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REVIEW

Almanac 2012, cell therapy in cardiovascular disease: The national society journals present selected research that has driven recent advances in clinical cardiology ☆

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Abstract The rapid translation from bench to bedside that has been seen in the application of regenerative medicine to cardiology has led to exciting new advances in our understanding of some of the fundamental mechanisms related to human biology. The first generation of cells used in phase I–II trials (mainly bone marrow mononuclear cells) are now entering phase III clinical trials with the goal of producing a cell based therapeutics that can change the outcome of cardiac disease. First generation cell therapy appears to have addressed safety concerns as well as showing 'activity' in numerous published meta-analyses. With the knowledge gained to date, the field is moving towards the next generation of cells—the 'engineered' cell—that has been developed to display a phenotype that will further enhance the myocardial repair/salvage process. This almanac review covers the latest basic research that may soon have application to humans as well as the results of the latest clinical trials.

Contents

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1. Update on cell therapy for the treatment of cardiovascular disease

Cell therapy is one of the most important 'new horizons' in cardiovascular disease. It offers new opportunities to develop therapeutics that could revolutionise the way we treat patients and a field of research that combines an increased understanding of the pathophysiology of the cardiovascular disease with some of the most basic biological concepts involved in embryology. The resultant growth of preclinical research in the cardiovascular system and the rapid translation into humans has led to benefits for human biology as a whole. The field is rapidly advancing; here, we present key developments in the last 2 years. In order to reflect the synergy between basic and translational research, this review is therefore divided into two sections.

2. Basic science update on cell therapy in cardiovascular disease

2.1. New models enhancing our understanding of regeneration zebrafish

There is a long history of research on amphibian heart regeneration with the most adopted model the zebrafish given its substantial regenerative capacity and amenability to genetic manipulation. The zebrafish heart fully regenerates after the surgical amputation of the cardiac apex: an injury that corresponds to a loss of approximately 20% of the total ventricular mass.[1] Initial experiments suggested that undifferentiated progenitor cells were the principal source of regenerating cardiomyocytes in zebrafish; however, two recent gene mapping studies clearly demonstrate that pre-existing committed cardiomyocytes are instead the main source.[2,3] These two groups independently generated transgenic zebrafish in which the cardiomyocyte-specific *cmlc2* (also known as *myl7*) promoter drives the expression of tamoxifen-inducible Cre recombinase. These animals were crossed with a reporter line in which Cre-mediated excision of a *loxP*-flanked stop sequence induces constitutive expression of green fluorescent protein (GFP). In the offspring of this cross, all pre-existing cardiomyocytes and their progeny were induced to express GFP by tamoxifen treatment. Therefore, if the regenerated myocardium was derived from undifferentiated progenitor cells, the new ventricular apex should be GFP^-. Instead, both groups found that the vast majority of the newly regenerated cardiomyocytes were GFP^+, suggesting that the heart regeneration in zebrafish is principally mediated by the proliferation of pre-existing cardiomyocytes. This is contrary to the previously held belief that the generation of new cardiomyocytes from stem cells was the underlying aetiology.

2.2. Mice versus zebrafish

Although they lack the regenerative capacity of the zebrafish heart, postnatal mammalian hearts also undergo a degree of cardiomyocyte renewal during normal ageing and disease. Recently, a study[4] showed that the differences between mammalian and fish hearts may not necessarily apply early in development. Using approaches from the zebrafish model, the authors resected the left ventricular (LV) apex of 1-day-old neonatal mice and observed a brisk regenerative response similar to that in the adult zebrafish. By 3 weeks after injury, the defect had been replaced by normal myocardial tissue, which showed normal contractile function by 8 weeks. Genetic fate-mapping studies indicated that this regeneration was mediated by the proliferation of pre-existing cardiomyocytes, again as in the zebrafish. Notably, this regenerative capacity was not observed in 7-day-old mice, suggesting that its loss may coincide with cardiomyocyte binucleation and reduced cell-cycle activity. Nonetheless, this study indicates that zebrafish-like regenerative mechanisms are latent in mammalian hearts. It also provides a genetically tractable model for dissecting the blocks to these mechanisms in the mammalian adult.

2.3. Alternative sources of cardiomyocytes: new concepts and advanced understanding

2.3.1. Fibroblasts as source of cardiomyocytes

It has recently been demonstrated that fibroblasts in infarcts could potentially be reprogrammed directly to cardiomyocytes. Fifteen years ago, researchers showed that fibroblasts could be differentiated into skeletal muscle in vitro or in the injured heart