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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.

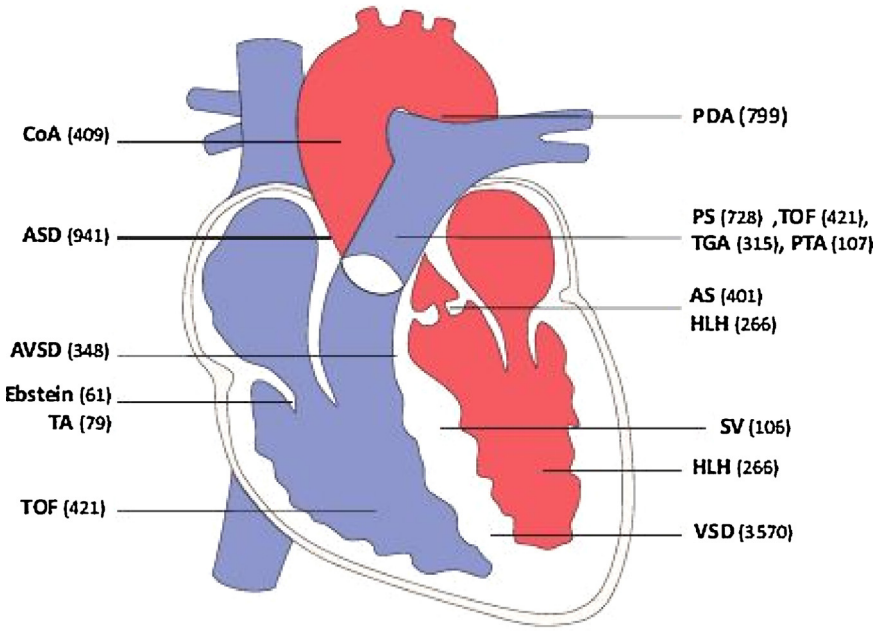

Fig. 1. Heart malformations location that are often identified in infancy, and estimated prevalence based on the CONCOR database. Numbers written beside indicate the birth prevalence/million live births. AS (aortic stenosis); ASD (atrial septal defect); AVSD (atrioventricular septal defect); CoA (coarctation 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]).

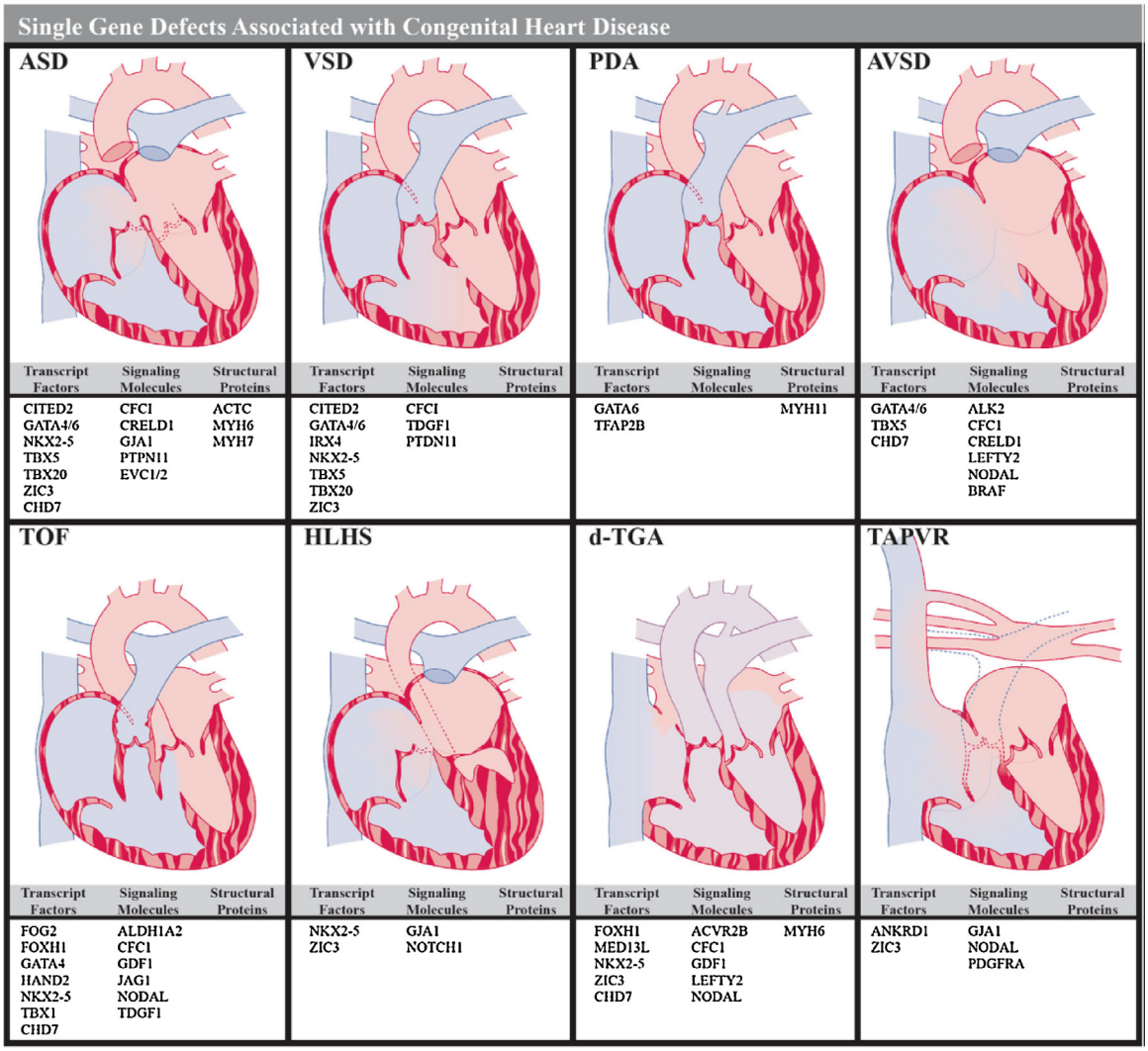

Fig. 2. Modeling single gene defects related with isolated CHD. an Eight forms of CHD are shown and genes related to that form of CHD are listed below by category (transcription factors; ligands, receptors, signaling molecules; structural proteins). The variability in the types of genes, which can cause a single form of CHD and the numerous forms of CHD that can be caused by disruption of a single gene are highlighted [62,63].

2.2. Foetal and umbilical cord cells

As regards diffusion and advances of pre-natal cardiac imaging, it is now feasible to diagnose cardiac defects in a larger population. Fetal cells and umbilical cord cells represent good therapeutic candidates and, in the future, *in utero* repair of cardiac defects, the use of these cells will become a routine practice. Umbilical cord is collected during birth; umbilical cord blood mononuclear cells (UCBMNCs) can be isolated from the blood, while mesenchymal stem cells were extracted from the Wharton's jelly. This stem cells are able to differentiate into endothelial cells and cardiomyocyte-like cells [15,16]. In 2010, the Mayo clinic revealed the first U.S. stem cell trial using autologous umbilical cord blood cells to treat children with HLHS (http://www.mayo.edu). Fetal-derived stem cells can be isolated from the amniotic fluid, which include both pluripotent and committed stem cells [17]. Fetal cells could be stored, in accordance with the vast experience gathered with umbilical cord blood cells, and used for multi-stage corrections.

Two clinical trials are underway using autologous umbilical cord blood cells for HLHS (Fig. 4). A phase I study at Duke University is presently collecting and infusing the cells in newborn infants, and Mayo clinic is planning a trial involving cell injections into the right ventricle (RV) of children going through a scheduled Glenn operation. Previous study is also going to evaluate the improvement of neural injury in the treated infants. Most of the cell therapies that have been reported in children possessess targeted dilated cardiomyopathy. Among the findings in 4-month to 17-year-old children, left ventricular ejection fraction (LVEF) rises by roughly 20%, and clinical symptoms ameliorated dramatically after the transplantation of BMC or peripheral stem cells. [18–21]

2.3. Embryonic stem cells

Embryonic stem cells (ESCs), the prototypical stem cell, can develop into all cell types in the body, including pancreatic beta-cells, neural cells, and cardiomyocytes [22]. The isolation of mouse ESCs was first reported in 1981 [23]. ESCs found application in several aspect of tissue regeneration, However, there are several undesirable limitations with the practical application of hESCs, such as ethical problems, teratoma formation, and immune rejection, which have impeded the initiation of clinical trials in

patients with cardiovascular disease [24]. It is clear that a better knowledge of molecular and genetic pathways for ESC differentiation and cardiac development could deter contamination with undifferentiated ESCs, inhibiting teratogenesis when transplanted into the body [25]. Alternatively, to solve the ethical issues and immune rejection, induced pluripotent stem cells (iPSCs) might be a more attractive alternative, as they are autologous [22].

2.4. Induced pluripotent stem cells

Lately, iPSCs have been produced using a novel technology, involving the introduction of some transcription factors related to pluripotency into adult terminally differentiated cells, such as dermal fibroblasts, making them to change to an embryonic stem cell-like stage [26]. The iPSCs differentiation into functional murine cardiomyocytes has been demonstrated [27]. In 2007, Yu et al. favorably reprogrammed human somatic cells to iPSCs (Fig. 3) using four genes including Nanog, Oct4, Sox2, and Lin28 [28], and these human iPSCs have been shown to posseess the potential to differentiate into functional cardiomyocytes [29].

Importantly, in spite of slight epigenetic differences associated with reprogramming, iPSCs fully resemble ESCs in terms of differentiation capacity, morphology, gene expression profile, and teratoma formation [30]. The use of iPSCs bypass the ethical dilemmas and immune response problems of ESCs, since they are autologous derived; however, a concerns for their clinical application is their incorporation with oncogenes and viruses [25]. Hence, for safety reasons, nonvector approaches for pluripotent induction should be developed[31,32] without the need for oncogenes [33] giving a way for future clinical applications [22,32,34].

2.5. Skeletal myoblasts

Satellite cells or skeletal myoblasts, a precursor for skeletal muscle, were studied extensively in animal models of myocardial infarction before they enters into the clinical arena, due to the merit of their high expansion capacity in culture, myogenic commitment, autologous origin and good resistance to ischemia [25].

Reports from experimental studies showed that implanted myoblasts lead to increase contractility and ventricular wall thickening, thereby improving infarcted myocardium function. Based on positive results, skeletal myoblasts were the first cell type [25] to be studied in human trial for cardiac repair [35] (Tables 1–3).

Recently, the SEISMIC trial by Duckers et al. reported that injection of autologous skeletal myoblasts in patients with HF is safe and relieves symptoms based on a trend toward improved exercise tolerance in the cell-treated group despite no significant effect in LVEF [36]. However, despite improving cardiac function when transplanted into ischemic myocardium, these cells were unable to transdifferentiate into cardiomyocytes and integrate electromechanically with the host myocardium, thereby increasing the risk of sustained ventricular tachycardia (VT), a life-threatening arrhythmia. [25] Collectively, since there is no cardiomyocyte regeneration, failure to integrate with host

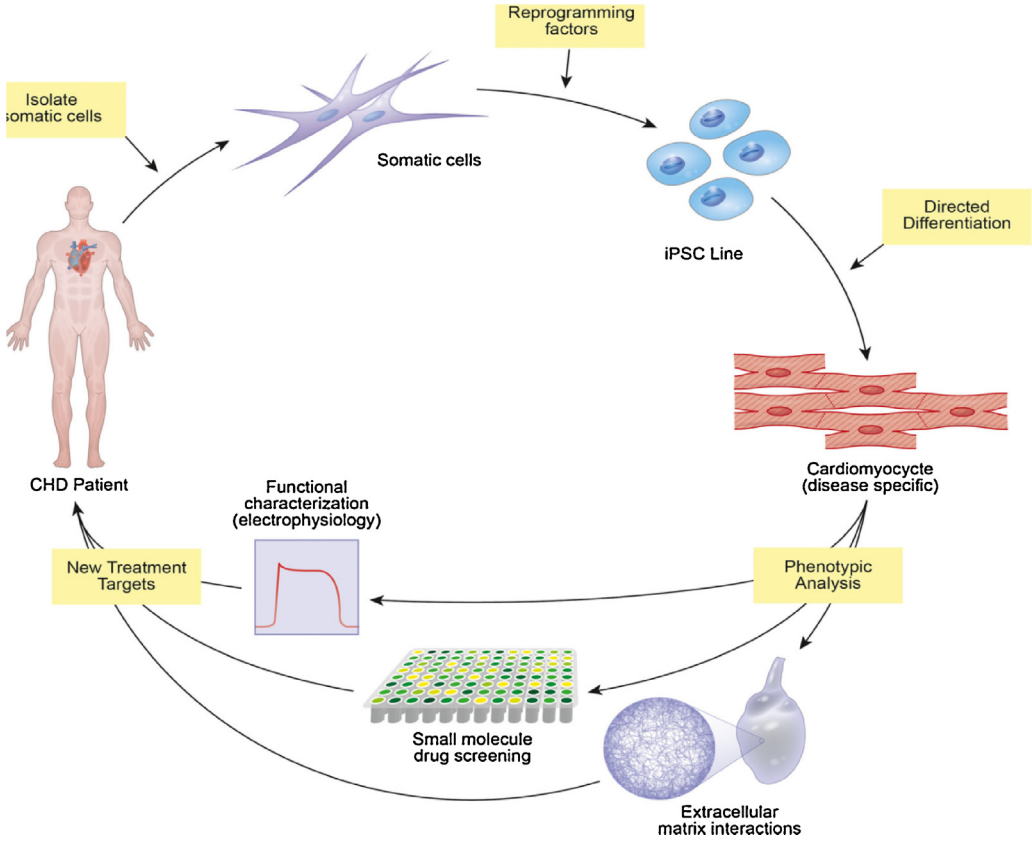

Fig. 3. The use of hiPSCs to model CHD. This diagram represents the process of isolating somatic cells (blood or fibroblasts) from patients, reprogramming the cells using four factors (Oct3/4, Sox2, Klf4, c-Myc or LIN28) to generate iPSC lines, directed differentiation to CMs, and phenotypic assays performed on hiPSC-CMs to characterize the pathophysiology of individual CHD with the goal of understanding disease mechanisms and informing new therapeutic options. A wide variety of phenotypic analysis could be carried out. The schematic highlights functional characterization of hiPSC-CMs, small molecular perturbation of pathways, identification of drug targets and the interaction of hiPSC-CMs or CPCs with the extracellular matrix. [64].

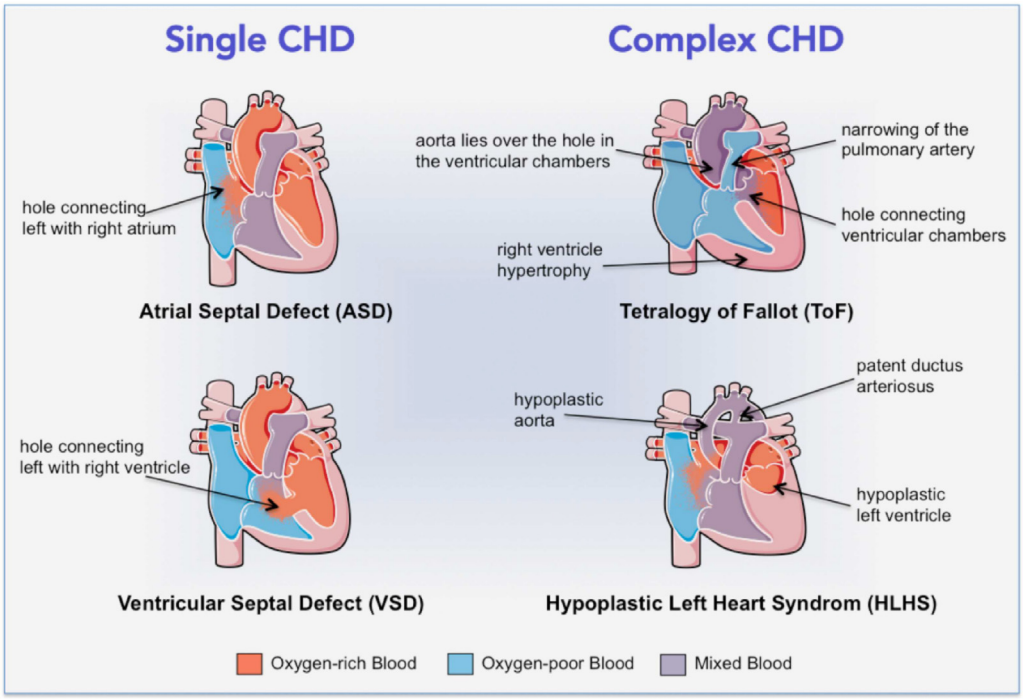

Fig. 4. Diagram illustrating the cardiac structural alterations in common single and complex CHD [42].

Table 1
Advantages and Disadvantages of Various Stem Cell Types for Cardiac Repair.

Cell Type	ESC	SM	BMC	CSC	iPSC
Proliferative capacity	Yes	Yes	Yes	Yes	Yes
Arrhythmia	ND	Yes	No	No	ND
Cardiomyogenic differentiation	Yes	No	Controversial	Yes	Yes
Ethical problem	Yes	No	No	No	No
Immune response	Yes	No	No	No	No
Tumor formation	Yes	No	No*	No	ND
Results in clinical trial	No	Mixed	Mixed	Positive	No

ND (not determined). * It has been reported that formation of bone and substantial intramyocardial calcification in infarcted hearts occurred after delivery of bone marrow cells in animal models [65,66]. So far, there are two phase I clinical trials reporting that resident cardiac stem cells (c-kit+ cells or cardiosphere-derived cells) exerted beneficial effects when transplanted postinfarction in ischemic heart disease patients [14,67].

myocardium, potential lethal arrhythmia, and mixed results, further research is required prior to future clinical applicability.

2.6. Bone marrow-derived stem cells

The bone marrow is a heterogeneous tissue, consisting of different subpopulations, including hematopoietic stem cells (HSCs) and endothelial progenitor cells (around 2–4%), very rare mesenchymal stem cells (MSCs) (0.001–0.01% of the nucleated cells), and large proportions of committed progenitor cells and their specific differentiated progeny [37].

The use of bone marrow mononuclear cells (BMMNCs), purified progenitor cells (CD34+ or CD133 +), endothelial progenitor cells (EPCs), and MSCs in experimental and clinical studies has provided informative data related to human CVDs. [38] However, as they are multipotent, it should be noted that bone marrow-derived cells could differentiate into a variety of cell types when transplanted, thereby carrying a potential risk of bone, cartilage, and adipose tissue formation in the heart [39]. HSCs, identified by the expression of cell surface antigens such as CD34, CD133, c-kit (CD117), and stem cell antigen-1 (Sca-1), are lineage negative (Lin–). These cells can be obtained from the bone marrow, umbilical cord, and peripheral blood, giving rise to all blood cell types. HSCs have been extensively studied and used to treat a variety of hematological disorders in the clinic, such as anemia, leukemia and lymphoma [34].

It is believed that more clinical studies will provide further insights into the therapeutic efficacy and help solve issues regarding bone marrow-derived cell transplantation in patients with CHD, including optimal cell dosing, cell type, and timing and route of delivery.

In a study by Rupp et al., infant retained chronic heart failure status, after he underwent cardiogenic shock as a result of obstruction of ductus arteriosus after a hybrid stage I protocol that included ductal stenting and bilateral pulmonary artery banding. The subject retained a status of NYHA class III heart failure with a dilated RV and reduced ventricular function, even 7 months after a stage II procedure. The ejection fraction of the systemic RV was 22% and the level of brain natriuretic peptide (BNP) was 2200 pg/mL. In this critical condition, autologous bone marrow cells (BMC) were transplanted back to the patient through intracoronary bolus injection. A year after the stem cell therapy, his clinical condition had improved drastically, his BNP level had reduced to 132 pg/mL, and his RV ejection fraction had also been improved to 44%. The same group of researcher reported two other cases of cell therapy with BMC for CHD in children with heart failure (double outlet RV with pulmonary atresia and ventricular septal defect) [40]. Supportive data remained elusive despite the fact that clinical presentation improved in both patients.

Limsuwan et al., reported a case of BMC transplantation in a 9-year-old girl with congestive heart failure secondary to myocardial infarction (MI). After transcoronary infusion of BMC, LVEF improved from 30% to 47% [41]. Although all studies till present are limited to case reports with little numbers of patients, the dramatic improvements shown in most of these studies resulted in the assumption that children have a high potential of cell therapy heart regeneration and reactivity.

Table 2
Selected human genetic syndromes associated with CHD.

Disease	Gene Defect	Incidence/live births[a]	Phenotype (non-cardiac)	% with CHD[b]	Common CHD[b]	CHD Described[b]
Aneuploidy Syndromes Down Syndrome	Trisomy 2	1:700	Dev delay, short stature, low tone	40–50%	AVSD, VSD	ASD, TOF, PDA
Turner syndrome	Monosomy X (XO)	1:2500	Short stature, lymphedema webbed neck	30–50%	Coarctation, BAV, VSD	HLHS, HTN Aortic dilation
Edwards Syndrome	Trisomy 18	1:6000	80% female, dev delay, arthrogryposis	90%	ASD, VSD, PDA	Coarctation, HLHS
Microdeletion Syndromes DiGeorge/VCFS	del22p11.2	1:4000	Hypocalcemia, immune deficiency	80%	TOF, TA, IAA (B)	VSD, ASD, Arch anomalies
Williams- Beuren	del7q11.23	1:8000	Hypercalcemia, Renal disease, dev delay, failure to thrive	80%+	SVAS, PPS	Coarct, valve disease, ASD, VSD
Jacobsen	del11q23	1:100,000	Abn platelets, dev delay, short	50%	VSD, Ao valve anom	HLHS (5%) Coarct
Syndromic Single Gene Disorders Noonan	PTPN11, BRAF, SOS, KRAS, CBL, RIT1	1:1000–1:2500	Short stature, webbed neck	80%	Dysplastic PV, ASD, VSD, HCM	AVSD, PDA
Alagille	JAG1 NOTCH2	1:70,000	Extrahepatic biliary atresia, vertebral anomalies	90%+	PPS, TOF	ASD, VSD, AS, Coarctation, HLHS
Ellis-van Creveld	EVC1; EVC2	1:60,000–1:200,000	Short stature, polydactyly, dental abn	50%+	ASD	Common atrium, AVSD PAPVR
Holt-Oram	TBX5	1:100,000	Upper limb malformations	75%	ASD, VSD	AVSD, conduction defects

ASD atrial septal defect, AS aortic stenosis, AVSD atrioventricular septal defect, BAV bicuspid aortic valve, HCM hypertrophic cardiomyopathy, HLHS hypoplastic left heart syndrome, HTN hypertension, IAA interrupted aortic arch, PAPVR partial anomalous pulmonary venous return, PDA patent ductus arteriosus, PPS peripheral pulmonary stenosis, PV pulmonary valve, SVAS supravalvular aortic stenosis, TA truncus arteriosus, TAPVR total anomalous pulmonary venous return, TOF tetralogy of Fallot, VSD ventricular septal defect.
[a] Incidence in the United States.
[b] Most common types and other reported types of CHD [62,63].

Table 3
Framework for systems biology approaches to heart development and congenital heart disease [68].

	Perturbation	Biological system	Phenotyping	Molecular Measurement	Computational modelling
Choices	• Gene targeting • RNA interference • Protein Interference • Environmental changes	• Zebrafish • Frog • Fruitfly • Mouse • Rat • Human	• Single to systems level • Histology • Anatomy • Morphology • Haemodynamics • Physiology	• Genome • Epigenetics • Transcriptome • Proteome • Metabolome • Physical, genetic, and functional interactions	• Data integration, filtering and clustering • Functional enrichment • cross-species analysis • probabilistic interference • Network dynamics, modelling and visualization
Technology	• Knock out/in • siRNA, shRNA • chemical mutagenesis • small molecules • Diet, stress	• whole heart • compartments • cardiomyocyte, vascular cell, cardiac firoblast • cells expressing particular markers	• ECHO/MRI/ECG • catheter • histology • microscopy • live stream imaging	• microarray • sequencing • genotyping • NMR,MS, FACS • IP,Y2H,M2H • ChiP	• Database of functions, pathways, interaction • Regression analysis, Bayesian networks • Differential equation/biophysical simulation • directed/hierarchical layouts
Challenge	• High-through	• Availability • Maintenance • Reproduction	• High-throughput • time-series • oncology • machine readability	• limited and heterogeneous materials	• dynamic network phasing over time

2.7. Adult cells

Despite the potential of iPS and fetal cells, so far most clinical and preclinical studies have used post-natal cells for both safety reasons and ease in adult tissues. Several types of cells derived from post-natal tissues can be use [42].

3. Recent advances in stem cell therapies for CHD

Weiss et al., 2013 [43] studied the safety means to perform an initial evaluation of the potential efficacy of systemic MSC administration to patients with moderate to severe COPD. In their study patients completed the full infusion protocol, 74% completed the 2-year follow-up. They observed that there were no infusional toxicities, and no deaths or serious adverse events considered related to MSC administration. There were no significant differences in the overall frequency of COPD exacerbations, number of adverse events, or worsening of disease in patients treated with MSCs. No significant differences in PFTs or quality-of-life indicators; however, an early, significant decrease in the levels of circulating C-reactive protein (CRP) was observed in patients who were treated with MSCs and had elevated CRP levels at study entry. They concluded that systemic administration of MSC appears to be safe in patients with moderate to severe COPD

and provides a basis for subsequent investigations of cell therapy [43].

Lambert et al., 2015 [44] assessed the possibility and effects of cell therapy in a pig of overloaded RV dysfunction. Human MesP1þ/SSEA-1þ cardiogenic mesodermal cells were administered using multiple intra myocardial injections 4 months after surgical procedure mimicking the repaired tetralogy of fallot, and their effects were observed 3 months later on rhythmic, hemodynamic, and histologic parameters. All the pigs survived without any complication, and stem cell therapy was clinically well tolerated. Although contractility, functional, and energetics parameters arises similarly in both groups, benefits as regards arrhythmic susceptibility were observed in the treated group, associated with a significant decrease of peri-myocyte fibrosis. Such a decrease could be due to paracrine effects, as no human cells could be detected within the myocardium. Cell therapy using intramyocardial injections of human MesP1þ/SSEA-1þ cardiogenic mesodermal cells seems to be helpful regarding overloaded RV tissue remodeling and arrhythmic susceptibility, but this mode of administration is not enough to give a significant amelioration in RV function [44].

Wehman et al. (2016) was the first to study the use of MSCs as a therapeutic mechanism to preserve RV function and attenuate remodeling in the setting of pressure overload neonatal porcine model [45]. Their treatment attenuates remodeling of the myocardium by enhanced neovascularization, reduced inflammation, cardiac hypertrophy, and increased recruitment of endogenous cardiac stem cells. Mechanistically, they showed for the first time that MSC treatment stimulates the antihypertrophy factor GDF15, and its related SMAD proteins. The inspiring results obtained have implications in congenital cardiac pressure overload lesions [45].

Agarwa et al., 2016 [46] investigated for the first time, the role of age of human pediatric cardiac progenitor cells (hCPCs) on ventricular remodeling in juvenile heart failure model. hCPCs collected from children undergoing reconstructive surgeries were separated into 3 groups based on age: neonate, infant, and child. They subjected adolescent arrhythmic rats to sham or pulmonary artery banding surgery to induce a model of RV heart failure. Two weeks following surgery, hCPCs were injected into the RV musculature noninvasively. Analysis of cardiac function 4weeks post-transplantation showed significantly increased tricuspid annular plane systolic excursion and RV ejection fraction, and significantly decreased wall thickness and fibrosis in rats transplanted with neonatal hCPCs as compared with saline-injected rats (control).

Systems biology or computational modelling and analysis were carried out on arrays and gave clue into potential mechanisms at the gene and microRNA level. Mechanisms including proliferation and migration assays, as suggested by computational modelling, demonstrated improved proliferative and chemotactic capacity of neonatal hCPCs as compared with infant/child hCPCs. *In vivo* immunostaining suggested increased recruitment of stem cell antigen 1-positive cells in the RV. They concluded that reparative potential of hCPCs is age-dependent, with neonatal hCPCs exerting the highest beneficial effect compared with infant and child hCPCs.

4. Conclusions

Cardiovascular disease, particularly CHD, represents the main medical health care burden in the world. The cure for CHF remains limited to heart transplantation. But, with the advent of stem cell research-based therapy, researchers has shifted their attention because of the vast potentials of stem cells for cardiac regenerative medicine. However, the data from several clinical trials using cell transplantation strategies showed inspiring, but marginal, effects partly due to inefficient engraftment and low cells survival rate [47–51]. We still have a long way to go before stem cell-based cardiac therapy becomes fully established clinically [52–55]. More sophisticated research and well-designed clinical trials are needed to elucidate and clarify unanswered questions, such as the ideal stem cell type, stem cell dosing, and optimal timing for delivery [56–58]. Stem cell therapy seems to be safe and effective in children. We propose that isolating these cells from neonate (Fig. 5) will give a robust heart regeneration as compared to adults. To unveil stem cell therapy beyond its possibility and safety, further study is required, including largescale randomized clinical trials to certify the efficacy of stem cell therapy [59,60].

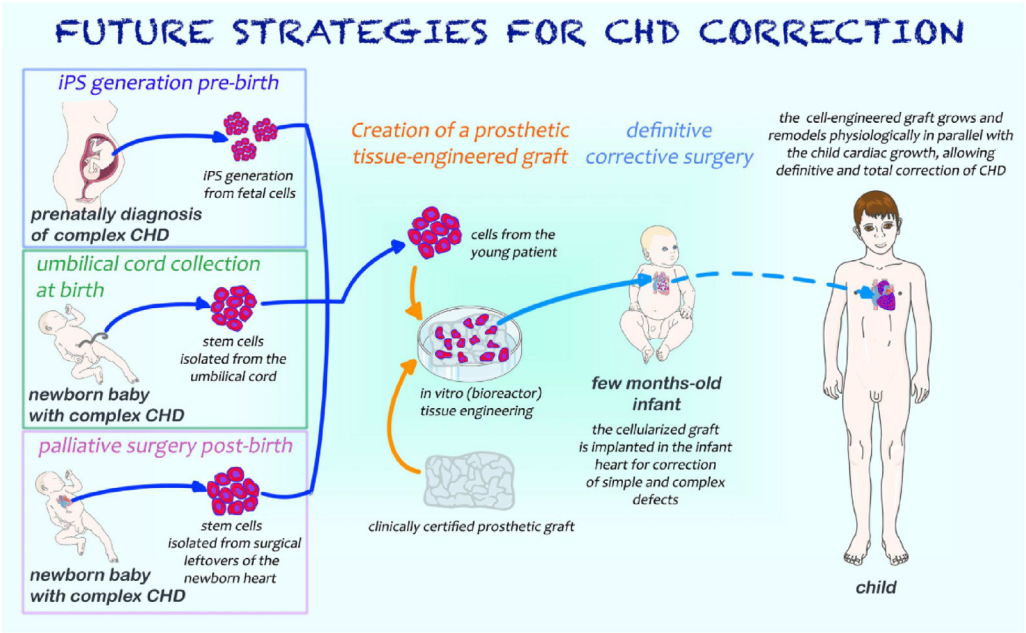

Fig. 5. Illustration of possible future strategies for the surgical management of newborns with CHD. [42].

Conflict of interest

The authors declare that they have no conflict of interest.

Compliance with ethical standards

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