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Review

Stem cell therapies for congenital heart disease

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ABSTRACT

Congenital heart disease (CHD) is the most prevalent congenital anomaly in newborn babies. Cardiac malformations have been induced in different animal model experiments, by perturbing some molecules that take part in the developmental pathways associated with myocyte differentiation, specification, or cardiac morphogenesis. The exact epigenetic, environmental, or genetic, basis for these molecules perturbations is yet to be understood. But, scientist have bridged this gap by introducing autologous stem cell into the defective hearts to treat CHD. The choice of stem cells to use has also raised an issue. In this review, we explore different stem cells that have been recently used, as an update into the pool of this knowledge and we suggested the future perspective into the choice of stem cells to control this disease. We propose that isolating mesenchymal stem cells from neonate will give a robust heart regeneration as compared to adults. This source are easily isolated. To unveil stem cell therapy beyond its possibility and safety, further study is required, including largescale randomized, and clinical trials to certify the efficacy of stem cell therapy.

Contents

1. Introduction

CHD is as an abnormality in the structure of the heart which occurs before neonate birth, while the fetus is developing [1]. It is the most prominent congenital anomaly in newborn babies, with about 6 to 13 per 1000 live births prevalence. In the UK alone, there

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is a report of ~4600 babies born having CHD every year [2,3]. Progress in medical management of newborns with CHD and surgical techniques fails to reduce the mortality and morbidity related to serious forms of CHD, which comprises of the first cause of death by congenital abnormalities [3]. Clinical needs of CHD have been shifted to adulthood in the last decade. A recent estimations shows that 80% of infants and neonates with CHD can probably reach adulthood [3,4]. There were about 2800/1 million population adults with CHD, and more than half of them possesses a moderate to severe defect according to the 32nd Bethesda Conference, Department of Health, report in 2006 [5]. These patients usually develop heart dysfunction (Fig. 1) and failure as well as respiratory, neurological, and coagulation problems (*British Heart Foundation Statistics Database:* www.heartstats.org). The socio-economic burden of CHD is high and increasing swiftly. U.S. hospital costs for CHD was totaled $1.4billion in 2004 [6].

In this update review, we explore different stem cells that have been recently used for CHD, and suggested the future perspective into the choice of stem cells to control this disease.

2. Stem cells therapy employed for CHD

Several clinical trials with stem cell therapy have been studied in adult patients with CHD, and they showed that stem cells transplantation promotes left ventricle (LV) function, infarct size, and cardiac remodeling [7]. Studies in children on the other hand are restricted to case reports. Rupp et al. reported a case of cell therapy in 11-month-old infant possessing hypoplastic left heart syndrome (HLHS) (Figs. 2 and 4) [7].

Conceptually, stem cell-based therapy aims to regenerate new myocardium, restore blood flow, and improve contractility by delivering stem or progenitor cells to the injured region of the heart [8]. In general, there are two strategies for the treatment of CHD using a cell-based approach: cellular cardiomyoplasty (cell transplantation) and cardiac tissue or organ engineering. In this review we are more concerned about stem cell transplantation. The choice of cells for transplantation are given below.

2.1. Cardiac progenitor cells

Mammalian heart is believe to be a terminally differentiated organ, having no intrinsic strength to regenerate following myocardial injury, recent identification of several types of cardiac stem/progenitor cells has extensively countered this dogma through the discovery of a subpopulation of c-kit+ and Lin– cardiac stem cells (CSCs) resident in the rat heart, reported by Anversa et al., 2003 [9]. Anversa et al. device a methods for the isolation and expansion of c-kit+ human CSCs (hCSCs) from small myocardial specimens. When injected into immunocompromised mice and rats, these cells differentiated into cardiomyocytes and ameliorated the LV performance of infarcted hearts [10].

Among several stem cell types, CDCs possesses a balanced profile of paracrine factor production and greatest myogenic differentiation potential *in vitro*. The *in vivo*, CDCs provides a superior amelioration of cardiac function, the highest cell engraftment, and myogenic differentiation which has been showed in experimental myocardial infarction [11]. Another group has also demonstrated that human CDCs isolated from neonates showed a strong regenerative potentials both *in vitro* and *in vivo* as compared to the adult-derived CDCs [12].

Another source of endogenous resident cardiac progenitor cells with regenerative potential for the adult heart is the epicardium, with several groups reporting the discovery of epicardium-derived myocardial and vascular progenitors in embryonic mouse and adult human heart. [13] In contrast with other populations of CSCs, cardiospheres and CDCs have been reported to contain a mixed population consisting of c-kit+ cardiac progenitor cells and cells expressing CD90 (mesenchymal-related) and CD31/CD34 (endothelial progenitor-related) markers.

Furthermore, Messina et al. described a method to culture CSCs (grown as multicellular clusters, termed cardiospheres) to produce a mixed population, that EF at baseline was only moderately impaired (39%), giving little room for improvement by 6 months [14]. Because of the positive results, further findings with longer follow-up and larger phase II studies are required to confirm the true persistent clinical benefits of c-kit+ CSCs and CDCs.

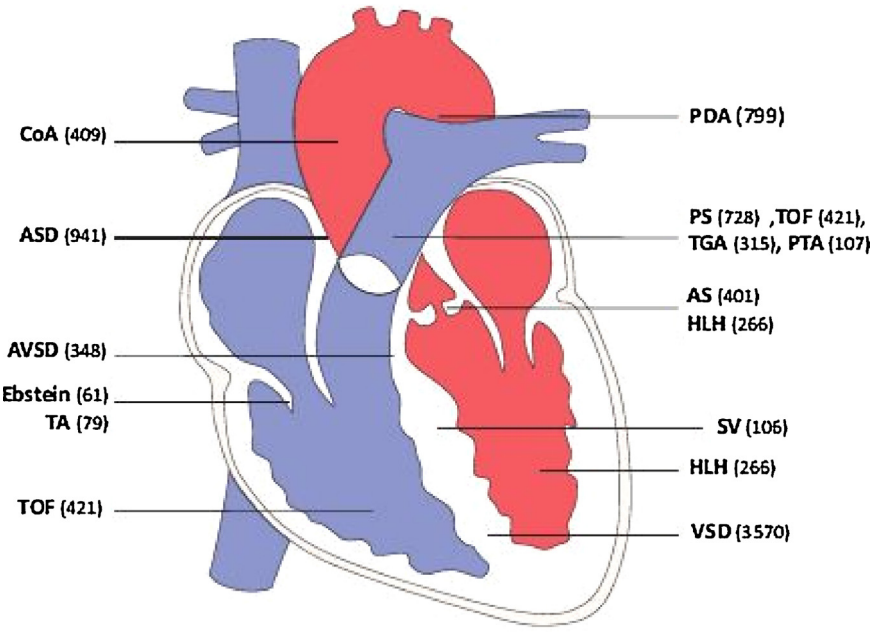

Fig. 1. Heart malformations location that are often identified in infancy, and estimated prevalence based on the CONCOR database. Numbers written beside indicate the birth prevalence/million live births. AS (aortic stenosis); ASD (atrial septal defect); AVSD (atrioventricular septal defect); CoA (coarctation of the aorta); Ebstein (Ebstein anomaly); HLH (hypoplastic left heart); MA (mitral atresia); PDA (patent ductus arteriosus), PS (pulmonary stenosis); PTA (persistent truncus arteriosus); TA (tricuspid atresia); TGA (transposition of the great arteries); SV (single ventricle); TOF, tetralogy of Fallot; and VSD, ventricular septal defect. (Adapted from [61]).