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Review

Stem cells and cardiac arrhythmias

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Abstract. Recent discoveries in the physiology and pathology of myocardial progenitor cells have allowed researchers to better understand a variety of cardiac pathologies and look at the pathophysiology of arrhythmias from a different perspective. Since the myocardium is composed of a syncytium of electrically interconnected cells, the process of incorporation of newly formed or imported cells into its structure is particularly important. Progenitor cells are stimulated by spontaneous electrical activity, a lengthy action potential, and easily induced triggering activity. All these can lead to arrhythmias development *via* the three classical mechanisms (reentrancy, automatism, or triggering activity). Transplanted stem cells can influence the electrophysiological properties of cardiomyocytes, thus creating a proarrhythmic substrate. The islets of unbound cells can form an anatomical block, causing unidirectional blockages and recurrent arrhythmias. Similarly, stem cells are capable of establishing heterotopic excitation foci with cardiac stimulatory activity. Finally, the paracrine factors produced by stem cells can also cause proarrhythmic effects. The review examines the factors that influence the proarrhythmic properties of administered stem cells and the mechanisms of arrhythmia development. The results indicate that further research should be carried out to establish the possible impact of stem cells on the development of arrhythmias.

Key words: Arrhythmia — Heart rhythm — Proarrhythmic substrates — Progenitor cells — Stem cells

Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; CDCs, cardiosphere-derived cells; CSCs, cardiac stem cells; CSps, cardiospheres; ECPSCs, endogenous cardiogenic progenitor cells; ECSCs, endogenous cardiogenic stem cells; ERP, effective refractory period; ESCs, embryonic stem cells; hPSCs, human pluripotent stem cells; HSCs, hematopoietic stem cells; IGF-1, insulin-like growth factor 1; MSCs, mesenchymal stem cells; SCM, skeletal myoblasts.

Introduction

According to the concept of «structural homeostasis» (Yushkov et al. 2019), the efficiency and reliability of functioning of an individual organ or system are ensured by the fact that it is formed from stem cells and constantly renewing specific elements (like the assembly of a children's Lego construction set). In this case, the specific elements are formed in the or-

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gan itself. If the latter is of high quality and the interaction between them is reliable, then the system itself is reliable and the organ is healthy. If qualitatively defective elements appear in it and, at the same time, qualitatively defective elements are not sufficiently eliminated or the normal interaction between the elements is disrupted, then this leads to organ pathology. Thus, the quality of progenitor cells and their interaction with the microenvironment ("niche" – functional system) determine the nature and duration of the disease (this mechanism combines = common hereditary and non-hereditary diseases). Arrhythmias, abnormalities of the heart's rhythm, are a perfect example of this concept.

Basic characteristics and renewal of cardiomyocytes and cardiac stem cells

Although the adult mammalian heart was originally considered a terminally differentiated organ, it can produce new cardiomyocytes and microvasculature throughout life. Cardiomyocyte renewal occurs at a rate of 1% *per* year at the age of 25 and slows with age (Bergmann et al. 2009). This phenomenon is provided by a small population of cardiomyocytes (Ali et al. 2014), the so-called resident cardiac stem cells (resident CSCs), possessing such properties as self-renewal and multipotency, which, however, are limited by the myocardial phenotype (Nadal-Ginard et al. 2005). They can give rise to cardiomyocytes, smooth muscle, and endothelial cells with the possibility of replenishing coronary microcirculation (Torella et al. 2006). This small pool of progenitor cells provides structural myocardial homeostasis, serves as a cell source for the replenishment of cardiomyocytes after injury and is involved in the remodeling process (Torella et al. 2006).

Cardiospheres (CSps; the term introduced by Messina et al. in 2004) can act as a source of stem cells (Messina et al. 2004). These self-renewing multicellular clusters were obtained from postpartum biopsy samples and have the properties of adult stem cells of the heart (Barile et al. 2013). CSps are a mixture of different types of cells, including resident CSCs, spontaneously differentiated cardiomyocytes, and even vascular cells (Messina et al. 2004). The number of cells positive for the c-Kit stem cell marker in the myocardium of healthy people is quite high, about 89964 ± 31224 in 1 cm^3 of tissue in children up to 3 years of age, but decreases with age, with approximately 11353 ± 9031 cells in persons 17–30 years of age, 8518 ± 2643 cells in persons 35–45 years of age, and counting only 3327 ± 234 cells in 1 cm^3 in the areas of chronic post-infarction aneurysm (Dergilev et al. 2010).

The problem of stem cell arrhythmogenicity has already manifested itself in the initial stages of its use for the treatment of heart disease (Zhang et al. 2002). However, researchers' attention is mainly focused on studying the state of transplanted cells, their differentiation, and survival in the affected organ, which create the risk of developing arrhythmias, although the latter occur in patients before and without cell therapy. The role of endogenous progenitor cells, including resident ones, is practically not reflected in the literature. Arrhythmias can be assumed to be the result of disturbances in the normal differentiation of resident stem cells into cardiomyocytes and pacemakers in the process of physiological renewal. In this review, we have tried to systematize the available data supporting this idea.

Embryonic stem cells (ESCs) are the population of cells that can differentiate into mature heart cells and can be phenotyped by the nature of the ion current, mechanisms of regulation of intracellular calcium concentrations and expression of connexin (Laflamme et al. 2007). It has been shown that ESCs are characterized by fast sodium current, L type Ca^{2+} current, "funny" current (If) and inward rectifier potassium channel current (IK1) (Satin et al. 2004; Sartiani et al. 2007), and an immature relation-ship between contraction and relaxation (Dolnikov et al. 2006). When ESCs are implanted into the damaged myocardium, additional zones of excitable cells are created, which form gap junctions not only with other ESCs but also with the surviving cardiomyocytes of the heart muscle.

Using various membrane markers and transcription factors, several types of endogenous cardiogenic stem cells and endogenous cardiogenic progenitor cells (ECSCs/ECPSCs) have been identified. When it comes to ECSCs, there were at least seven resident populations of the heart in an adult mammal heart, including the human heart (due to the single antigen used for their primary isolation) (Smith et al. 2014). The description of these different ECSCs populations (Table 1) led to a paradoxical situation, when the heart, previously described as a nonrenewable organ, has become the organ with the largest number of different types of resident stem and progenitor cells. However, in addition to Islet-1 (ISL-1) ECPSCs, which are the direct offspring of a specific embryonic population of ECPSCs and are present in very small numbers in the adult heart (Genead et al. 2009), and epicardial stem cells (also called cardioresident colony-forming units of fibroblasts, presumably derived from the proepicardial organ (Chong et al. 2011)), the significant overlap between their primary and secondary markers indicates that different populations of ECSCs/ECPSCs are closely related. Thus, it is not surprising that almost all adult ECSCs previously defined as distinct types of cells are likely to represent various developmental and/or physiological stages of a unique resident type of stem cells with a multipotent regenerative capacity (Dey et al. 2013; Smith et al. 2014).

Furthermore, both hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs), the bone marrow cells that could differentiate into different types of stem cells,

Table 1. Different types of cardiac progenitor cells

Phenotype	Markers	Source
c-Kit + ECSCs	CD34–, CD45–, Sca-1+, Abcg2+, CD105+, CD166+, GATA4+, NKX2-5+/– or low, MEF2C+	mouse, rat, dog, pig, homo
Sca-1 + ECSCs	CD34–, CD45–, FLK1–, c-Kit+/– or low, GATA4+, NKX2-5+/– or low, MEF2C+	mouse, homo
Side population cells	CD34+, CD45+, Abcg2+, Sca-1+, c-Kit+, NKX2-5–, GATA4–	mouse
CSps -derived cells	CD105+, CD34+, CD45+, Abcg2+, Sca1+, c-Kitlow	mouse, rat, dog, pig, homo
CFUFs	Sca-1+, PDGFR-α+, CD31–, c-Kitlow, CD45–, FLK1–, CD44+, CD90+, CD29+, CD105+	mouse
Cardiac mesangioblasts	CD31+, CD34+, CD44+, CD45–, Sca-1+, c-Kit+	mouse, rat
ISL-1 ECPSCs	CD31–, Sca-1–, c-Kit–, GATA4+, NKX2-5+	mouse, rat, homo

ECSCs, endogenous cardiogenic stem cells; CSps, cardiospheres; CFUFS, colony-forming unit fibroblasts; ECPSCs, endogenous cardiogenic progenitor cells.

were found in the myocardium. One of the populations, MSCs, differentiates into cells of neuronal type, which can be implanted in the ischemic brain (Zhao et al. 2002), while CD34(+) cells have been shown to induce therapeutic angiogenesis in animal models of myocardial ischemia, thus contributing to preservation of cardiac function (Mackie and Losordo 2014).

There is a certain hierarchy between progenitor cells, according to which, the less differentiated a cell, the greater its potency and regenerative potential. In this regard, bone marrow progenitor cells (HSCs and MSCs) found in the myocardium occupy an intermediate place between ESCs and resident stem cells of the heart. Although a direct link between resident stem cells and cardiomyocyte renewal in the physiological aging process has not yet been established, it is widely accepted that they are likely involved in the formation of new cardiomyocytes after heart damage and can reduce the risk of developing concomitant diseases. At the same time, its defective microenvironment under pathological conditions limits the regenerative capacity of the myocardium, while the transplantation of *ex vivo* proliferating stem cells promotes the replacement of tissue damage areas due to their direct transdifferentiation into cardiomyocytes, a proliferation of resident stem cells, and inducing the cardiomyocytes to reenter the cell cycle (Mayfield et al. 2014).

Therefore, resident stem cells provide physiological renewal of the myocardium, while under pathological conditions exogenous progenitor cells migrate to the site of injury (and therefore they are proposed to be used in the treatment of heart diseases) and thus, after myocardial infarction and heart failure, cardiomyogenesis increases (Senyo et al. 2013). At the same time, the regenerative potential of resident stem cells, which ensures the renewal of cardiomyocytes in a healthy heart, turns out to be insufficient to eliminate tissue defects after extensive damage, and the precursors' migration (i.e. from the bone marrow) is needed. With that, tissue damage by itself forms strong chemotactic signals for stem cells, creating the basis for their recruitment (mobilization) towards damaged cells. In experimental myocardial infarction, intramyocardial, intracoronary (Chen et al. 2004; Amado et al. 2005), or intravenous (Nagaya et al. 2004) delivery of MSCs resulted in their migration to injured areas, preventing ventricular remodeling, and dramatically restoring cardiac function (Gnecchi et al. 2005). Clinical studies later corroborated the therapeutic impact of MSCs in myocardial damage, however, the clinical effect was sometimes rather mild (Wollert et al. 2004; Assmus et al. 2006).

It turned out that only apoptotic cardiomyocytes provide MSCs recruitment. Neither live nor necrotic cardiomyocytes possess this property. The connection between apoptotically dying cells and recruited cells with regenerative potential is provided by their interaction with the HGF/MET receptor (Vogel et al. 2010). Thus, the migration of MSCs to apoptotic tissue cells is HGF-mediated.

The role of the SDF-1/CXCR4 receptor as a trigger for the recruitment of bone marrow progenitor cells into the left ventricle of the heart has been demonstrated (Abbott et al. 2004). Clinical studies showed that CD34-positive progenitor cells were involved in myocardial repair and regeneration, which contributed to the preserved function of the heart (Mackie and Losordo 2011). Furthermore, prior to coronary occlusion, injections of recombinant SDF-1 into the left ventricular cavity greatly reduced the extent of the infarction in mice (Hu et al. 2007). Ziegler et al. (2012) developed a bifunctional protein consisting of an SDF-1 domain and a glycoprotein VI (GPVI) domain with high binding affinity to the SDF-1 receptor CXCR4 and extracellular matrix proteins that become exposed after tissue injury to improve the efficiency of SDF-1-mediated heart protection (Ziegler et al. 2012). After an experimental myocardial infarction, SDF1-GPVI was found to trigger the migration of

CXCR4 receptor-positive bone marrow progenitors, resulting in rapid differentiation of endothelial cells, cell survival, and a strong proangiogenic effect. SDF1 released by active platelets promoted the entry of CD34 positive progenitor cells into arterial thrombi and their differentiation into endothelial progenitor cells *in vivo* (Massberg et al. 2006; Stellos et al. 2008). Platelets also affected those effects of SDF1-mediated progenitor cells. Clinical studies found that platelet SDF1 content in patients with myocardial infarction corresponded to the number of circulating progenitor cells and was associated with an improved prognosis and restoration of left ventricular function (Stellos et al. 2009; Geisler et al. 2012). Later, a study on the role of IGF-1 (insulin-like growth factor-1) in the regulation of the homing of MSCs has appeared (Li et al. 2007; Huang et al. 2012).

The migration of progenitor cells into the zone of cardiac injury in myocardial infarction provides a rationale for cell therapy in heart disease. Skeletal myoblasts (SCMs) were probably one of the first types of cells used in cardiac pathology for replacement therapy. Although these cells may contract and have excitability, their contraction-relaxation coupling is fundamentally different from that of typical cardiomyocytes (Reinecke et al. 2009). Undifferentiated myoblasts can express connexins and form gap junctions in the absence of differentiation, but they lose this ability in a new substrate and may lack mechanical synchronization and electrical integration necessary to form an islet.

Resident CSCs (Beltrami et al. 2003; Smith et al. 2008) are considered to be suitable for the treatment of heart disease. When injected through the aortic root, c-Kit heart cells derived from a normal rat heart invade the zone of myocardial infarction and stimulate tissue regeneration, enhancing the function of the left ventricle. However, in the current literature, there is no discussion of heart rate stability or instability. Furthermore, cells expressing Kit^+ are believed to represent bone marrow cells rather than heart cells (Macia and Boyden 2009).

Cardiosphere-derived cells (CDCs) have shown encouraging effects in animal and clinical studies (such as the CADUCEUS trial) (Malliaras et al. 2013). The ALLSTAR (The ALLogeneic Heart STem Cells to Achieve Myocardial Regeneration) trial found that intracoronary CDC administration resulted in improved segmental myocardial function without a significant increase in the frequency of ventricular arrhythmias, laying the groundwork for its use to reduce the necrosis zone in patients with myocardial infarction (Ostovaneh et al. 2021).

Mononuclear bone marrow cells were first used in clinical practice in 2001, and soon advanced to the stage of clinical trials as early therapy for myocardial infarction (Strauer et al. 2011). This rush was accompanied by a small number of preclinical experiments in mice, which showed a high level of myocardial engraftment and the ability to differentiate into cardiomyocytes (Orlic et al. 2001). Thus, the *in vitro* arrhythmogenic capacity of mouse cardiomyocytes derived from multipotent ESCs and embryonic cancer cells was described by Zhang and colleagues in 2002 (Zhang et al. 2002).

Recent findings on the physiology and pathology of myocardial progenitor cells have allowed researchers to better understand numerous cardiac pathology processes and examine the pathophysiology of arrhythmias from a slightly different angle. Since the myocardium contains a syncytium of electrically linked cells, the incorporation of newly formed or imported cells into its structure is particularly important.

A heterogeneous population of cardiac endogenous progenitor cells produces CSps in suspension cultures, which are made up of clonally generated cells. The nucleus of such a sphere contains proliferating c-Kit-positive cells, with differentiating cells expressing cardiac and endothelial cell markers at the periphery (Barile et al. 2007). Heart cells produced from human pluripotent stem cells can easily enter a damaged heart and generate a spontaneous action potential (Chong et al. 2014). Implanted cells can become a source of electrical excitation if they have aberrant electrophysiology and/or spontaneous electrical activity.

Stem cells and arrhythmias

Electrical properties of cells (generation of potentials and conductivity)

Ionic currents in undifferentiated and differentiated MSCs have been found to have a resting potential between −30 mV and −40 mV (Heubach et al. 2004; Valiunas et al. 2004; Li et al. 2006; Sundelacruz et al. 2008). Resting potentials of other cardiac cells range from −85 mV to −90 mV for normal cardiomyocytes, 90 mV for His-Purkinje system cells, 60 mV for atrioventricular node cells and 55–60 mV for sinus node cells. As a result, the resting potential of MSCs is the most similar to that of sinus node cells. Furthermore, studies of ESC cellular electrophysiology demonstrated a modest increase in their action potential and trigger activity (Igelmund et al. 1999; Zhang et al. 2002; Kehat et al. 2004). This congenital pacemaker activity is believed to be caused by high input impedance and sodium current density (Sartiani et al. 2007).

Classical mechanisms (reentrancy, automatism, or triggering activity) contributing to arrhythmogenic activity

Progenitor cells are characterized by spontaneous electrical activity, long action potentials, and easily induced trigger ac-

tivity. All of these can lead to the development of arrhythmias *via* the three classical mechanisms (reentrancy, automatism, or triggering activity) (Mocini et al. 2005). As a result, the sinus rhythm of the animal might be disturbed by the rhythm of newly generated or transplanted cells.

Stem cells and reentry

The term reentry denotes a phenomenon in which an electrical impulse, moving in a closed circle (loop, ring) around a fixed anatomical structure (infarction scar, zones of functional deceleration, and blockage of conduction in a viable myocardium), returns to the place of its origin (circus movement).

A multitude of mechanisms associated with progenitor cells could trigger the formation of a functional deceleration zone and conduction blocking. Even though these cells can express plasma membrane ion channel currents (Heubach et al. 2004), when a large number of electrically uncontrollable cells appear in the myocardium, as in the case of administration of electrically nonexcitable autologous mononuclear cells from the bone marrow, they can act as current absorbers and inhibit the propagation of action potentials. The injection of fibroblasts and their progenitors into the atrioventricular node reduces conduction rate as well (Bunch et al. 2006; Lyon et al. 2008). In the absence of an electrical connection, stem cells can lead to expansion of the conduction blockade area. For example, the human ESCs that stain positive for connexin 43 do not have functional electrical interaction (Kehat et al. 2004). They are clustered within the infarction scar or border zone after successful transplantation from the bone marrow into an adult's ischemic heart, but they do not demonstrate intracellular calcium transition mechanisms in response to membrane depolarization in situ (Scherschel et al. 2008).

The number of cells and how they reach the myocardium determine the efficiency of stem cell therapy and the development of arrhythmias. As a result, the intracardiac route tends to generate cell clusters (Leobon et al. 2002; Reinecke et al. 2002).

The conduction between cardiomyocytes is also slowed by stem cells. The sodium-dependent conduction between the host myocardium and stem cell areas is provided by sodium current-producing cells (ESCs). If propagation is solely dependent on Ca^{2+} (the so-called slow response (The Rockefeller University 1975; Cranefield and Dodge 1980), the implanted stem cells generate delayed conduction zones, laying the groundwork for reentry (Macia and Boyden 2009). Long-term co-incubation of human MSCs with newborn rat cardiomyocytes demonstrated a low conduction velocity (from 4 to 17 cm/s) and a reduction in resting potential to −40 mV (against 67 mV in the norm), implying potential arrhythmogenicity (Pijnappels et al. 2006). Conduction is similarly inhibited after SCM are transplanted into the hearts of dogs with and without infarction (Fouts et al. 2006), why the Cardiomyocytes' action potentials are lengthened and repolarized are slowed by MSCs (Macia and Boyden 2009).

Stem cells and abnormal automatism

If other excitable cells display higher spontaneous activity than the original endogenous pacemaker cells, normal sinus rhythm can be lost. Human ESCs (hES) that produce clusters of spontaneously beating cardiomyocytes may also be like this. Thus, Kehat et al. (2004) demonstrated their ability to operate as a rate-responsive biological pacemaker by transplanting clusters of spontaneously beating cardiomyocytes produced from hES cells into a pig with total atrioventricular blockage (Kehat et al. 2004). In contrast to experiments in small animals (Shackleton et al. 2006; Stingl et al. 2006), transplantation of cardiomyocytes obtained from ESCs to non-human primates (monkeys) with myocardial infarction resulted in the appearance of non-lethal arrhythmias in non-human primates (monkeys) with myocardial infarction (Chong et al. 2014). This is likely due to the lower heart rate in primates. Higher heart rates favor excitation conduction along pathways, as shown in mice (600 beats *per* min) and guinea pigs (230 beats *per* min), while macaques (nonhuman primates) with heart rates between 100 and 130 beats *per* min are more susceptible to automatic transplantation and ventricular arrhythmias (Chong et al. 2014; Almeida et al. 2015).

Furthermore, during the differentiation process to the final mature phenotype, stem cells might go through intermediate stages when the internal electrical properties of cell membranes are unstable, potentially contributing to rhythm abnormalities (Zhang et al. 2002). Depolarization of the cardiomyocyte's resting membrane should be predicted by the following connection (Xie et al. 2009). The degree of depolarization is determined by the membrane potential of the connected stem cell, as well as the degree of intercellular communication (communication resistance) between two cells and cell size (Tan and Joyner 1990; Henriquez et al. 2001).

The excitability of cells reduces when the resting membrane is depolarized by more than 30 mV; sodium channels, which are normally closed by voltage, are inactivated, resulting in a decrease in the rate of rising and conduction (Shaw and Rudy 1997; Kleber and Rudy 2004; Hubbard et al. 2007). In addition, the plateau period shortens and the duration of the action potential lengthens. Increased action potentials can cause tissue-level unidirectional obstruction, which can contribute to the formation of recurrent arrhythmias (de Bakker et al. 1993; Coronel et al. 2013).

The establishment of "current sink" or "current source" events may be caused by electrotonic connections between

stem cells and cardiomyocytes (Rohr 2004). This occurs when the load of the excited region supplying the depolarizing current does not match the amount of current necessary to excite the next region (Rohr 2004; Smith and Coronel 2014). The depolarization of cardiomyocytes by stem cells suggests that the regions where stem cells are applied are more depolarized and that the depolarizing current emitted by these heterocellular regions is insufficient to stimulate the regions of endogenous cardiomyocytes around them (Smith and Coronel 2014).

Cardiomyocyte depolarization not only slows the rate of ascent and conduction but also affects the duration and shape of the action potential. Changes in restorative properties and effective refractory period (ERP) can lead to arrhythmias (Qu et al. 1999; Tran et al. 2007). ERP, along with conduction deceleration and unidirectional blocking, plays an important role in the development of recurrent arrhythmias as was shown in experimental myocardial infarction in pigs, where intravenous MSC therapy reduced ERP and led to the development of arrhythmias (Price et al. 2006).

Another mechanism of arrhythmias is the creation of heterogeneity of repolarization in cells. The duration of repolarization is important for the heart's electrical stability, and increased dispersion of the action potential's duration is a proarrhythmic substrate for the induction of functional heart block (Akar and Rosenbaum 2003). The electrical excitability of therapeutic cells should ideally be equal to that of the host myocardium's action potential. However, this does not apply to stem cells, which have a much shorter action potential, and the interaction of electroactivated cells with varied action potential durations with cardiomyocytes enhances repolarization heterogeneity. As a result, when the action potential in neighboring cardiomyocytes is in the plateau phase, stem cells exit the refractory period and become active, producing a locally propagating wave of excitation that, due to the same mechanisms, can propagate further, passing to adjacent excitable areas. As a result of this chaotic, continuous, and spreading excitement, fibrillation can occur (Salama and Choi 2007).

It has been demonstrated that if implanted cells occupy a small area (approximately 200 m by 20 m); their intrinsic cardiac stimulatory activity cannot overpower the normal sinus rhythm (Kehat et al. 2004). Cells produced from hES, on the other hand, can generate pacemaker potentials that can be exploited for biopaculatory treatment of bradyarrhythmias employing biopacemakers by producing greater dense areas of implantation (Qu et al. 2003; Plotnikov et al. 2004; Xue et al. 2005). Surprisingly, after engraftment *in vivo* of only ESCs, fibroblasts, or SCM, a rather comprehensive study of mice hearts after myocardial infarction (Roell et al. 2007) did not even mention the enhancement of spontaneous automatic rhythms.

Stem cells and triggered activity

Triggered activity is impulse initiation in cardiac fibers that is dependent on afterdepolarizations (Smit and Coronel 2014).

The interaction of stem cells with cardiomyocytes

In general, key factors involved in the development of arrhythmias are: arrhythmogenic substrates, including ion channel dysfunction on the background of inflammation and oxidative stress, which also occurs during stem cell implantation, trigger – a high level of intracellular calcium, acidosis, and modulating elements – a change in autonomic tone (Andelova et al. 2020).

Recent studies, which note an important role in the development of arrhythmias of intercellular communication mediated by Cx semichannels, as well as pannexin channels, summarized in several reviews, are very attractive (Andelova et al. 2020; Dhein and Salameh 2021). The heart works as a functional syncytium, which is realized through intercellular interaction supported by gap junction channels. These channels connect two adjacent cells. Each cell contributes to a hexameric hemichannel (connexon). Connexins that form them are a family of proteins that consist of 21 isoforms in humans and 20 in rodents. In the heart, the main isoforms are Cx43 (43 kDa connexin, ubiquitous), Cx40 (mainly in the atria and conduction system), and Cx45 (between cardiomyocytes and fibroblasts). Gap junctions are subject to remodeling processes in cardiac diseases such as atrial fibrillation, myocardial infarction, or cardiomyopathy (Dhein and Salameh 2021). A decrease in connexin expression can lead to a decrease in conduction velocity.

Thus, MSCs and newborn rat cardiomyocytes generate functionally active gap junctions (nexuses) containing Cx43 during co-culturing (Beeres et al. 2005; Chang et al. 2006; Pijnappels et al. 2006). The introduction of tetrodotoxin in these cultures allowed researchers to demonstrate that heterocellular communication is the leading mechanism of conduction slowdown, as the synchronization of two asynchronously beating fields of cardiomyocytes requires electronic communication between MSCs and cardiomyocytes (Beeres et al. 2005; Askar et al. 2013). Thus, the elimination of Cx43 in human MSCs or carbenoxolone administration led to a failure in synchronization of two asynchronously beating fields of cardiomyocytes (de Croot et al. 2003; Beeres et al. 2005; Pijnappels et al. 2006). Therefore, it appears that a more efficient grip is beneficial, while a defective grip is potentially arrhythmogenic.

Transplanted stem cells can functionally bind with host cells (Rubart et al. 2003) and form a functional and synchronized network with the host myocardium (Chong et al. 2014). They can influence the electrophysiological properties of cardiomyocytes, thus creating a proarrhythmic substrate (Chang et al. 2006; Askar et al. 2013).

The weakening of intercellular contacts because of decreased connexin expression (Lyon et al. 2008) may be a mechanism for the development of arrhythmias, resulting in the formation of an anatomical block upon the appearance or introduction of new cells and a change in the electrical properties of recipient tissue. This is partly dependent on the type of transplanted cell, as connexin-43 expression is essential for both electromechanical integration and protection against electrical instability after transplantation (Lyon et al. 2008). Connexin-43, a membrane protein from the family of gap junction proteins encoded by the human GJA1 gene that allows low molecular weight compounds to diffuse between neighboring cells and is involved in the synchronization of heart contractions and embryonic development, is one of the key players in this process. After injection into the infarction border zone in the mouse heart, ESC-generated cardiomyocytes display connexin-43 and exhibit excellent communication with host cardiomyocytes (Roel et al. 2007). In mouse myocardial infarction, these cells improve suppressed excitability in the border zone, increasing the conduction rate and reducing the development of conduction blockage. Inducible ventricular tachycardia is reduced because of these changes in biophysical parameters. Bone marrow MSCs from the bone marrow also express connexin-43 and have been shown to improve cardiac function in animal models of myocardial infarction. The development of gap junctions between human MSCs and rat neonatal cardiomyocytes with the conduction of electric potentials can be seen when they are cocultured (Chang et al. 2006). Skeletal myoblast transplantation can improve contractile function in patients with left ventricular dysfunction and chronic myocardial infarction (Hagege et al. 2006), but skeletal myoblasts lack connexin-43 expression (Al Attar et al. 2003; Leobon et al. 2003), and experiments have shown that they cannot form gap junctions with cardiomyocytes in vitro (Reinecke et al. 2000) and *in vivo* (Scorsin et al. 2000; Leobon et al. 2003; Fouts et al. 2006).

Research manuscripts reporting large datasets that are deposited in a publicly available database should specify where the data have been deposited and provide the relevant accession numbers. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during the review. They must be provided prior to publication.

Interventional studies involving animals or humans and other studies that require ethical approval must list the authority that provided approval and the corresponding ethical approval code.

Anatomical block

Cells that do not fit the syncytium can be positioned between cardiomyocytes in such a way that they break or inhibit the creation of contacts between them (Duffy 2008). The introduction of embryoid cells into the ventricular myocardium demonstrated the fundamental possibility of the formation of new islets of cells with cardiac stimulatory activity (Lyon et al. 2008). Islets of unbound cells can form an anatomical block, causing the front of the electric wave to seek an alternative path, resulting in a long activation period in a given region. This might cause unidirectional blockage and recurrent arrhythmias if it causes a slowdown in heterogeneous conduction (de Bakker et al. 1993).

Microenvironment and differentiation of CSCs

Embryonic cardiac cells can differentiate into both cardiomyocytes and pacemaker cells. Experiments demonstrating the impact of the microenvironment on cardiac stem cell differentiation and pacemaker cell formation are accumulating. After co-culturing of hPSCs, which can differentiate into various types of cardiac cells, with visceral endoderm-like cells of the END-2 line, spontaneously beating clusters (50 beats/min) were observed (Schweizer et al. 2017). At this early stage of development, these clusters express the pacemaker-specific genes HCN4, TBX3, and TBX18, while the sarcomeric gene products are still minimal.

The shape of the action potential at this stage is similar to that of nodal-type cells, and the slow rates and small amplitude indicate that these cells are still immature. Transferring these clusters from the serum-free coculture medium to the medium enriched with fetal bovine serum shortly after they begin to beat increases nodular cell differentiation while suppressing cardiomyogenic differentiation. The distinctive genes of the sinoatrial node remain at a high level after 6 weeks under these conditions, while the functioning transcripts of the myocardium (NKX2.5, TBX5) are at a low level. Regular activity and a high frequency of beats (70–90 beats/min) characterize the clusters, which are triggered by spontaneous Ca^{2+} transient processes that resemble the calcium hourly properties of genuine cardiac pacemaker cells. In co-culture experiments, they can excite neonatal rat ventricular myocytes and are sensitive to adrenergic/cholinergic stimulation (Schweizer et al. 2017).

Ca^{2+}-activated potassium channels regulate not only the fate of neural stem cells (high and medium conductivity channels) but also the differentiation of pluripotent cells into cardiac cells. Due to their activation in ESCs by 1-ethyl-2-benzimidazolinone, a specific subtype of cardiomyocytes, pacemaker-like (nodal) cells, is generated without the need for genetic modification (Kleger et al. 2010).

According to the literature, the absence of the anexogenous inhibitor Wnt, which was added to enhance cardiomyocyte yield during ESC development, resulted in a higher yield of spontaneously beating cardiomyocytes with action potential parameters similar to those of natural sinoatrial

node pacemaker cells. The increase in the expression of genes and gene products that mark nodal cells (Hcn4, Tbx18, Tbx3, and Shox2) characterized the cell phenotype. The exogenous ligand Wnt3a, which enhances canonical Wnt/-catenin signaling, similarly increases cardiac stimulating myocyte output while lowering pancardial differentiation positive for cTNT. On the other hand, inhibitors of Wnt/-catenin signaling cause an increase in cardiomyocyte growth at the expense of pacemaker cells and improve heart function after myocardial infarction (Moon et al. 2017; Liang et al. 2020). Therefore, endogenous Wnt signaling stimulates the creation of cardiomyocytes, whereas its inhibition promotes the generation of cardiac pacemakers (Liang et al. 2020).

Bone marrow mesenchymal cells, or MSCs, are now thought to be the best stem cells for biological transformation into cardiac stimulatory cells. When the cardiac-specific transcription factor TBX18 (t-Box protein 18) is introduced into MSCs, these cells are transformed into pacemaker cells with stable cardiac stimulation activity (Hu et al. 2014; Li et al. 2018).

Pluripotency – the formation of other types of cells

Due to their pluripotency, stem cells can differentiate into numerous types of cells, which can contribute to the development of arrhythmias. The path of development of progenitor cells is thus dictated by changes in their morphology (McBeath et al. 2004). It was discovered that when bone marrow cells were forced to take a round form, 45% of them began to change in the direction of adipose tissue cells, while 50% of the cells forced to take an elongated shape began to transform to the phenotype of bone tissue cells (McBeath et al. 2004). Shear stress accelerates the formation of hematopoietic progenitor cell colonies by increasing the friction force caused by blood flow across the surface of cells that line the aorta (Adamo et al. 2009). The differentiation of stem cells may play a role in the development of arrhythmogenic right ventricular cardiomyopathy (ARVC), a heart muscle disease characterized by partial or complete progressive fibro-fatty replacement of the right ventricular myocardium and associated arrhythmias (Frank et al. 1978; Marcus et al. 1982). As a result of inhibition of canonical Wnt signaling in ARVC, it was discovered that a fraction of second heart field progenitors converted primarily into adipocytes (Lombardi and Marian 2010).

It is possible that the creation of the os cordis is also a result of stem cell differentiation. In the 1960s, Selye demonstrated bone development in the myocardial in rats by ligating the apex of the heart (Feinstein et al. 1957). Os cordis has been documented in otters, camels (James 1965; Egerbacher et al. 2000; Mohammadpour 2007; Balah et al. 2014; Daghash and Farghali 2017), and chimpanzees (Moittié et al. 2020), but not in other animals. The os cordis is found near the junction of the atrial and interventricular septa, and spreads anteriorly into the right atrioventricular ring. A second bone can occasionally be found in the left atrioventricular ring (James 1965). Although the exact position, size, and quantity of the os cordis vary by species, it is always found near the AV node in the *trigonum fiobrosum* and is made up of trabecular bone, bone marrow, and fat. Although its role is unknown, it is believed to support and protect the heart valves (James 1965; Frink et al. 1974). Other animal species with cartilage (cartilage tissue) in their cardiac skeletons include horses, pigs, dogs, cats, mice, rats, snakes, white rhinos, and Syrian hamsters (Schummer et al. 1981; Young 1994; Duran et al. 2004; Schummer et al. 2013; Balah et al. 2014; Erdoğan et al. 2014).

Focal atrial tachycardia, which is defined as atrial activation that begins rhythmically in a small area (focus) and spreads centrifugally, has also been linked to stem cell differentiation (Saoudi et al. 2001). When the topography of ectopic foci in dogs with focal atrial tachycardia was determined, it was discovered that, similar to humans, 63% of ectopic foci were dispersed within the right atrium and 37% were distributed from the pulmonary veins (Chen et al. 2000; Santilli et al. 2010). Thus, both abnormal automatism and triggering activity in the pulmonary veins, either alone or in combination with the reentry mechanism, have been postulated to have a role in the onset of atrial fibrillation (Chen et al. 2000).

As a result, stem cells are believed to be capable of establishing heterotopic excitation foci, similar to how hematopoietic progenitor cells are believed to be capable of forming heterotopic hematopoiesis foci. The introduction of embryoid cells into the ventricular myocardium demonstrated the fundamental possibility of the formation of new islets of cells with cardiac stimulatory activity (Lyon et al. 2008).

Because the dimensions of the pacemaker, the frequency of the generated impulses, and its position in the hierarchy of the conducting system's structures are all linked in the heart, the manifestation of the formed focus' activity is influenced by both the frequency and the size of the generated potentials. The sinoatrial node, the first-order pacemaker in the human heart, is about 10–30 mm in length and 5–7 mm in width (Chandler et al. 2011; Csepe et al. 2016), while the atrioventricular node, the second-order pacemaker, is about 5–6 mm in length and 2–3 mm in breadth (Anatomy and physiology of the conducting system of the heart 2009). Thus, it was demonstrated that the intrinsic cardiac stimulatory activity of rat neonatal cells and hESCs cannot overcome the normal sinus rhythm if they occupy a limited area (for example, 200 m by 20 m) (Kehat et al. 2004) and only create pacemaker potentials when greater dense areas are formed (Qu et al. 2003; Plotnikov et al. 2004; Xue et al. 2005). Currently, research is underway to develop biological pacemakers based on the ability of

various types of stem cells to differentiate into pacemaker cells (Chauveau et al. 2017).

Cell fusion

Cell fusion, in addition to electromechanical communication, may be another mechanism for the development of arrhythmias. Cells extracted from the bone marrow selectively fuse with cells from the bone marrow, liver, and heart (Alvarez-Dolado et al. 2003; Nygren et al. 2004), with a fusion rate of 3.8% (Ardehali et al. 2013).

Paracrine mechanism

Paracrine factors produced by stem cells may be another route by which stem cells might cause proarrhythmic effects. Several studies have documented the proarrhythmic effect of paracrine factors (Dhein 2004; Pedrotty et al. 2009; Askar et al. 2013; Smit and Coronel 2014), despite the fact that the "paracrine hypothesis" (Dhein 2004; Gnecchi et al. 2008) explains primarily the mechanisms of endogenous regeneration *via* the activation of resident CSCs and does not focus on their possible negative effects.

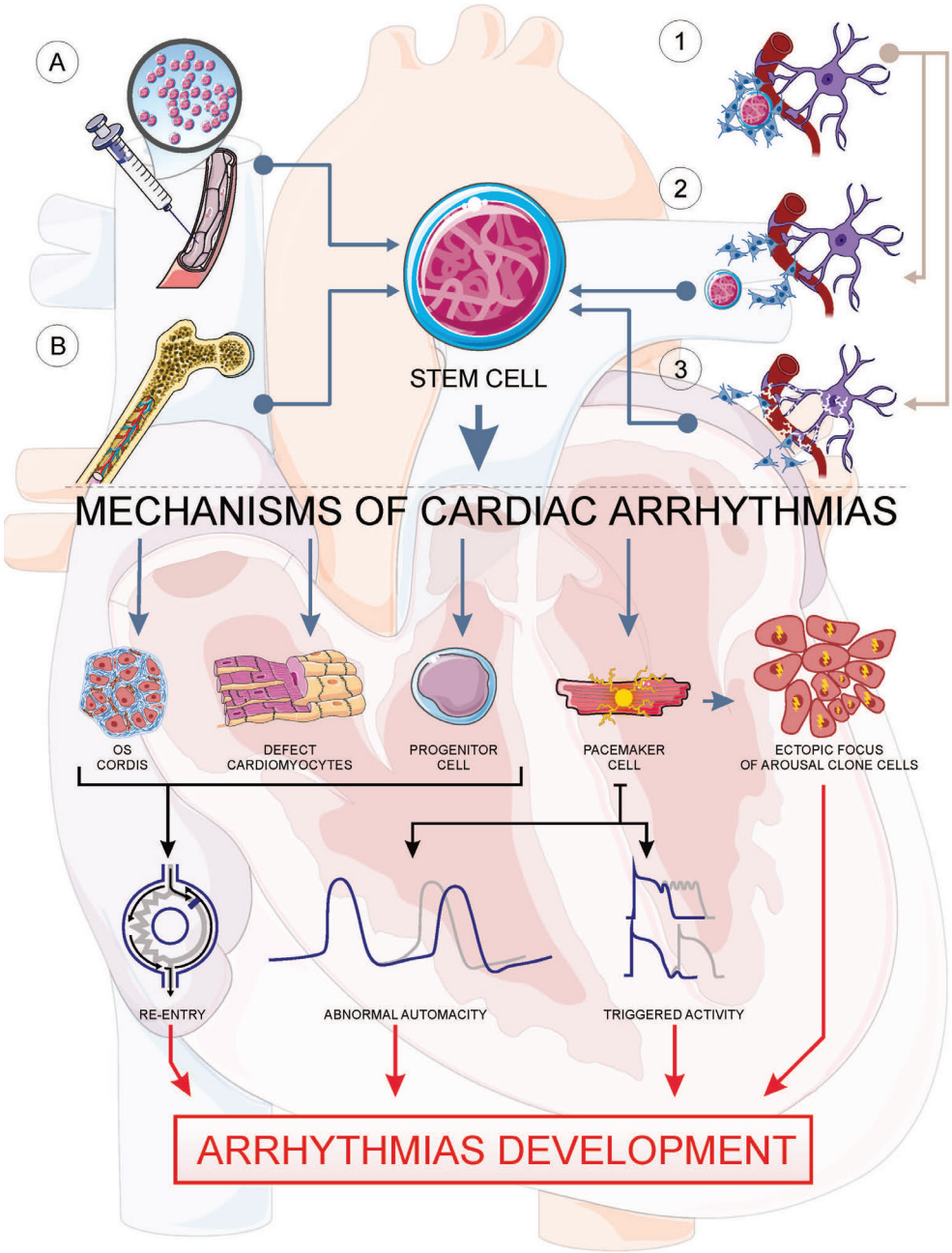

Figure 1. The role of stem cells in the pathogenesis of arrhythmias. Stem cells in the myocardium can be of both exogenous and endogenous origin. Exogenous stem cells can come from the bone marrow or be administered into the circulating blood or directly to the myocardium. Cells of endogenous origin are resident myocardial stem cells from normal "niches" (1), leaving the latter under the influence of pathogenic factors (2) or due to the "niche" destruction (3). Arrhythmias may develop 1) *via* the re-entry mechanisms, as a result of differentiation of stem cells into cells of another type of tissue (os cordis) or defective cardiomyocytes, and due to the differences in physical and electrical properties of myocardial cells, 2) as a result of differences in the activity of natural pacemakers, 3) as a result of the formation of new additional pacemakers.

Sympathetic hyperinnervation

Another mechanism that can promote arrhythmogenesis is sympathetic nerve sprouting stimulation (Li et al 2017). In experimental myocardial infarction in pigs (Pak 2003; Rubart et al. 2003) and dogs (Kim et al. 2010), stem cells stimulate the growth of sympathetic cardiac nerves, increasing the risk of arrhythmias.

Finally, local damage or edema caused by injection of stem cells into the myocardium and subsequent release of cytokines from inflammatory cells can serve as a predisposing factor for the development of arrhythmias (Almeida et al. 2015).

Conclusions

The objective of this review was to determine whether stem cells play a role in the development of arrhythmias. The myocardial, like no other tissue cell, is not autonomous, which means it cannot function without being impacted by its environment. Violations of the microenvironment's interactions with resident and migrating stem cells are of special interest from this perspective. Experiments and clinical observations demonstrate that while a stem cell is in a "niche," it is in a state of rest–G0, having become free as a result of leaving the niche, or destruction of the niche, or migration into the tissue from circulating blood, or injections with a therapeutic purpose directly into the tissue. Subsequently, the stem cell continues to multiply and differentiate into cardiomyocytes or pacemaker cells. However, because of its pluripotency, it can also develop into many types of tissue cells (for example, bone) (Fig. 1).

In the direction of differentiation, there is a microenvironment that has a substantial impact. Disturbances in the stem cells themselves, as well as in the microenvironment, might cause the relationship to become pathological. Reentry with the formation of zones with electrophysiological properties different from neighboring zones (os cordis, accumulation of defective cardiomyocytes, accumulation of progenitor cells), loss of cell contacts, and the formation of ectopic foci of excitation are all examples of how this process can lead to the development of arrhythmias. The presented data will allow one to see new, somewhat unexpected, aspects of the formation of arrhythmias, allowing one to improve the methods of treatment of this pathology and take into account the possibility of complications in cell therapy of various diseases. However, the problem itself requires further study.

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