 complex, P-selectin, Annexin V, CD62p and platelet factor 4 (PF4). Compared to healthy controls, patients with MDD were shown to have increased levels of PF4 whilst total platelet counts were unchanged [123]. Other research illustrates that subjects with depressive symptoms have a higher percentage of circulating CD62p positive platelets [123]. Similar results were consistently reported by different groups [124, 125]. A more recent study which included 26 CAD patients discovered a positive correlation between depressive symptom severity and platelet factor abundance [126]. Therefore, platelet activation can be consid-

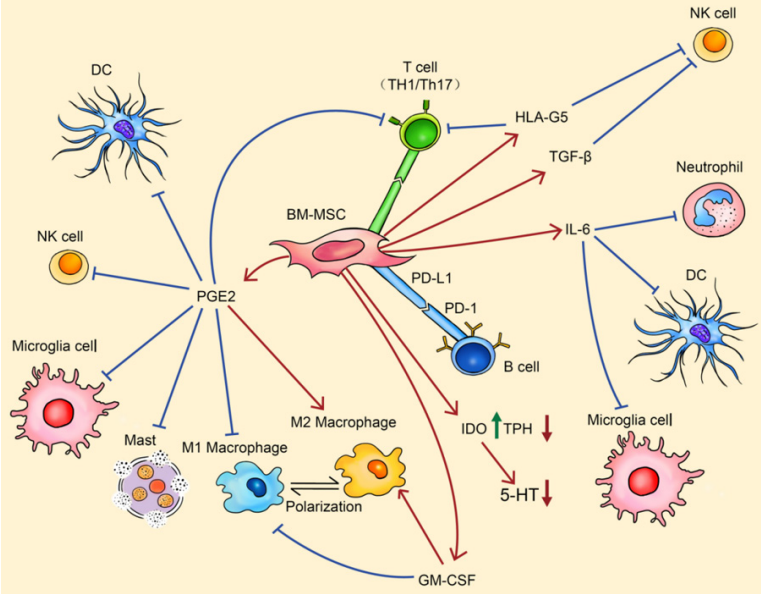

Figure 4. BM-MSC regulates the immune system. By PD-1 mediated cell-cell contact, BM-MSC can inhibit the activation of adaptive immune cells. By secreting PGE2, HLA-G5, TGF-β, IL-6 and GM-CSF, BM-MSC can inhibit the activation of almost every type of immune cells. The regulatory effects can be observed by a pro-inflammatory to anti-inflammatory cell polarization (such as M1 macrophage to M2 macrophage). Meanwhile, IDO secreted from BM-MSC can down-regulate the biosynthesis of 5-HT. Arrows in red indicate stimulative effects while arrows in blue show inhibitory effects. Abbreviations: BM-MSC, bone marrow-derived mesenchymal stem cell; PD-L1, programmed death ligand 1; PD-1, programmed death 1; DC, dendritic cells; NK, natural killer; PGE2, prostaglandin E2; HLA-G5, human leucocyte antigen G5; TGF-β, transforming growth factor-β; IL-6, interleukin 6; IDO, indoleamine 2,3-dioxygenase; TPH, tryptophan hydroxylase; 5-HT, 5-hydroxytryptamine; GM-CSF, granulocyte macrophage colony stimulating factor.

ered to be a link between cardiovascular disease and major depression [127]. Besides this, activated platelets can recruit and mobilize multiple immune cells, including neutrophils [128] and macrophages [129, 130], which further damage the blood vessels and so contribute to worsen prognosis [131].

In addition, the activation of platelets is also associated with the release of 5-HT and the activation of the 5-HTR2A in the platelet membrane. It is well known that 5-HT leads to platelet aggregation [132], and can be used as a predictor for cardiac events [133] for dozens of years. On the other hand, recent studies have further confirmed the role of platelets in psychocardiology. For example, Peitl et al found that patients with depression had impaired 5-HT storage [134] while Williams et al confirmed increased 5-HTR2A levels in platelets in such patients [135]. Multiple SSRIs, on the other hand, show anti-platelet functions. In ADP induced aggregation tests, impedance was reduced by 23% and 29% on treatment with escitalopram and nortriptyline respectively [136]. However the latest publications evaluating the anti-platelet capacity of all types of SSRIs, have drawn opposing conclusions [137, 138] indicating that more research with enlarged sample size may be required. Furthermore, even should their anti-platelet effects be confirmed, whether SSRIs are able to reduce the incidence rates of MACE would still be contentious. For instance, after analyzing the data from 238,963 patients with depression, Coupland et al expressed the opinion that a reduced risk of MI can be detected in SSRIs users [139]. Opposing conclusions were reached by Iasella et al who claimed that SSRI patients shared higher MACE risk than patients on placebo treatments (HR 1.21, 95% CI 1.02-1.43, P=0.030) [140].

We speculate that therapeutic effects of BM-MSC transplantation on platelet activity may occur through the inflammatory and serotonergic pathways mentioned before. Moreover, the ability of BM-MSC transplantation to regenerate endotheliocytes can also contribute to its anti-platelet outcome as damaged vessel endothelium is a major contributor to 5-HT induced platelet aggregation. Furthermore, emerging evidence suggests a direct inhibitory effect *via* interaction between CD73 and CD39 which are expressed on the membranes of BM-MSCs and platelets respectively [141]. This cell-cell interaction based inhibitory effect is of great importance as BM-MSCs, unlike MSCs from other origins, do not express podoplanin, which is a ligand of the C-type lectin-like receptor (CLEC-2). The tissue-specific expression of adhesions molecules results in tissue-specific hematoblastic reactions whereby BM-MSCs decrease platelet aggregation while umbilical cord MSCs promote platelet aggregation [142].

Regulation of autonomic nervous system (ANS)

The balance of sympathetic and vagal activity controls a wide range of cardiovascular outputs including heart rate and blood pressure. Abnormal increases in sympathetic activity cause many adverse cardiovascular events [143, 144]. Recent studies even suggest that electrocardiographic indicators of elevated sympathetic activity can predict sudden cardiac death in patients with MI and HF [145, 146]. Catecholamines (epinephrine and norepinephrine), used as molecular markers for sympathetic activity, were also shown to be raised in patients with CVD [147] as well as patients with mental disorders [69]. The over-accumulation of epinephrine and norepinephrine may also be seen as a consequence of the activation of the hypothalamic-pituitary-adrenal (HPA) axis, which is also dominated by the ANS. Importantly, other biomarkers of stimulation of the HPA axis, such as aldosterone and cortisol/corticosterone, are found to be higher in the serum of patients with depressive symptoms [148-150]. On the other hand, an increase in cortisol is associated with significantly increased mortality [151]. Alternately, imbalances in the ANS can raise the potential to develop other independent cardiovascular risk factors such as hyperlipidemia, obesity and insulin tolerance.

Besides the ANS, the activity of the HPA-axis is also associated with 5-HT signaling pathways. *In vivo* animal experiments suggest that transduction of HPA-axis responses relies on 5-HTR1A and 5-HTR2A, but is independent of 5-HTR2C [152, 153]. By using a social isolation rhesus macaque model, Sorenson et al demonstrated that short allele (ss) SERT genotype is linked to impair HPA-axis function and finally results in elevated levels of cortisol [154]. Accordingly, effects of SERT and its methylation on cortisol release were further confirmed in humans [155, 156]. These discoveries answered the question regarding the involvement of 5-HT in the regulation of the HPA-axis raised 20 years ago when scientists, for the first time, observed an effect of the SSRI-citalopram on HPA-axis regulation in rats [157]. Additionally, superexcitation of the HPA-axis normally leads to pro-inflammatory responses. This can be verified by positive correlations between levels of cortisol/norepinephrine and levels of multiple inflammatory markers including TNF-α, IL-6, IL-10 and CRP [158-160]. Interestingly, although 5-HT is also a primary mediator of inflammation, it seems that this HPA-axis-induced immune response is not associated with 5-HT metabolism [161], but is affected by glucocorticoid receptor pathways [162], adrenergic receptor signaling [163] and the status of ATP-sensitive potassium channels [164]. This may partly explain why high concentrations of cortisol do not directly cause abnormal platelet functions in hypercortisolaemic patients [165].

Apart from the HPA-axis, a decrease in heart rate viability (HRV), another marker of a disabled ANS, is also detected in psychocardiological disease. HRV, which consists of a series of parameters including SDNN, SDANN, RMSSD, PLVAR10 and LF/HF, is considered to reflect the ability of the heart to deal with physiological drives, a decreased HRV indicates an excessive enhancement of sympathetic activity. It has been observed that MDD patients have significantly reduced RMSSD compared with healthy controls [166]. Similar results were observed in patients with other mental illness such as schizophrenia [167], bipolar disorder [167] and anxiety [168]. A decline in HRV is a well-known predictor for poor prognosis of CVD, development of MACE and even cardiac death [169, 170]. Notably, when compared to MI patients without depression, depressed MI patients seem to have more significantly decreased HRV [171]. Strong links have also been suggested between HRV and inflammation. In patients with juvenile dermatomyositis, SDNN, pNN50 and RMSSD are all negatively correlated to levels of hsCRP [172]. In the CARLA study which included 1671 participants from the general population, multiple HRV parameters were shown to be negatively associated with levels of hsCRP, sTNF-R1 and IL-6 [170]. Besides this, the observed effect of SSRIs on HRV also indicates a potential engagement of 5-HT metabolism [173].

Tissue regenerative, anti-inflammatory and anti-platelet properties may all contribute to the therapeutic effects of BM-MSC in terms of ANS modulation in animal models with ANS dysfunctions [174]. Moreover, BM-MSC transplantation has been shown to decrease the levels of norepinephrine and corticosterone in a rat brain injury model [120] and a diabetic rat model [175] respectively. Similar effects were also detected in cardiomyopathy rats where the expression of CYP11B2, the aldosterone syn-

Table 1. Single nucleotide polymorphisms in psychocardiology

SNP Access No.	Genes	Alleles	Functions related to psychocardiology
rs3917010	VCAM1	A>C	Increased risk of MI; predict depressive symptoms in CVD patients
rs1324072	CR1	C>G	Predict depressive symptoms in CVD patients
rs1424386	CHRM2	G>A	
rs2239106	CACNA1C	A>T	
rs216856	vWF	T>C	
rs216873		T>C	
rs3125	HTR2A	C>G/T	Predict depressive symptoms in CVD patients; increase in suicidal ideation; risk of bipolar disorder; risk of MDD
rs6265	BDNF	C>T	Increase incidence of cardiovascular events; increase anxiety; increase suicidality

Abbreviations: VCAM1, Vascular Cell Adhesion Molecule 1; CR1, Cannabinoid Receptor 1; CHRM2, Vholinergic Receptor Muscarinic 2; CACNA1C, Calcium Voltage-gated Channel subunit alpha1 C; vWF, von Willebrand Factor; HTR2A, 2-HT receptor 2A; BDNF, Brain-Derived Neurotrophic Factor.

thase, was significantly inhibited at the mRNA level after the transplantation [176]. In addition to modulation of the HPA-axis, BM-MSCs also appeared able to boost HRV both in animal experiments [177] and clinical trials [178]. Overall, we conclude that the modulatory effects of BM-MSC transplantation on the ANS considerably contribute to its potential applications in psychocardiology.

Other factors

Many other factors may also participate in the development of psychocardiological illness and can be regard as targets of BM-MSC therapy. Lower level of BDNF is proved to be associated with multiple metal disorders [179-182] and it shows direct regulatory effects on 5-HT metabolic genes SERT and TPH-1 [183]. As well as neurological activities, such as neurogenesis and neural plasticity, BDNF also plays essential roles within the cardiovascular system. It not only promotes the development of cardiovascular organs during embryogenesis, but also exhibits anti-apoptotic, anti-fibrosis and anti-inflammatory properties on endotheliocytes and cardiomyocytes [184]. Therefore, the ability to secret BDNF, as mentioned above and shown in **Figure 2**, may further increase the utility of BM-MSC transplantation in psychocardiological disease. Besides this, BM-MSCs are capable of managing oxidative stress, which is actively involved in the development of mental illness [185] and CVD [186, 187], through different signaling pathways [188, 189].

In addition to above physiological and pathological mechanisms, recent studies suggest that genetic and epigenetic changes also contribute significantly to the link between mental illness and CVD. So far, at least eight single nucleotide polymorphisms (SNPs) have been identified as being associated with both psychiatric disorders and CVD [190-194] (**Table 1**). While these changes can't be reversed by pharmacological and surgical treatments, they may be alleviated by the introduction of BM-MSCs carrying other polymorphic forms.

Evidence from pre-clinical and clinical trials

A tremendous number of research articles have extensively discussed the usefulness of BM-MSC transplantation in treatments of CVDs (please find details in previous reviews [17, 195, 196]). In this review, we have briefly summarized the main outcomes of 7 clinical trials reported since 2015 which can be found in **Table 2** [197-203]. Generally, recent promising results indicate potential applications for BM-MSC transplantation in several cardiac diseases. However, its utility in psychocardiological disease is not fully understood as none of the above trials considered the impact of transplantation on mental health status, such as depressive and anxiety-like behaviours.

Although a regulatory effect on mental status can't be observed directly in CVD patients, it can be implied in animals with other conditions. Tsyb et al first described anti-depressive effects of BM-MSCs in a brain trauma rat model through use of plus maze tests [204]. Moreover, in a Flinders sensitive line (FSL) depression rat model, left lateral ventricle injection of BM-MSCs significantly improved performance in forced swim tests (FST) and dominant-submissive relationship (DSR) tests [32]. Similar results were also generated in a subarachnoid hemorrhage (SAH) rat model where depressive behaviors, which were assessed by sucrose preference test (SPT), were reversed by BM-MSC [205]. Additionally, anti-depressive effects

Table 2. Clinical trials using BM-MSC in cardiac diseases

Disease	Sample size*	Injection method	Source	Cell number	Follow-up time	Main outcomes	Reference
IHF	37/18	Myocardial	Autologous	10^7-10^8	6 months	Reduced LVESV; Improved LVEF, stroke volume of and myocardial mass.	[198]
ICM	30/0	Myocardial	Allogeneic	$2*10^7/10^8$	1 year	Reduced scar size; Improved LVEF in 10^8 group; Improved NYHA class.	[200]
CHF	120/231	Myocardial	Autologous	$6*10^8$	1 year	Reduced LVESV and LVEDV.	[202]
ICM	10/0	Myocardial	Autologous	$6*10^7$	1 year	Improvements in LVEF, LVESV, 6-min walk test and NYHA functional class.	[199]
AMI	8/8	Intravenous	Allogeneic	$6*10^7$	2 years	No significant differences.	[197]
DCM	37/0	Myocardial	Allogeneic & Autologous	$9*10^7$	1 year	Increased EF, 6-min walk distance and decreased MLHFQ score in Allo-group.	[201]
DCM	17/20	Intracoronary	Autologous	$5*10^8$	1 year	Improved LVEF, NYHA class and myocardial perfusion.	[203]

*Sample size was shown as: numbers in experimental group/numbers in control group. Abbreviations: AMI, Acute Myocardial Infarction; IHF, Ischaemic Heart Failure; LVESV, LV end-systolic volume; LVEDV, LV end-diastolic volume; ICM, Ischemic Cardiomyopathy; NYHA, New York Heart Association; CHF, Congestive Heart Failure; DCM, Dilated Cardiomyopathy; MLHFQ, Minnesota Living With Heart Failure Questionnaire.

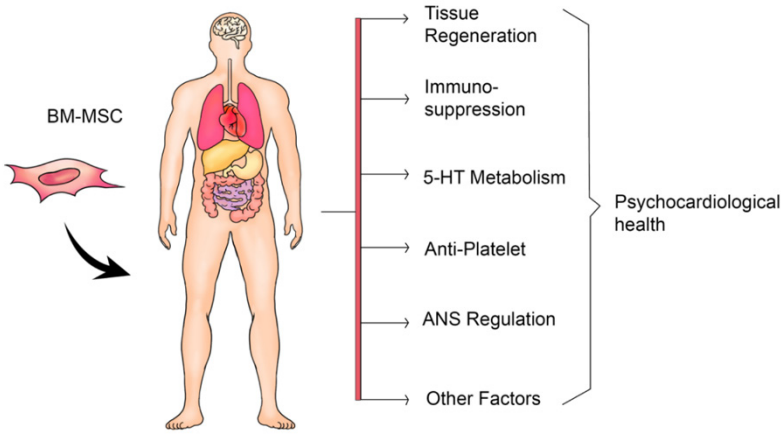

Figure 5. Overview of BM-MSC transplantation in the treatment of psychocardiological disease. BM-MSC exerts therapeutic effects by regenerating tissues, repressing immunological responses, regulating 5-HT biosynthesis, inhibiting platelet aggregation, balancing ANS. Abbreviations: BM-MSC, bone marrow-derived mesenchymal stem cell; 5-HT, 5-hydroxytryptamine; ANS, autonomic nervous system.

of BM-MSCs were further confirmed in traumatic brain injury (TBI) rodent models by two separate research groups [206, 207]. However, it should be particularly noticed that the antidepressive effects of BM-MSC may rely heavily on the methodology adopted. Coquery et al have demonstrated that although intrahippocampal transplantation of BM-MSCs promoted neural plasticity, it failed to rescue depressive behaviours in a rat depression model [208]. Overall, we suggest that an effect on mental health is reliably observed with appropriate transplantation methods, but it is still too early to compel its clinical application in psychiatric disorders at this point.

Conclusion

CVD and mental health disorders are two types of disease that worldwide affect the largest populations. Comorbidity of these diseases leads to a significantly worse prognosis which calls for the concept of psychocardiology. From a sociological perspective, mental disorders can increase the incidence of CVD by influencing daily activities. Depressed patients are less involved in regular exercise [209], and regularly adopt unbalanced diets [210]. Besides the well-known cardiovascular risk factor, obesity, physical inactivity has also been shown to be an independent predictor of cardiac death [211, 212]. In return, CVD patients are more susceptible to mental illness as a result of economic stress. Biologically, the development of psychocardiological disease is associated with dysfunctions of multiple systems, including the immune system, 5-HT metabolisms, platelet aggregation, the ANS, etc.

In this review, we summarize the ability of BM-MSC transplantation to control almost all biological aspects of psychocardiological illness (**Figure 5**). Pre-clinical and clinical results also suggest the effectiveness of BM-MSC transplantation in treating both CVD and men-

tal disorders. All together, we propose that BM-MSC therapy is the most promising methodology for treatment of these interwined disorders. However, future research and trials are urgently needed as our current understanding does not match the requirements to apply BM-MSC transplantation clinically. We suggest that future research should be conducted focusing on at least 3 questions: 1) What are the effects of BM-MSCs in psychocardiological disease animal models (such as a post-MI depression model) [213]? 2) What exact mechanisms underlie the therapeutic effects seen in the above models? 3) What effects of BM-MSCs are seen in patients with CVD and mental illness in terms of both cardiovascular and behavioural performance?

Acknowledgements

The authors thank Dr. Robert Jackson for polishing the language and Ms. Qian Zhang for the graphing.

Disclosure of conflict of interest

None.

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