Editorial

The use of cardiac progenitor cells for transplantation in congenital heart disease and an innovative strategy for activating mitochondrial function in such cells

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Prior to the 20th century, most cardiologists assumed that the mammalian heart had no regenerative ability once the myocardium was injured as the result of a pathological event, such as ischemia. In 2003, Anversa and colleagues first reported that the mammalian heart contained cardiac stem cells (1). At the same time, Oh and colleagues reported on the identification and isolation of cardiac progenitor cells (CPCs), and first validated the effectiveness of treating ischemic-reperfusion injuries by transplanting CPC (2). In 2009, Bergmann and colleagues concluded that the human myocardium has regenerative potential throughout life (3). Since the findings reported by Thomson *et al.* concerning the characteristics of embryonic stem cells (ESC) (4) and by Yamanaka *et al.* concerning the construction of induced-pluripotent stem cells: iPSc (5), various types of CPCs derived from ESC or iPSc have been reported, suggesting that damaged myocardial tissue could recover via cardiac regeneration. Phillipe and colleagues first reported on the efficiency of ESC in a clinical setting (6), and Sawa and colleagues reported on a clinical trial in which iPSc were used in Japan (7). Although the clinical usage of ESC or iPSc is progressing, it has major limitations, including substantial cost and time, the limited efficiency of transplanting cardiac stem cells, and the immunity of the transplanted cells. It should be noted, however, that there are more than ten million patients who are potential candidates for heart failure, and that a severe shortage of heart donors exist in the world (8). These emerging problems need to be immediately faced by developing safer, higher cost-benefit-ratio, and more practical methodology for addressing these issues.

Heart failure in childhood is not uncommon, although surgical repair or palliation has improved structural heart disease as it is related to congenital heart disease. Many cardiologists have conducted stem cell therapy trials for various congenital heart diseases to survey their possible favorable outcomes related to improving cardiac function (9). Phase I and II studies concerning the intracoronary injection of autologous cardiosphere-derived cells (CDCs), which have cardiac stem-like characteristics (10) and had been clinically used in adult cardiac regenerative therapies (11,12), have been shown to be a reliable and safe approach to the treatment of patients suffering from single ventricle status (13,14). The methodology used in these studies possess some limitations, in that a few study participants can be enrolled as the control group considering medical ethics (15). A retrospective cohort study was conducted to validate the therapeutic effects of infusing CDC in patients suffering from single ventricle status 2 years after the treatment (16).

They retrospectively integrated the data from CDC-infused patients to detect previously unknown information, compared to a large population of controls without CDC infusions during the same period. This integrated cohort study showed that an intracoronary infusion of CDC resulted in significantly better ventricular function with decreased incidences related to late-term failure, unexpected catheter intervention, and adverse events in the group, who had single ventricle physiology and had undergone stage 2 or 3 palliation during the 2-year study periods. Patients who received treatments based on CDCs had a lower incidence of adverse events. Baseline cardiac function had predictive value for functional improvement after cell therapy. We currently do not fully understand the commitment of heart failure with preserved ejection fraction (HFpEF) during childhood, largely due to heterogeneity and latent genetic factors related to congenital heart disease, as well as a variety of techniques used in the operation. We have no definitive therapy for ameliorating cardiac function under a chronic overload of volume or pressure, and patients with HFpEF might have a worse prognosis. Interestingly, all mortality and late-term complications were significantly reduced only in the patients with HFrEF, and not in patients with HFpEF after CDCs therapy, while the heart function and the status of heart failure was ameliorated in the both children with HFpEF and HFrEF after CDCs infusion. A long-term follow-up study is currently underway in order to elucidate the differences in therapeutic responses among the phenotypic diversity in heart failure associated with single ventricle physiology.

Additional results obtained using animal models under either HFrEF or HFpEF showed that CDCs could improve diastolic dysfunction due to a reduction in the extent of fibrosis and inflammation as well as hypertrophic and ischemic myocardia (17,18). There have been many reports indicating that transplanting pure cells could not be effective without some artificial tissue-manufacturing technology, because of the severity of oxidative stress, fibrosis, and inflammation in a failing heart (10,19). Cardiac oxidative stress is mainly caused by the formation of mitochondrial reactive oxygen species (ROS) in the myocardium. Thus, we attempted to enhance CPCs by delivering resveratrol into mitochondria via a mitochondrial drug delivery system (DDS) (a MITO-Porter system). We constructed mitochondria activated CPCs (referred to herein as MITO cells) and confirmed the efficacy and efficiency of the MITO cells using an *in vitro* doxorubicin-induced cardiomyopathy model. Mice that received MITO cell transplants had a significantly longer survival than those with conventional CPC transplants. Mitochondrial ROS and apoptosis were both significantly decreased in the hearts with MITO cell transplants, in which the expression levels of OXPHOS proteins and genes were all preserved, compared to the control group. To treat doxorubicin-induced cardiomyopathy, MITO cell transplantation could be more efficient compared to conventional cell therapy (20).

Cell therapy combined with some form of medical technology, which could be a surgical technique, sheet technology, or a DDS, could be more beneficial for the treatment of heart failure, compared to simple cell therapy. We hope that this type of research will continue and that the techniques that are developed will eventually help many children with heart failure because adult stem cell (CPC or CDC) therapy has a great advantage over pluripotent stem cell (ESC or iPSc) transplants.

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Footnote

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