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Review

Umbilical cord blood-derived mesenchymal stem cells: New therapeutic weapons for idiopathic dilated cardiomyopathy?

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ABSTRACT

Dilated cardiomyopathy is the most frequent etiology of non-ischemic heart failure. In a majority of cases the causal mechanism is unknown, giving rise to the term 'idiopathic' dilated cardiomyopathy (IDCM). Major pathological derangements include patchy interstitial fibrosis, degenerated cardiomyocytes, and dilatation of the cardiac chambers, but recent evidence suggests that disease progression may also have the signature of cardiac endothelial dysfunction. As we better understand the molecular basis of IDCM, novel therapeutic approaches, mainly gene transfer and cell-based therapies, are being explored. Cells with regenerative potential have been extensively tested in cardiac diseases of ischemic origin in both pre-clinical and clinical settings. However, whether cell therapy has any clinical value in IDCM patients is still being evaluated. This article is a concise summary of cell therapy studies for IDCM, with a focus on recent advances that highlight the vascular potential exhibited by umbilical cord blood-derived mesenchymal stem cells (UCBMSCs). We also provide an overview of cardiac vasculature as a key regulator of subjacent myocardial integrity and function, and discuss the potential mechanisms of UCBMSC amelioration of IDCM myocardium. Consideration of these issues shows that these cells are conceivably new therapeutic agents for this complex and elusive human disorder.

1. Introduction: idiopathic dilated cardiomyopathy

Dilated cardiomyopathy is the most frequent etiology of non-ischemic heart failure and is characterized by ventricular chamber enlargement (adverse remodeling) or dilatation and systolic dysfunction with normal left ventricular (LV) wall thickness [1,2]. With remarkable annual prevalence (1:2500) and incidence (1:15,000–18,000) rates in adults [3,4], dilated cardiomyopathy affects either sex and people of any ethnic origin, who suffer a progressive decrease in LV contractility and often sudden death; approximately 50% of individuals are reported to die within 5 years of diagnosis [5]. In a majority of cases the causal mechanism is unknown, giving rise to the term 'idiopathic' dilated cardiomyopathy (IDCM). Causes are multifactorial and include genetic or environmental factors, which can manifest clinically at a range of ages [4]. Despite higher survival rates with evidence-based drugs, devices, and surgery [5], the only definitive treatment is heart transplantation, which is often restricted to a select minority due to the scarcity of organ donations. The health costs of IDCM are great worldwide [6]. Histologically, the major pathological derangements include patchy interstitial fibrosis, degenerated cardiomyocytes, and dilatation of the cardiac chambers, but recent evidence suggests that disease progression may also have the signature of cardiac endothelial dysfunction [7].

New therapeutic approaches are being explored to counteract irreversible myocardial damage and subsequent alterations in remodeling in IDCM. For example, the application of cells with regenerative potential is currently being explored [8,9] with an increased understanding of the molecular basis of disease [10–12] and supplementary therapies, such as those based on gene transfer [13]. In both pre-clinical and clinical settings, cell-based therapies for cardiac diseases of ischemic origin (*i.e.*, acute myocardial infarction and chronic ischemic heart disease) keep the stakes very high. In contrast, the potential benefit of cell therapy for IDCM is still being evaluated.

This article is a concise summary of cell therapy studies for IDCM, with a focus on recent advances that highlight the vascular potential exhibited by umbilical cord blood-derived mesenchymal stem cells (UCBMSCs). We also provide an overview of cardiac vasculature as a key regulator of subjacent myocardial integrity and function and discuss the potential mechanisms of UCBMSC amelioration of IDCM

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myocardium. Consideration of these issues shows that these cells are conceivably new therapeutic agents for this complex and elusive disorder.

2. IDCM: a myocardial disease arising from alterations in the cardiac endothelium

Histological examination of the myocardium in IDCM reveals some characteristic macroscopic hallmarks, including altered cardiac muscle integrity, myocyte atrophy, and increased deposition of collagen and lipids around myocardial filaments (Fig. 1) [14–16]. Notably, cardiac endothelial dysfunction has been associated with progression and poor prognosis of the disease [7]. Over the past few years, research in this field has been aided, in part, by the implementation of sophisticated imaging techniques, such as angiography and computer tomography, which show the mismatch between artery size and left ventricular mass, clear side branch paucity, and shorter, thinner epicardial arteries in IDCM [17,18]. More importantly, reduced and sparse microvasculature has been detected in both patients and animal models that present with disease characteristics resembling those in humans (Fig. 1) [18–21].

Medical research has been advanced by the development of animal models with pathological traits similar to those seen in patients. In contrast to myocardial infarction [22–26], IDCM research has been hampered because none of the early animal models completely conveyed the complex traits of heart failure, including fibrosis, inflammation, and apoptosis, which evolve over a period of months and years [7,27]. Small animal models commonly generated to investigate disease etiology and progression and to assess possible novel therapeutic targets fall into two different categories: non-genetic and genetic [7]. Remarkably, in 2010, Huang et al. reported a mouse model of chemically induced cardiomyopathy that exhibited similar reduced blood flow, coronary branching, and capillary density as found in patients [21]. This model, which culminates in the development of life-threatening cardiomyopathy after exposure to the anticancer anthracycline doxorubicin [28], has been proposed for the assessment of functionally improved IDCM-derived circulating myeloid cells, which exhibit impaired stromal cell-derived factor 1-mediated migration and enhanced myocardial revascularization and cardiac function [12].

Studies in large animals are pivotal for progressing towards clinical translation. Pacing-induced heart failure models (in dogs and pigs) are frequently used because they result in myocardial remodeling and chamber dilation [29,30]. Rapid ventricular pacing induces a low output cardiomyopathic state and neurohormonal activation similar to that seen in human IDCM. Further experiments in this model have provided insights into the molecular and cellular basis of IDCM [31], and opportunities to test the efficacy of potential treatments [30,32]. Rapid pacing-inducing tachycardia leads to marked but reversible alterations in the discontinuation of cardiac stimulation, whereas coronary microembolization establishes a refractory heart failure [29].

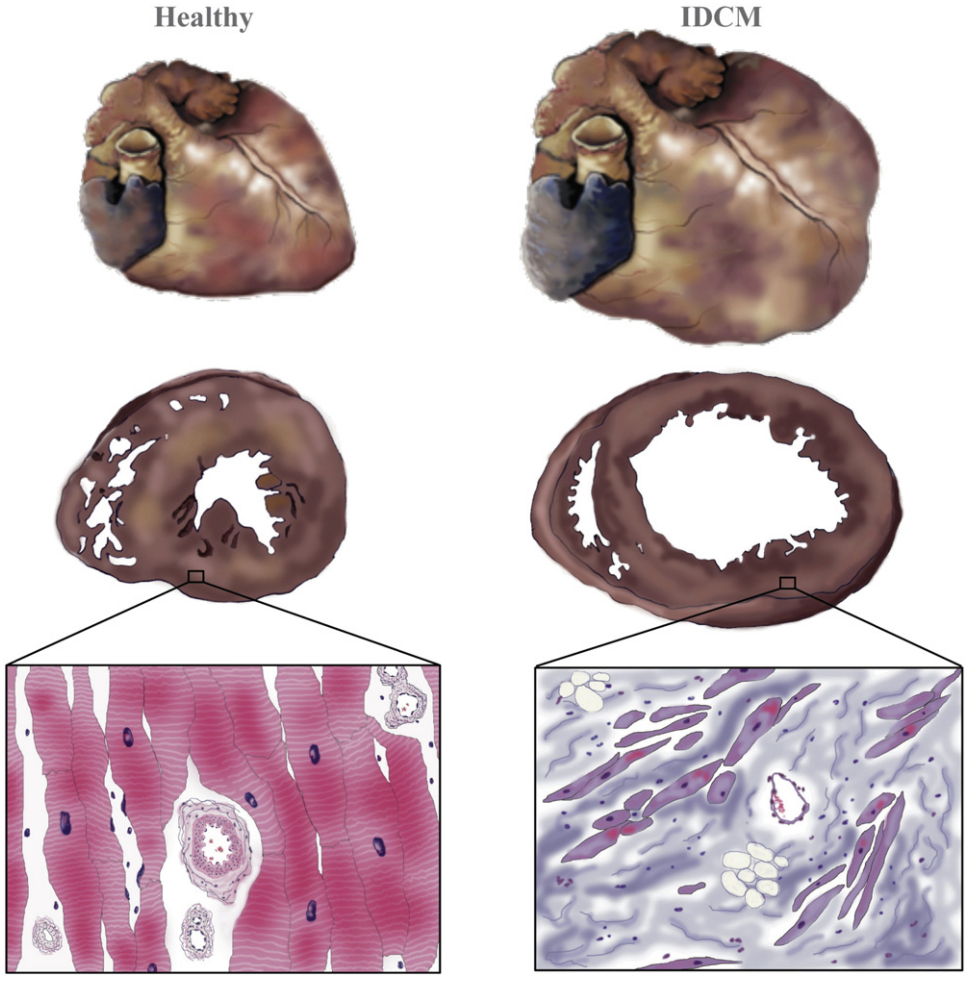

Fig. 1. Illustration showing the main macroscopic and microscopic alterations found in IDCM. Macroscopically, compared to a healthy heart, a diseased heart exhibits marked epicardial coronary artery mismatch with the left ventricular mass and side-branch reduction. Further histopathological analysis reveals few blood vessels and interstitial fibrosis surrounding the myocardial filaments and vasculature in IDCM myocardium. Increased myocyte atrophy and loss, as well as the deposition of lipids, are microscopic characteristics found in patients. IDCM = idiopathic dilated cardiomyopathy.
Designed and hand-drawn by C.G-M.