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Review

Healing the Broken Hearts: A Glimpse on Next Generation Therapeutics

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Abstract: Cardiovascular diseases are the leading cause of death worldwide, accounting for 32% of deaths globally and thus representing almost 18 million people according to WHO. Myocardial infarction, the most prevalent adult cardiovascular pathology, affects over half a million people in the USA according to the last records of the AHA. However, not only adult cardiovascular diseases are the most frequent diseases in adulthood, but congenital heart diseases also affect 0.8–1.2% of all births, accounting for mild developmental defects such as atrial septal defects to life-threatening pathologies such as tetralogy of Fallot or permanent common trunk that, if not surgically corrected in early postnatal days, they are incompatible with life. Therefore, both congenital and adult cardiovascular diseases represent an enormous social and economic burden that invariably demands continuous efforts to understand the causes of such cardiovascular defects and develop innovative strategies to correct and/or palliate them. In the next paragraphs, we aim to briefly account for our current understanding of the cellular bases of both congenital and adult cardiovascular diseases, providing a perspective of the plausible lines of action that might eventually result in increasing our understanding of cardiovascular diseases. This analysis will come out with the building blocks for designing novel and innovative therapeutic approaches to healing the broken hearts.

Keywords: cardiac development; congenital heart diseases; cardiac therapy

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1. Cardiogenesis and Congenital Heart Diseases

Cardiac development is initiated soon after gastrulation as the precardiogenic mesoderm, derived from the early primitive streak, migrates towards both sides of the developing embryo [1,2]. Left and right cardiac crescents are then configured and will subsequently be fused in the embryonic midline to form the early primitive cardiac straight tube (Figure 1) [3]. Experimental evidence in mice demonstrated that impaired development of these early developmental stages is incompatible with life [4,5]. Soon after the primitive cardiac straight tube is configured, an invariable rightward movement occurs in the developing heart that represents the first sign of morphological left–right asymmetry [6–8] (Figure 1). Importantly, the impaired occurrence of such rightward looping can lead to severe consequences for the developing embryo. If complete reversal of rightward looping (including other organs) occurs, the embryo develops *situs inversus* providing thus a mirrored image position of all body structures [6], a condition that can be compatible with life [9]. However, if partial or absence of rightward looping occurs, the embryo develops severe congenital cardiac defects that, in many cases, are incompatible with life [10–12], unless surgical correction perinatally occurs.

Soon after cardiac rightward looping takes place, embryonic atrial and ventricular chambers emerge that are interconnected between them by flanking segments such as the inflow tract, the atrioventricular canal, and the outflow tract [13]. These flanking segments are characterized by the presence of endocardial cushions, that are more prominent in the atrioventricular canal and outflow tract as compared to the inflow tract [13] (Figure 1). Importantly, the configuration of these cardiac chambers emanates from two distinct

cell populations, namely the first and second heart fields, respectively [14,15]. While the first heart field primarily contributed to the future left ventricle, the second heart field contributes to the rest of the cardiac chambers, i.e., in the anterior part of the heart to the future right ventricle and outflow tract and in the posterior part of the heart to the atrioventricular canal, embryonic right and left atria and the inflow tract. Impaired deployment of the second heart field leads to congenital heart defects that are incompatible with life, as the outflow tract, the right ventricle, and much of the atrial chambers are missing [16].

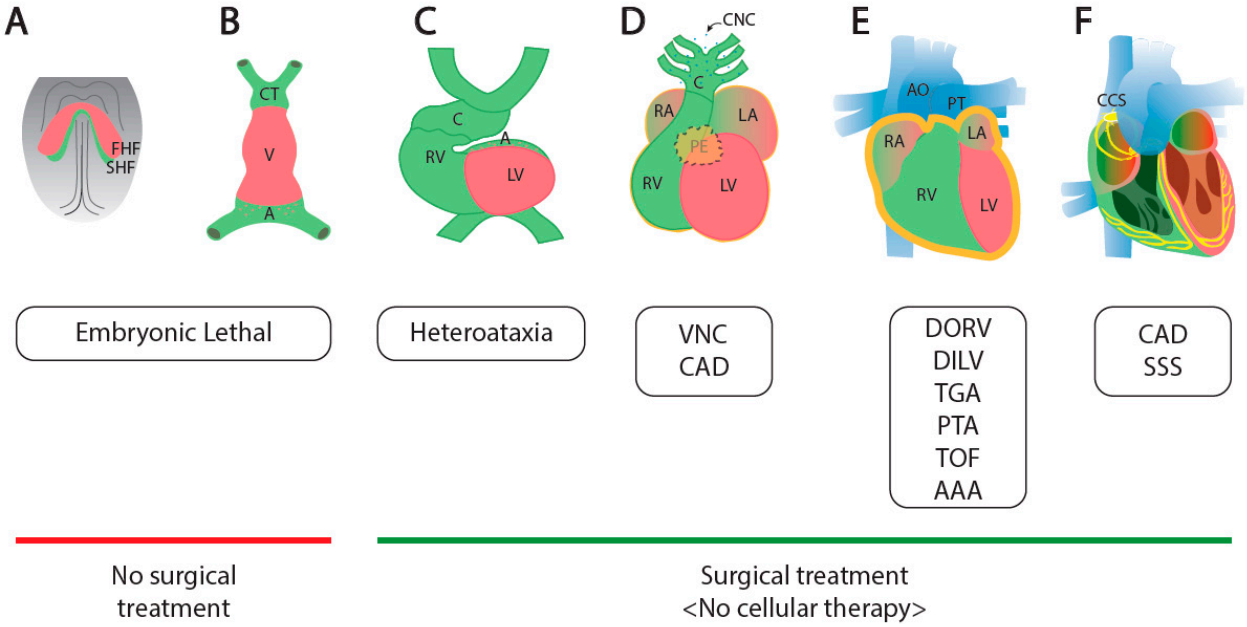

Figure 1. Schematic representation of the main steps of cardiogenesis. Starting from the cardiac crescent (**A**) into the cardiac straight tube (**B**), followed by the rightward looping (**C**). Soon thereafter, atrial and ventricular chambers are configured (**D**) with the contribution of extracardiac cells such as the proepicardial derived cells that externally lined the naked embryonic myocardium (**D**) and septation occurs leading to a four-chambered heart (**E**) with its own electrical wiring, i.e., the cardiac conduction system and vascular supply, i.e., coronary vasculature (**F**). VNC, ventricular non-compaction, CAD, coronary artery disease, DORV double outlet right ventricle, DILV double inlet left ventricle, TGA, transposition of the great arteries, PTA, permanent truncus arteriosus, TOF, tetralogy of Fallot, AAA, aortic arch abnormalities, SSS, sick sinus syndrome.

Configuration of the embryonic cardiac chambers further develops by a progressive external lining of the naked embryonic myocardium with the embryonic epicardium and by the progressive formation of distinct ventricular myocardial layers, i.e., the trabecular and compact layers (Figure 1). Both processes are intimately related as if no epicardial lining occurs, the ventricular compact myocardium fails to properly develop [17,18] resulting in a phenotype reminiscent of the ventricular non-compaction defect in adult human patients [19,20]. Importantly the contribution of the embryonic epicardium goes far beyond merely externally lining the myocardium, in such a way that epicardial-derived cells contribute to the fibroskeleton of the heart, the forming cardiac valves, and more importantly to the coronary vasculature [21–24]. Thus, impaired epicardial development also critically compromised several of these cardiac structures and led to congenital defects that are incompatible with life [17,25].

Concomitantly, the flanking segments display an engrossment of the endocardial cushions as a consequence of the filling of these cushions with endocardial-derived mesenchyme [26,27]. Endocardial cushion development is essential for providing adequate and encompassing filling and extrusion of the circulating blood through the embryonic cardiac chambers [28]. In addition, endocardial cushion remodeling is also essential for

proper valve development [26,27]. Failure in endocardial cushion development leads to congenital valve defects that can compromise cardiac output and thus life [29,30].

To accomplish a double circuitry, the embryonic heart subsequently initiates a process of septation or tabication of all cardiac components [31,32] (Figure 1). Atrial septation is developed by the progressive deployment of a first incomplete atrial septum followed by a second, also incomplete, atrial septum [33]. Such a developmental process warrants that blood flow can passes along both, right and left atrial chambers, while no pulmonary circulation is operative. At birth, the pulmonary circulation shunt permits such communication to be sealed. Failure of atrial septal development and/or closure leads to one of the most common cardiac congenital malformations, i.e., interatrial septal defect [34]. Such defect is normally compatible with life and in several cases becomes naturally sealed in early postnatal development without requiring surgical interventions [35]. However, if not spontaneously sealed, it can be surgically corrected postnatally [36–38].

On the other hand, ventricular septation is accomplished by the formation of an ingrowth muscular ventricular septum that separated the future right and left ventricular chambers [39]. To completely separate both chambers, proper connection and contribution of a membranous portion to the ventricular septum is required, derived from the flanking atrioventricular canal segment [40]. Muscular ventricular septal defects are the most common type of ventricular septal defects and, in many cases, do not require surgical interventions [41,42]. On the other hand, impaired contact between muscular and membranous components and/or failure to properly develop membranous components lead to severe and rather frequent ventricular septal defects that represent a clear life-threatening condition requiring intrauterine and/or perinatal surgical interventions [43–45].

In addition to septation of the major cardiac chamber components, the atrioventricular canal and outflow tract also develop intensive embryonic remodeling leading to the formation of separate inlet and outlet connections to the forming right and left ventricular chambers, respectively. Impairment of adequate remodeling of the atrioventricular canal frequently leads to double inlet left ventricle, while impaired outflow tract septation leads to a range of severe developmental defects such as permanent truncus arteriosus or double outlet right ventricle, respectively [46,47]. In all cases, surgical interventions are required as such congenital heart diseases are incompatible with life [48–52]. However, developmental valvular defects occurring at the maturation stage might lead to mild or to totally silent valvular abnormalities ranging from tricuspid and/or mitral atresia to congenital bicuspid aortic valves. Importantly, an extracellular contribution of the neural crest cells is essential for correct outflow tract septation but dispensable for atrioventricular canal septation [53–55].

While cardiac septation is presented herein as discrete entities, most of these developmental processes occur concomitantly, providing exquisite synchronization [13]. Thus, it is not surprising that in many cases, multiple defects concomitantly occur, leading to complex congenital malformations such as the Tetralogy of Fallot and/or Ebstein's abnormality [56–60]. While our understanding of the cellular and molecular mechanisms that lead to these complex cardiovascular defects is in constant advance, there are still many missing pieces in this complicated puzzle.

In addition to the morphogenetic events leading to the morphogenesis of the heart, two additional events are equally critical during cardiogenesis: (a) the development of the electrical wiring of the heart, i.e., the cardiac conduction system, and (b) the formation of an irrigation system, i.e., the cardiac vasculature (Figure 1). The pacemaker components of the cardiac conduction system originate from a subset of myocardial sleeves of the flanking segments, particularly from the inflow and atrioventricular canal, leading to the formation of the sinoatrial node and atrioventricular node, respectively [61,62]. On the other hand, the fast ventricular components are derived from cells emanating from the ventricular chambers [63,64]. Impaired morphogenetic events leading to pacemaker dysfunction are rare events [65,66] that eventually required cardioverter defibrillation implantation.

Cardiac vasculature arises from distinct cell populations during embryogenesis. Epicardial-derived cells greatly contribute to avian species, while in mice the epicardial contribution is more limited, being more relevant to the sinus venous (coronary veins) and the endocardium (coronary arteries) [67,68]. The impaired contribution of these cells population greatly hinders cardiovascular development and thus is incompatible with life. Milder congenital cardiac vasculature defects might arise as a consequence of the development of a single coronary artery, the abnormal origin of the coronary arteries, or the singular trajectory of these vessels, yet the developmental origin of these anomalies remains to be elucidated [69].

2. Adult Cardiac Performance and the Bases of Malfunction

Adequate cardiac performance is essential for life. Impaired cardiac performance can be progressively acquired during adulthood by distinct triggering factors [70]. Among the most common cardiovascular risk factors, obesity, diabetes, and elevated cholesterol levels are the most relevant [71]. Focusing on adult cardiovascular diseases, two distinct types can be globally recognized: (a) those leading to structural remodeling of the cardiac chambers, and (b) those affecting the wiring of the heart, i.e., electrical disturbances or arrhythmias. In a subset of cases, both structural and electrical defects are observed.

Myocardial infarction represents the most prevalent cardiovascular disease worldwide [72]. Myocardial infarction is secondary to acute ischemia produced by coronary artery occlusion. As a consequence, a part of the ventricular mass lacks proper oxygen levels and a necrotic area is produced. To compensate such failure, fibrosis is initiated, and an inflammatory response is also activated [72]. Depending on the severity, extent and duration of the ischemic period, such myocardial region will be able to be partially recovered. Overall, structural remodeling of the ventricular chambers occurs, which eventually can even compromise the electrical activity and thus lead to spontaneous ventricular arrhythmias [73,74]. Timely revascularization after myocardial infarction, including thrombolytic treatment, percutaneous coronary intervention, and bypass surgery are key to improving cardiac function at the early stages of myocardial infarction and thus limiting post-infarction remodeling [75–77]. However, these approaches are not applicable to all patients. Attempts to limit infarct size can also be achieved by using pharmacotherapy but their efficiency is limited [78,79]. Therefore, novel approaches are required.

Myocardial infarction is a cardiac disease characterized by cardiomyocyte cell death due to a lack of oxygen supply. Some structural changes can be observed after 10–15 min of the onset of ischemia, i.e., relaxed myofibrils and/or sarcolemma disruption [80]. Thus, one of the most challenging medical needs nowadays is to provide cell sources to heal the infarcted heart.

In order to regenerate the damaged area within the infarcted heart, multiple studies using different cell sources have been performed (Figure 2). For example, skeletal myoblasts have the ability to proliferate and differentiate to generate myofibers within the myocardium [81]. In the first decade of the XXI century, some clinical trials were performed, e.g., POZNAN, MAGIC, etc. . . . , supporting all of them the advantages of using skeletal myoblasts in patients with chronic heart failure, the differentiation capacity into muscle fibers independently of the environmental influences, and their good growing and proliferation rates with high resistance to ischemia [82–84]. In concordance, in vivo perfusion of satellite cells is able to generate aligned muscle fibers on the damaged area, in dogs [85]. Even although considering these good results, all the authors concur that the main drawback of this cell source is that the electrophysiological conductance between skeletal muscle and cardiomyocytes is not properly established, since differentiated skeletal myoblasts downregulate the expression of both N-cadherin, connexin 43, and dihydropyridine receptor, providing thus arrhythmogenic foci, representing the major problem of skeletal myoblasts transplantation [86–91].

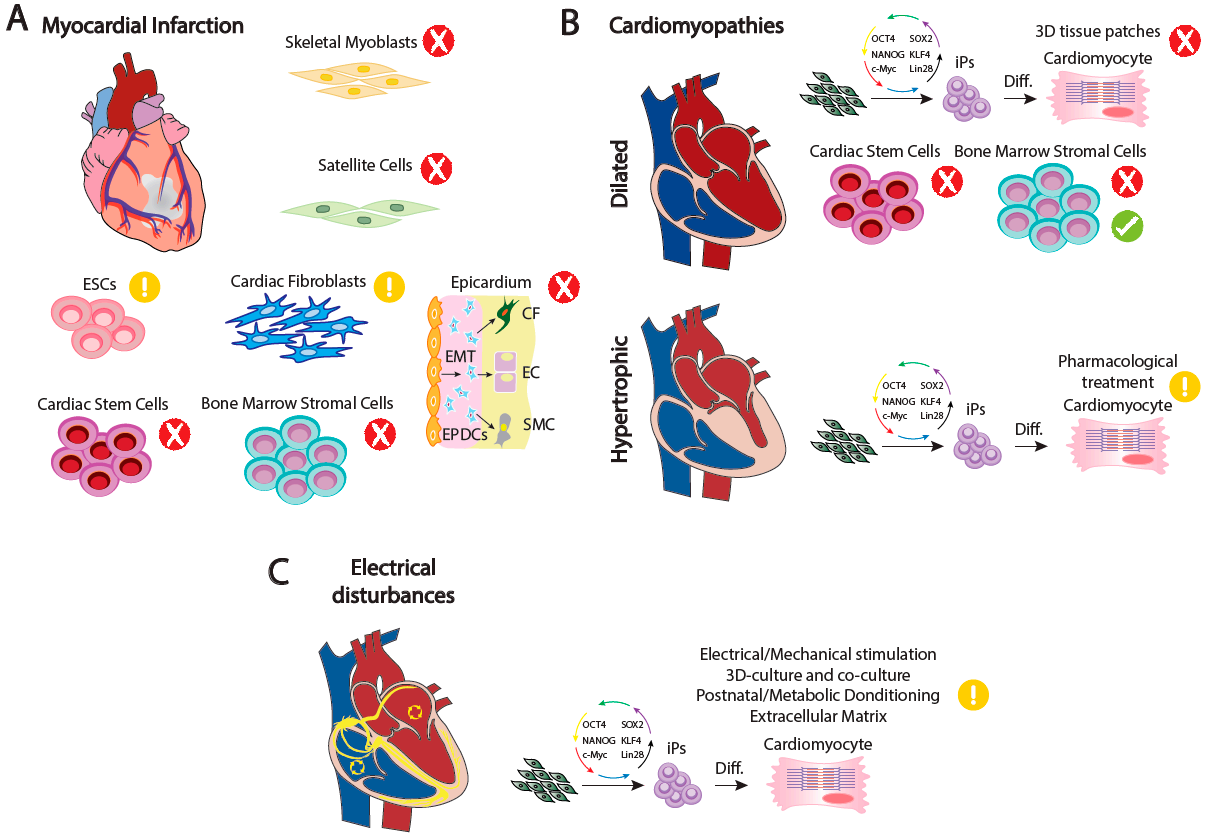

Figure 2. Schematic representation of the main adult cardiac pathologies, indicating the major advances using cell therapy to treat the damaged heart.

Moreover, it is well known, embryonic stem cells (ESCs) have the capacity to differentiate into cardiomyocytes [92–94]. ESCs transplantation experiments have been conducted in rats to stabilize the infarcted zone and to promote the generation of new myocardium. This procedure has shown an improvement in cardiomyocytes survival rate as well as in the neovascularization of the infarcted zone [95]; however, such application has not been translated yet to the clinical area by ethical and biological concerns, such as the possibility of teratoma formation and graft refusal [96–98]. Another cell source is cardiac fibroblasts, these cells promote cardiomyocyte proliferation through the release of cytokines; however, further studies in humans need to be carried out to assess the ability of these cells to be electrically coupled [99,100]. Bone marrow stromal cells are capable to differentiate into cardiomyocytes, and endothelial and vascular smooth muscle cells after injection into sheep and adult mice after myocardial infarction, regenerating 68% of the infarcted area [101,102]. While a large array of clinical trials has been developed using these cells in MI, the global results are rather limited and disappointing [103–105]. An additional type of cell used for myocardial regeneration are cardiac stem cells (CSCs), which are able to generate new cardiomyocytes and as well as have the capacity to stimulate existing cardiomyocytes proliferation [106], however their characterization is still rather controversial and thus their clinical use is still on hold. It has been demonstrated that c-kit + CSCs are committed to the myogenic program through the expression of Nkx2.5 and Gata4 transcription factors, whereas VEGF secretion improve angiogenesis [107,108]. More recently, a new source of cells has gathered special attention, as it has been demonstrated that the outer cardiac layer, i.e., the epicardium, can be triggered to acquire myocardial fate [109,110] and the implication of the epicardium is instrumental to provide myocardial regenerative potential in distinct myocardial injury models [111–114]. Thus, within next coming years, novel cell sources will be assayed and hopefully in a short near future cardiac regenerative medicine will come to light.

Although there are many advances in cardiac cell therapy, no cell type has been pointed out as optimal option, and furthermore there are still many issues that need to be thoroughly addressed such as the cell number and administration procedures, long-term cell engraftment, mechanisms of stem cells action and if it would be necessary any recurrence in the treatment [115].

Considering stem cell therapy has generated high clinical interest for myocardial regeneration, it was needed to identify the best procedure for stem cell delivery. It has described different types of administration; one of them is the direct surgical intramyocardial injection, which is the most direct, precise, and accurate method for stem cell injection in the infarcted area of the heart, although it is an invasive technique with a high risk of complication and mortality including embolization and cardiac arrhythmias [116,117]. Another different method is catheter-based intramyocardially administration. This technique can be used in surgically high-risk patients, due to its less invasive nature. Before initiation of the procedure, it is needed to identify the most effective catheter-based approach based on the anatomic needs and thus requires extensive image guidance within the ventricle [118–120]. Additionally, intravenous infusion is a simple and less invasive route that only can be used with post-AMI patients, although it is considered that has low efficiency in delivering infused cells to the heart [121,122]. Using the infusion technique, cell therapy can be performed via the coronary artery, being the most clinical method used after MI because generate homogeneous cell engraftment. The main issue with this technique is that cannot be used into not well-perfused areas [118,123]. Finally, the retrograde coronary venous delivery system is based on the use of a single or double balloon catheter to reach the infarcted area, but through the venous system is difficult to outreach the different zones [124,125]. As it has been stated, during different clinical studies, the above-mentioned techniques have a poor cell engraftment and survival rate, in this case, a new method is being implemented, concretely the creation of an engineered monolayer tissue which needs to be transplanted into the damaged area, providing a physical scaffold enhancing adherence. Some studies demonstrated that engrafted cells into the ischemic myocardium are able to grow properly and moreover the area is irrigated by newly formed vessels improving cardiac function [126]. Finally, the use of cell therapy involves the possibility of an uncontrolled growth of the cell population that may become into a teratoma formation when HESCs are used or even genetic aberration whenever using iPSCs, these issues raise serious safety concerns and can hamper the advancement of cell-based therapies [127,128].

Concomitantly with cell therapy, cytokines treatment has been used in damaged hearts, and they are thought to promote angiogenesis in the ischemic tissue [129]. To date, a large list of cytokine agents has been reported in both pre-clinical and clinical trials as detailed below (Table 1), with diverse biological outputs.

Table 1. List of the different cellular and molecular therapeutic options provided to date to treat the damaged heart.

Cell Theraphy		
Cell Types	**Disease**	**STATE of the Research**
Skeletal Myoblasts	Myocardial Infarction	Clinical Trials
Satellite Cells	Myocardial Infarction	Basic Research
Embryonic Stem Cells	Myocardial Infarction	Basic Research
Cardiac Fibroblasts	Myocardial Infarction	Basic Research
Bone Marrow Stem Cells	Myocardial Infarction Dilated cardiomyopathy	Clinical Trials
Cardiac Stem Cells	Myocardial Infarction Dilated cardiomyopathy	Basic Research
Epicardium	Myocardial Infarction	Basic Research
Human iPSCs	Dilated cardiomyopathy Hypertrophic cardiomyopathy Electrical distrubances	Basic Research

Table 1. *Cont.*

Cell Theraphy		
Cell Types	**Disease**	**STATE of the Research**
Cytokines Treatment		
Cytokin	Function	State of the research
FGF1	Cells mitosis	Basic Research
FGF2	Cell migration Angiogenesis	Clinical Trials
FGF4	Cell proliferation Angiogenesis Metalloproteinases	Clinical Trials
VEGF	Cell proliferation Migration Neovascularization	Clinical Trials
GCSF	Cell mobilization	Clinical Trials
GMCSF	Cell mobilization Angiogenesis	Basic Research
EPO	Cell proliferation Cell mobilization	Basic Research
GH and IGF-1	Reduced collagen deposition Reduced fibrosis	Clinical Trials
ANG1	Vessel maturation	Basic Research
HGF	Angiogenesis Antiapoptosis	Basic Research
PIGF	Cell growth Cell survival Cell migration	Basic Research
SCF	Cell mobilization	Basic Research
Cardiac Extracellular Matrix Treatment		
cECM protein	Function	State of the research
Elastin	Differentiation Proliferation Clonal expansion	Basic Research
Tenascin-C Fibronectin	Cardiac regeneration	Basic Research
Agrin	Cardiac regeneration	Basic Research
Matrix Patches	Recapitulate embryonic myocardium environment	Basic Research
Hydrogels	Cell mobilization Revascularization Cardiac marker expression	Basic Research
Modified RNAs therapy after MI		
modRNA	Function	State of the research
VEGFA	Cell proliferation Vascularization Angiogenesis	Clinical Trials
IGF1	Cardiomyocyte survival rate	Basic Research

Fibroblast growth factor (FGF) has paracrine, autocrine, or endocrine functions [130]. FGF1 has a mitogenic role on vascular smooth muscle cells of the injured area [131] while the low molecular weight of FGF2 promotes endothelial cell migration and angiogenesis. Several clinical trials have been conducted demonstrating the safety and feasibility of this therapy although it has been reported some dose-dependent hypotension symptoms. A phase II clinical trial called FIRST failed to improve exercise tolerance and myocardial reperfusion with a single dose of FGF-2 [132,133]. Finally, FGF4 which is not present in the adult ischemic heart induces endothelial cell proliferation, metalloproteinases secretion, and vascular endothelial growth factor (VEGF), which finally ends in angiogenesis stimulation.

In this regard, AGENT clinical trials demonstrated no or only modest therapeutic effects suggesting the need for a combination of therapies to obtain clinical success [130].

Vascular endothelial growth factor (VEGF) is able to stimulate endothelial cell proliferation, migration, and survival leading to neovascularization, this process is regulated by VEGF receptors 1 and 2, also known as Flt-1 and Flk-1, respectively. Euroinject One trial concluded that VEGF treatment does not induce an improvement of the stress-induced myocardial abnormalities, although enhances regional wall motion [134–142].

Granulocyte colony-stimulating factor (GCSF), this hematopoietic cytokine promotes the digestion of adhesion molecules favoring cell mobilization. Moreover, GCSF stimulates the production of anti-apoptotic proteins, through the activation of Janus kinase/signal transducer and activator of transcription pathways, decreasing cardiomyocyte death and limiting the infarct scar size, after MI administration. Although this cytokine is quite useful, needs to be used with caution because it can promote inflammation and cardiac remodeling. FIRSTLINE AMI and STEMI are two clinical trials where an improvement in the cardiac function after GCSF treatment was observed [143–146].

Granulocyte-macrophage colony-stimulating factor (GMCSF), this cytokine promotes the circulation of CD34 + cells participating in the regenerative process in acute MI patients [147]. However, no clinical trials are yet available.

Erythropoietin (EPO), this cytokine is produced by several tissues after metabolic or hypoxia stress and enhances angiogenesis through the proliferation of endothelial cells and mobilization of bone marrow-derived cells [148,149]. Basic research has reported the beneficial effect of EPO through cell mobilization and increasing blood flow due to a good capillary density [150,151], yet such treatment has not moved into the clinical arena yet.

Growth hormone (GH) and insulin-like growth factor 1 (IGF-1), in this case, GH promotes the IGF-1 synthesis. This treatment pathway induces viable myocardium hypertrophy and reduces collagen deposition or fibrosis improving ventricular function. Clinical trials using GH therapy have demonstrated an increased LV wall thickness mass increase in severe dilated cardiomyopathy patients [152–155].

Angiopoietin (Ang), it has been demonstrated that Ang1 increases vascular density and vessels maturation post-MI administration, whereas Ang2 acts as an agonist of angiogenesis [156–159].

Hepatocyte growth factor (HGF), this factor is found in the heart after MI and possesses pro-angiogenic and antiapoptotic effects [160,161].

Placental growth factor (PIGF) is a cytokine that enhances the VEGF activity promoting endothelial cell growth, survival, and migration; however, PIGF treatment is related to the formation of atherosclerotic plaques [162–165].

Stem cell factor (SCF) is required for cell mobilization to the peri-infarct zone, favoring cardiac remodeling through the activation of the c-kit receptor [166–170]. Some animal studies have been conducted by using a combination of SCF and GCSF in mice where the cardiac function was improved [171].

Nonetheless, in addition to all the previously reported attempts to heal the damaged heart with stem cell therapy and/or cytokine treatments, global clinical success remains limited. That might be caused because, as a consequence of a MI, apart from cardiomyocytes lost, dynamic changes in the composition of the cardiac extracellular matrix (cECM) occur, regulating cardiac repair [172]. During the inflammatory phase of cardiac repair matrix metalloproteinases (MMPs) are activated, i.e., MMP1, MMP2, and MMP9 generating matrix fragments [173–175]. This fragmentation generates matrikines, i.e., elastin fragments, as well as collagen-derived peptides related to immune cells and fibroblast activation [176,177]. Finally, a provisional matrix is generated which may harbor inflammatory cells and new proliferative fibroblasts and endothelial cells [178,179]. In this scenario, it is of great importance to maintain the integrity of the cECM after a cardiac injury is a therapeutical target for clinical treatment. Some of them are related to the inhibition of MMPs although these interventions have produced different results depending on the heterogeneity of the human MI [180–182].

Several basic studies have demonstrated that matrices containing elastin are able to dive rat and mouse neonatal cardiomyocytes into dedifferentiation, proliferation, and clonal expansion process [183]. Moreover, in newts, it has been observed that after injury there is a matrix network comprising tenascin-C, fibronectin, and hyaluronan activating the regenerative program [184]. Bassat et al. [185] indicate that the administration of Agrin in adult mice after MI promotes cardiac regeneration although this therapy needs to be complemented with other mechanisms to obtain a functional regeneration. Additionally, for MI treatment a combination of matrix-based patches containing progenitor cells has shown enhanced effectiveness due to a recapitulation of the regenerative environment of the embryonic myocardium [186–188]. In the last decade, great efforts are focused on the generation of a human ECM containing cardiomyocytes derived from iPS to generate myocardial-like structures, although more studies are needed to launch this strategy for pre-clinical trials [189]. Moreover, there are some commercialized materials that are able to mimic the properties of the ECM, these are called hydrogels [190]. In general, hydrogel improves systolic and diastolic cardiac function, attenuates LV remodeling, reduces cardiac fibrosis, and supports angiogenesis after MI [191]. There are several studies using hydrogels, i.e., the injection of this kind of material in a rat MI model promoted an increased number of endogenous cardiomyocytes and maintained cardiac function [192]. In 2016, Mewhort and co-workers used a commercial acellular ECM derived from porcine intestine submucosa (SIS-ECM) over the epicardium after the ischemic injury (EIR). They observed that the use of this type of ECM does not promote myocardial fibrosis, limits the postoperative scar formation, there is a normal LV filling and epicardial thickening is enhanced. This treatment leads to stem cell mobilization increasing vascularization within the infarcted myocardium [193]. In the same line, decellularized urinary bladder extracellular matrix (UB-ECM) has been used in pigs after MI as an epicardial patch for LV repair. It was observed that UB-ECM promotes high revascularization in the damaged area and the enrichment of collagen and myofibroblasts, as well as a significant enrichment in cardiac marker expression [194]. Thus, these observations, pave the route to providing novel therapeutic approaches that might combine our current knowledge for the usage of stem cells, cytokines, and appropriated extracellular scaffolds.

Finally, and more recently, a modified RNA (modRNA) therapy for MI treatment has been reported. Such an approach is based on the use of a potent angiogenic factor, VEGF-A after ischemic injury [195,196]. Concretely, modRNA-VEGFA has a potential vascular and proliferative role during regeneration in ischemic heart disease patients. Moreover, it promotes capillary density and left ventricular ejection fraction increases, whereas it is observed a reduced infarct size and apoptotic cell frequency in animal models [197–199]. The first clinical trials demonstrated that VEGFA mRNA could have beneficial angiogenic effects [199]. modRNAs also have a cardioprotective role, for example, Huang et al. delivered modRNA for insulin growth factor (modRNA-IGF1) after heart injury in mouse, and they observed an increment in cardiomyocyte survival rate post-MI [200], although it has been demonstrated that modRNA-IGF1 can lead to the formation of epicardial adipose tissue leading to the formation of atherosclerotic plaques in the coronary vessels [201,202]. Although modRNAs is a promising cardiac therapy, further studies are needed to define the ideal administration method as well as the modRNA dosage in each delivery to achieve a long-lasting therapeutic effect [203].

In addition to myocardial infarction, structural cardiovascular diseases can be categorized into two major groups: (a) those leading to thickening of the ventricular chambers, i.e., hypertrophic cardiomyopathy (HCM), and (b) those leading to dilation of the cardiac chambers, i.e., dilated cardiomyopathy (DCM). Hypertrophic cardiomyopathy can be generated by germline mutations, being the most abundant those associated with sarcomeric proteins, but in many other cases, the onset of hypertrophic cardiomyopathy remains unclear [204,205]. Similarly, dilated cardiomyopathy can be associated with germline mutations, being the most representative of those associated with cell–cell communication proteins [206,207]. In both cases, hypertrophic and dilated cardiomyopathy can be consid-

ered an adaptation to the demanding requests to sustained normal cardiac performance and contemporary management strategies, including family genetic screening, risk stratification, thromboembolic prophylaxis, and cardioverter-defibrillation implantation provides cues to have normal or near-normal life expectancy. However, in some cases, such ventricular dysfunction progresses into an unsustainable situation leading to decompensated cardiac hypertrophy and/or dilation and thus to heart failure [208–211]. In these cases, a high risk of mortality is scored, and the medical treatment options are mostly reduced to heart transplantation.

As previously stated, dilated and hypertrophic cardiomyopathy are non-ischemic heart muscle diseases with structural and functional myocardial abnormalities. Concretely, DCM is a cardiac dysfunction generated by a progressive loss of left ventricle (LV) cardiomyocytes, leading to a thinner and stretched wall, as well as a larger chamber, making it harder for the heart to pump blood to the rest of the body. Likewise, HCM is a cardiac genetic disorder characterized by LV cardiomyocyte hypertrophy and disorganization, appearing in different areas of interstitial fibrosis. These effects generate an LV wall thickening characterized by a lower pumping capacity limiting the blood volume ejected by the LV in each heartbeat.

It has been widely evidenced that adult cardiomyocytes lost their proliferative potential soon after birth making them unable to heart repair [212], but in the last decade, it has been postulated that cardiomyocytes retain a very low proliferation rate in the adult heart [213–216]. Despite the poor ability of cardiomyocytes to proliferate, many efforts have been focused to achieve adult myocardial repair. Focusing our attention on cell therapy, a large battery of cell populations has been studied that could lead to heart repair within these structural cardiac diseases, particularly DCM (Figure 2).

In this line, a good source of cardiomyocytes is human embryonic stem cells or iPSCs. Direct injection or even a 3D generated cardiomyocyte tissue patches derived from these two cell populations have been assayed. After transplantation, it was observed that the new cardiomyocytes were not able to create a synchronous contraction jointly with the native cardiomyocytes, generating arrhythmogenic areas within the heart [217,218]. Moreover, cardiac progenitor cells are able to generate cardiomyocytes in vitro [219,220]. Considering this ability, cardiac progenitor cells and bone marrow-derived stem cells were used for cardiomyopathies treatment, trying to obtain proper engraftment of these two cell populations in the damaged area. After that, it was expected they could proliferate and differentiate into cardiomyocytes, but this attempt at heart repair failed [221,222]. Another cellular therapy, although it has not been applied in human trials yet, is the administration of growth factors using viral vectors to transdifferentiate fibroblasts into cardiomyocytes [223].

Different clinical trials have been conducted to treat DCM by using bone marrow-derived mononuclear cells or autologous bone marrow cells—one of them did not show any beneficial effect [224], whereas the others showed an improvement in LVEF [225,226]. Finally, a recent study, carried out by Hirai et al. [227], demonstrated that a DCM porcine model treated with cardiosphere-derived cells infusion improves cardiac function enhancing cardiomyocyte proliferation and angiogenesis, whereas myocardial fibrosis is reduced. This strategy is currently active in a phase 1a study with DCM pediatric patients [227]. Thus, waiting for such strategies is currently required.

Within the HCM context, the application of cell therapy has generated rather limited knowledge (Figure 2). Some years ago, Han et al. [228], analyzed the effects of pharmaceutical agents in an in vitro model of iPSC-derived cardiomyocytes, demonstrating the potential role of these cells in the development of personalized therapeutic medicine [228]. However, since then, limited information is available for stem cell therapy of HCM.

Electrical disturbances of the adult heart can be classified as those affecting the atrial chambers, i.e., supraventricular arrhythmias, those affecting the ventricular chambers, i.e., ventricular arrhythmias and those affecting the cardiac conduction system [229]. Supraventricular arrhythmias are the most frequent type of cardiac arrhythmias in the

human population, particularly atrial fibrillation. The prevalence of atrial fibrillation is almost 2% in the general population, raising up to 10% in the 80y + elderly [230,231]. The prognosis of atrial fibrillation is relatively benign in the early stages, i.e., onset as paroxysmal atrial fibrillation but can eventually lead to persistent and permanent atrial fibrillation, requiring pharmacological and subsequently surgical (ablation) interventions [232,233]. While our current understanding of the genetic and molecular bases of atrial fibrillation has greatly advanced over the last decade [234–237], our understanding of the cellular substrates underlying atrial fibrillation is still incipient, and therefore scarce attempts have been made to use regenerative medicine technology to heal the arrhythmogenic heart (Figure 2). Current strategies are focused on modeling in vitro systems that can provide hints for personalized precision medicine [238,239].

Ventricular arrhythmias are less prevalent than supraventricular arrhythmias, but the social burden is tremendous, and they frequently debut with syncope and/or sudden death [240–242]. Patients diagnosed with short QT, long QT, and Brugada syndrome are immediately prompted for cardioverter pacemaker implantation, and clinical management, if timely coursed, provides a rather normal or near-normal life expectancy. In line with evidence reported for atrial fibrillation, scarce attempts have been performed to design cellular therapeutic strategies to heal ventricular arrhythmias, while important efforts are currently underway to generate in vitro cellular models for such cardiac pathologies (Figure 2) [243–246].

Alternatively, impairment of discrete components of the cardiac conduction system are also reported, such as sick sinus syndrome [247], atrioventricular node block, and bundle branches blockage [248–251], respectively. Clinical management in those cases is variable, as it is, in many cases, the origin of such electrical disorders. Resynchronization therapy is currently an option, yet it can lead to electrical and/or mechanical desynchrony [252–256]. Therefore, searching for strategies to provide physiological synchrony is desirable and several approaches have been already performed to generate biological pacemakers [257,258]. Furthermore, the generation of in vitro cellular models will greatly enhance the discovery of such endeavors [259,260].

3. Conclusions and Perspectives

We have provided in this review a global overview of cardiogenesis, our current knowledge of congenital heart diseases, and how such defects can be repaired. Similarly, we also provided a global overview of the most common adult cardiac pathologies and the constant efforts to design novel therapeutic strategies. It is important to realize in the context of the upcoming World Heart Day, that synergic collaborations, between basic, translational, and clinical cardiologists are essential to boost these efforts, as they can be constantly observed in the emerging field of cellular therapy and personalized medicine.

If we look in-depth into the cardiac development field, cardiovascular developmental defects occurring along embryogenesis can lead to congenital defects that are incompatible with life, and to date no intervention can provide a solution, i.e., those affecting precardiac mesoderm configuration and/or heart field deployment. On the other hand, several defects can be surgically corrected either intrauterine, prenatally, and/or postnatally, providing novel and advanced therapeutic solutions for such congenital heart diseases. Understanding the cellular and molecular bases of cardiac development, and thus their plausible impairment consequences will continue to provide insights to mitigate the prevalence of cardiac congenital heart diseases. In particular, understanding the molecular cascades that govern cardiac development provided the bases for genetic screening of gene mutations that can serve as guidelines to direct adequate genetic counseling.

On the other hand, adult cardiac pathologies are routinely treated worldwide. Pharmacological and/or surgical treatments are currently available for both structural and electrophysiological cardiac pathologies. However, in some cases, such pharmacological and/or surgical procedures are suboptimal and thus new approaches are constantly searched. Over the last decades, we have witnessed a great interest in the development

of novel strategies using cell therapy. Distinct cell sources have been assayed, both at preclinical and clinical stages; however, the outcome for cardiac repair is still limited. A requirement to understand how each cell source works and try to avoid some undesired responses is compulsory. Furthermore, the local and exogenous cellular secretome and the extracellular environment should be taken into account, as emerging evidence supports a beneficial role if properly modified. As consequence, upcoming regenerative approaches designed to heal the damaged heart might require promising strategies of combining cell and niche modification therapies to promote cardiomyocyte proliferation while avoiding inflammation and immune responses. In addition, emerging gene therapy approaches using modified mRNAs are also coming to light. We are confident that within the coming years such therapeutic approaches will be gained and application in the clinical scenario would eventually be more broadly applicable.

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