Study Renews Hope for Effective Use of Circulating Blood Cells in Heart Regeneration Therapy

A research group led by Dr. Patrick C. H. Hsieh, an Associate Researcher at the Institute of Biomedical Science (IBMS), has recently confirmed that circulating blood cells can contribute to cardiomyocyte (heart cell) regeneration after heart attack, by fusion with existing cells and trans-differentiation. This finding gives hope for the eventual use of autologous hematopoietic (blood) stem cells in cardiomyocyte regeneration. The study challenges two reports published in the journal *Nature* in 2004, in which it was stated that hematopoietic stem cells did not form new cardiomyocytes after myocardial infarction (heart attack). The new study was published in the cardiovascular research journal *Circulation Research* on March 13.

Traditionally, bone marrow transplantation is used to study circulating blood cells during cardiomyocyte regeneration after heart attack. It is known that blood or bone marrow cells can circulate to the injured heart and express cardiomyocyte-specific markers. This suggests that hematopoietic cells may be able to contribute to cardiac repair by maturing into cardiomyocytes. However, in 2004, a group from Stanford University employed a parabiosis (surgical union of two animals so that they share body circulation) animal model to investigate the role of circulating cells in the injured myocardium and discovered that the hematopoietic cells do not acquire cardiac cell fate (Balsam et al. Nature 2004).

In 2014, Dr. Hsieh's group reported that the inflammatory response activated at the early stage of heart injury is critical for effective cardiomyocyte regeneration. In the current study, to resolve the long-standing controversy about the role of circulating cells in regenerating the injured myocardium, Dr. Hsieh's group took care to establish proper cross-circulation after paratiotic surgery, and surgically induced myocardial infarction only after stabilization of cross circulation. Stabilization of cross circulation ensured that the key signals activated at the early stage of inflammation after myocardial infarction could be transmitted in a timely and effective manner between the two surgically conjoined animals.

The group combined real-time molecular imaging and Cre-Lox transgenic mice to pulse-trace label adult cardiomyocytes. It was discovered that the bone marrow-derived circulating cells contribute to cardiomyocytes by fusing with the resident cardiomyocytes or via direct transdifferentiation to give rise to new cardiomyocytes. It is known that cell fusion can protect the cardiomyocytes from cell death and improve their survival. In addition, the ability of circulating hematopoietic cells to regenerate cardiomyocytes implies that they may serve as an alternative cell source to replenish lost cells. The finding thus challenges the studies reported by Stanford

University and University of Washington in 2004 and provides direct evidence that circulating hematopoietic cells play an important role in replenishing cardiomyocytes after injury.

Ischemic reperfusion (return of blood supply to an area of the heart after a period of lack of oxygen) results in heart failure, and is a leading cause of death worldwide. It is primary attributed to coronary artery occlusion, which subsequently leads to myocardial infarction. The heart is an organ with very limited reparative ability. Coronary artery occlusion leads to cardiomyocyte death and tissue fibrosis, which are followed by ventricular remodeling, dilation, impaired cardiac function and consequently heart failure and death. The goal of Dr. Hsieh's group is to translate their research findings into clinical applications. A better understanding of how circulating stem cells are regulated to give rise to cardiomyocytes would certainly help develop therapies which promote the differentiation into functional cells. In comparison to traditional cell therapy via exogenous delivery, using this approach, there is no fear of immune rejection or arrhythmia. Therefore, the results of this study have potential for development into clinical therapies for treating heart diseases.

The complete article is available at the *Circulation Research* journal website at: http://circres.ahajournals.org/content/early/2014/11/14/CIRCRESAHA.116.304564

The complete list of authors is: Jasmine M. Wu, Ying-Chang Hsueh, Hui-Ju Ch'ang, Chwan-Yau Luo, Li-Wha Wu, Hiromitsu Nakauchi and Patrick C. Hsieh