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More insights into mesenchymal stem cells as therapeutics

Challenges to the application of stem-cell therapy for treatment of cardiac disease include isolation and safe, stable long-term integration of cells. Stem cell isolation, delivery, survival and proliferation in host tissues have been the focus of many studies, but concerns about the long-term electrochemical integration and safety of implanted cells have been largely neglected. We have also published studies focused on enhancing the survival of MSCs transplanted in the harsh pathologic conditions of infarcted myocardium. However, we have found that improved MSC transplantation does not provide a proportional survival benefit that is compatible with a significant improvement in cardiac contractile function. One possible explanation for this discrepancy is that the focal application of MSCs that have not differentiated into electrically functional cardiomyocytes creates fixed heterogeneity between host tissues in the engrafted region, possibly predisposing the heart to ventricular arrhythmia. A previous report described the trilineage differentiating capacity of MSCs after implantation in an infarcted heart, but we have observed that MSCs do not differentiate into cardiomyocytes, at least not during the early phase after myocardial infarction, when the risk of sudden arrest or death is highest. Transplantation of undifferentiated MSCs seems to attenuate their beneficial effects and thus impede their ability to prevent sudden arrhythmic death. We concluded, therefore, that naïve MSCs are not optimal cells for cardiac regeneration in clinical settings and determined that MSCs must be modified before transplantation to possess cardiogenic properties and the ability to electromechanically integrate with the host myocardium. Inexcitable properties of undifferentiated MSCs contribute to decreases of conduction velocity, increasing the susceptibility to ventricular arrhythmia and leading to sudden death. In order to obtain a cardiogenic cell type capable of electromechanically integrating with host tissue for cardiac regeneration, we induced differentiation of MSCs with protein kinase C activation. We show that small molecules, including kinase inhibitors, can change the fates of stem cells in recognizable ways and that a protein kinase C (PKC) activator, phorbol myristate acetate (PMA), induces the expression of cardiogenic markers. This approach provides a new strategy in cell-based therapy for myocardial infarction that may prevent fatal arrhythmia and mortality and improve contractile function.

Speaker Biography

Ki-Chul Hwang is vice-president and professor of College of Medicine, Catholic Kwandong University and director at Institute for Bio-Medical Convergence, International St. Mary's Hospital of Korea. He received his doctor of philosophy degree from the Korea University in Republic of Korea and completed his postdoctoral fellowship at the Cleveland Clinic Foundation, Cleveland, OH, USA and the Victor Chang Cardiac Research, NSW University, Sydney, Australia. He has consecutively filled (Senior) editorial board at the World Journal of Stem Cells, American Journal of Stem Cells and Journal of Geriatric Cardiology. Much of his research career has focused on the adult stem cells and he is recognized to be at the forefront of the emerging field about functional enhancement in stem cells and its therapeutic role associated with many diseases.

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