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Mammalian Cardiac Muscle Regeneration: Structural and Functional Modulation of Adult Marrow Stromal Stem Cells

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Mammalian heart has been considered as a post-mitotic organ composed of highly specialized and terminally differentiated cardiac myocytes. Mammalian cardiac myocytes have traditionally been considered as post-mitotic cells with an extremely low or practically no capacity to divide and regenerate. However, lower vertebrates such as fish and amphibians retain a substantial capacity for myocardial regeneration. In adult frogs and newts, differentiated cardiac myocytes have the ability to undergo mitotic division after damage to the heart [1,2,3]. This regenerative process involves a partial cellular dedifferentiation characterized by the disassembly of the sarcomeres and supporting cytoskeleton in the myocytes before the initiation of mitotic cycle [4]. Recently, it has been shown that mammalian cardiac muscle has limited proliferative potential and restricted regeneration within the damaged myocardium. Hence, it may be beneficial to explore the limited natural capacity of mammalian cardiac muscle regeneration in light of the spontaneous cardiac muscle regeneration observed in these lower vertebrate animals.

The difficulty in regenerating damaged myocardial tissue has led researchers to explore the application of embryonic- and/or adult-derived stem cells as possible cellular sources for the regeneration of cardiac myocytes to reconstruct the ischemically compromised myocardium [5,6]. Using stem cells, it has been possible to stimulate mammalian cardiac muscle regeneration and researchers have investigated the potential of adult bone marrow stromal cells (BMSCs) for cardiac tissue repair and/or regeneration. It is well established that postnatal bone marrow harbors a heterogeneous population of adult stem cells and precursor cells that includes hematopoietic stem cells (HSCs), bone marrow stromal cells or mesenchymal stem cells (BMSCs/MSCs), multipotent adult progenitor cells (MAPCs) and endothelial precursor cells (EPCs) [7]. These cells have a unique combination of surface antigenic markers and have the potential to generate different sets of differentiated progeny. Adult stems cells, including BMSCs, exhibit a certain degree of developmental plasticity that enables them to differentiate across boundaries of lineage, tissue and germ layers. This differentiation potential of BMSCs has prompted exploration into the ability and capacity of these unique cells to differentiate into myocardium.

BMSCs are multipotent, capable of differentiating into the main cardiac cell lineages such as myocytes, endothelial and vascular smooth muscle cells in vitro and contribute to myocardial regeneration in vivo, when transplanted to the failing heart following myocardial infarction or non-infarction in mouse, rat, pig or sheep models [8]. Additionally, the ability of BMSCs to restore functionality may be enhanced by the simultaneous transplantation of other stem and progenitor cells. Finally, the significant advantage of using these BMSCs is their low immunogenicity. In addition, BMSCs have been reported to be immunomodulatory and immunotolerogenic both in vitro as well as *in vivo* [9]. Taken together, these facts suggest that BMSCs may represent the cellular candidate of greatest potential for adult autologous and/or allogeneic stem cell based cardiac regeneration.

Previous reports indicate that BMSCs can be directed to undergo in-vitro differentiation into multiple mesenchymal and non-mesenchymal cells, including myocyte-like and cardiomyocyte-like cells, which may exhibit contractility [10]. Preclinical and clinical studies have suggested that whole marrow isolates and/or cultured marrow stem cells may also contribute to cardiac repair *in vivo* and alleviate cardiac symptoms, although the mechanism for this remains obscure. These cells have also been grafted onto ischemic heart tissue, but their extent of functional integration remains unresolved. In addition, BMSCs may contribute to revascularization after myocardial injury. Taken together, these data suggest that BMSCs could play a vital role in cardiac regeneration, but this concept requires further validation.

Cumulative evidence demonstrates that exogenous stem cells when systemically infused, transplanted or directly infiltrated into cardiac lesions generate relatively few neo-cardiomyocytes, but some types of cells such as BMSCs and side population of HSCs contribute directly to the endothelial cell populations, especially near the infarcted zones [11]. A major issue that remains to be addressed is the extent to which introduced stem cells contribute directly to the formation of neo-cardiomyocytes versus their contribution to and/or stimulation of an enhanced local vascular response, which in turn may act as a supportive microenvironment for regeneration [12].

Restoring damaged heart muscle tissue, through repair or regeneration, therefore represents a fundamental mechanistic strategy to treat congestive heart failure. However, current emerging clinical studies using stem cells, including BMSCs to repair damaged cardiac tissue have produced varying results [13]. On the one hand, irrespective of the modes of administration, the marrow stem cells contributed to cardiac repair in vivo and prevented ventricular remodeling and alleviated cardiac symptoms; on the contrary, there occurred reduction in cardiac blood flow (myocardial ischemia) or pronounced congestive heart failure [14]. These reports clearly indicate that there exist gaps in the knowledge base pertaining to adult stem cell based cardiac regeneration, and much remains to be resolved for the successful translation of stem cell based cellular cardiomyoplasty from bench to bedside. Therefore, elucidation of various molecular

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mechanisms underpinning the integration and orderly maturation and differentiation of BMSCs into neo-cardiomyocytes during myocardial repair and regeneration necessitates the development of appropriate in vitro two-dimensional (2-D) and three-dimensional (3-D) models of cardiomyogenesis [15,16].

Unlike BMSCs, embryonic stem cells (ESCs) can be readily directed to differentiate into cardiomyocyte-like cells in vitro. The ESC-derived three-dimensional (3-D) embryoid bodies (EBs) contained clusters of spontaneously beating cardiomyocytes [17]. Subsequent reports have revealed that these ESC-derived cardiomyocytes undergo an orderly array of developmental gene expression that closely mimics that observed during normal cardiac embryogenesis. Besides, these ESCs acquire the physiopharmacological characteristics of terminally differentiated cardiac myocytes. The utility of ESCs in facilitating cardiac muscle regeneration is still in its incipient stages. A number of issues, including a propensity for some implanted ESCs to form benign or malignant teratomas in the heart, remains to be addressed.

Previous studies demonstrated that populations of characterized or uncharacterized BMSCs are capable of differentiating into cells resembling or expressing some of the characteristics of cardiac myocytes when cultured on two-dimensional (2-D) planar surfaces, especially under the influence of either the chemical factors and/or cellular interactions; however, these reports are not without controversy due to the lack of quantitative data [18,19]. All these studies excluded the influence of physical factors that are crucial to the maturation and differentiation of functioning cardiac myocytes. A notable and principle confounding factor introduced in most of these in vitro and ex vivo studies was the utilization of unpurified heterogeneous populations of BMSCs.

Current studies have explicitly demonstrated that under appropriate in vitro combination of physical, chemical and cellular environmental cues (local environmental cues) BMSCs can be induced to undergo a cardiomyogenic differentiation pathway [15,16]. Here a 3-D co-culture system was developed in which a pure population of $CD90^{+}$ rat BMSCs were co-seeded with rat embryonic cardiac myocytes (ECMs) and cultured on a highly aligned porous and biocompatible collagen-fiber tubular scaffold for differentiation and regeneration purposes. In this 3-D co-culture system, it was demonstrated that purified and characterized ($CD90^{+}$) adult BMSCs that are in cell-to-cell contact with ECMs express genotypic and phenotypic properties, which are characteristics of cardiomyocytes. The phenotypic characteristics include cycling of intracellular calcium, limited contractility, and reorganization of the actin cytoskeleton from the peripheral cytoplasm to form thick bundles of fibers in the perinuclear cytoplasm, containing associated desmin containing dense bodies. The genotypic changes observed in these BMSCs, which are in physical contact with ECMs include the upregulation of various cardiac-specific markers such as, cardiac α/β-MHC, sarcomeric MHC, desmin and GATA-4 [15].

The ultrastructural characteristics of these co-differentiating cells (ECMs\BMSCs) seem to give a momentary glimpse that ECMs are capable of undergoing partial dedifferentiation i.e. a diminution or disassembly of contractile elements similar to that seen in the lower vertebrates such as fish and amphibians during regenerative process [4]. The remodeling and reorganization of cytoarchitectural features of both BMSCs and ECMs in 3-D co-culture conditions suggest that both BMSCs and ECMs have the plasticity to reprogramme in synchrony towards cardiomyogenic lineage and commitment and validating the previous observations seen in 2-D co-culture systems [16]. This phenomenon of partial myofibrillar and sarcomeric dedifferentiation followed by redifferentiation of the these elements of in vitro cardiac myocytes in the vicinity of adult bone marrow-derived stem cells may contribute to a plausible explanation to most of the discrepancies seen in the case of *in vivo* preclinical and clinical trials.

Use of adult stem cells in the stimulation of mammalian cardiac muscle regeneration is in its infancy, and to date, it has been difficult to determine the efficacy of the procedures that have been employed. The outstanding question remains whether stem cells derived from the bone marrow or some other location within or outside of the heart can populate a region of myocardial damage and transform into tissue-specific cells and also exhibit functional synchronization [20]. As a result, this necessitates the development of an appropriate in vitro 3-D model of cardiomyogenesis and prompts the development of a 3-D vascularized cardiac muscle construct for tissue engineering purposes, especially using the adult stem cell, BMSCs.

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