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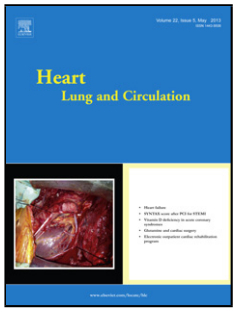

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Intercellular Signalling Cross-Talk: To Kill, To Heal and To Rejuvenate

Short Title: Cellular communication

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Abstract

Intercellular cross-talk is a fundamental process for spreading cellular signals between neighbouring and distant cells to properly regulate their metabolism, to coordinate homeostasis, adaptation and survival as a functional tissue and organ. In this review, we take a close molecular view of the underpinning molecular mechanisms of such complex intercellular communications. There are several studied forms of cell-to-cell communications considered crucial for the maintenance of multicellular organisms. The most explored is paracrine signalling which is realised through the release of diffusible signalling factors (e.g., hormones or growth factors) from a donor cell and taken up by a recipient cell. More challenging is communication which also does not require the direct contact of cells but is organised through the release of named signalling factors embedded in membranous structures. This mode of cell-to-cell communication is executed through the transfer of extracellular vesicles. Two other types of cellular cross-communication require direct contact of communicating cells. In one type, cells are connected by gap junctions which regulate permeation of chemical signals addressed to a neighbouring cell. Another type of cell communication is organised to provide a cytosolic continuum of adjacent cells joined by different tiny cell membrane extensions coined tunnelling nanotubes. In this review, we consider the various cell communication modes in the heart, and examples of processes in non-cardiac cells which may have mechanistic parallels with cardiovascular cells.

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Introduction

Clinicians are normally occupied with the disease and ageing of their patient at systems level, however they are also aware that intercellular cross-talk is fundamental for spreading cellular signals to share information between neighbouring and distant cells to properly regulate their metabolism, according to changes in localised physical and chemical stresses, and to coordinate homeostasis, adaptation and survival as a functional tissue and organ. In this review we take a close molecular view of the underpinning molecular mechanisms of such complex intercellular communications.

There are several studied forms of cell-to-cell communications considered crucial for the maintenance of multicellular organisms, and these may have particular importance for the functional roles of stem cells in tissues. The most explored is paracrine signalling which is realised through the release of diffusible signalling factors (e.g., hormones or growth factors) from a donor cell and taken up by a recipient cell. This type of communication involves a simple release of factors into the ambient environment and subsequent interaction with a membrane receptor or channel protein. For example, the release of cytokines such as transforming growth factor β (TGFβ) and growth factors such as fibroblast growth factor (FGF2) into the extracellular space by cardiac fibroblasts and myocytes which promote activation of the inflammasome, fibrosis and hypertrophy in the heart [1,2].

More challenging is communication which also does not require the direct contact of cells but is organised through the release of named signalling factors embedded in membranous structures. This mode of cell-to-cell communication is executed through the transfer of extracellular vesicles (EVs) [3], and involves formation of vesicles by a donor cell with subsequent release of vesicles into the extracellular space and absorption by a recipient cell. Such vesicles shuttle bioactive particles, proteins, lipids, metabolites and different types of nucleic acids such as DNA, mRNA, and microRNA [4-6]. Ribosomes may also be transferred using an exosomal vehicle [7,8]. In early studies, these vesicles were considered to be remnants of dead cells not playing an essential role, however subsequently all of these, some as small as 30 nm in diameter, were found to have biological roles with the potential to heal or to kill the recipient cells [9]. The size of vesicles varies from 30 nm to 1 μm. The smallest vesicles (30–100 nm) belong to the class named exosomes and larger particles (100–1000 nm) are generally named microparticles, although this classification of these vesicles by size is not strict. These two classes are different by their origin: while exosomes are formed in endosomal pathway, microparticles are the result of the cell budding. Extracellular vesicles play an

important role in the regulation of different physiological and pathological processes, thus participating in the development and progression of many diseases [9]. Extracellular vesicles, especially those produced by stem cells, cancer cells, immune cells, blood cells, and nervous system cells have become a hot study topic over recent years. The analysis of physiological fluids for EVs has become a diagnostic approach for different pathologies, including cardiovascular [10-12]. Notably, exosomes derived from stem cells can carry protective factors which can heal heart damage [13,14]. We will discuss this in detail below.

Two other types of cellular cross-communications require direct contact of communicating cells. In one type, cells are connected by gap junctions which regulate permeation of chemical signals addressed to a neighbouring cell, thus establishing electrical and mechanical synchronisation [15]. Such gap junctions can be organised by a channel with a size up to 1.5–2 nm permeable for solutes to about 1 kDa [16] including ions, oxidisable metabolites, adenine nucleotides, peptides and microRNA [17-19]. Some of these compounds (such as glucose) serve as a fuel [18], ions can regulate gating [20,21] and microRNA may be involved in a wide spectrum of activities with binary outcome. They may yield either positive effects; i.e., as shown for stem cell-derived microRNA-133a which can contribute to the activation of healing in infarct tissue [22] or similarly for microRNA-26a [23]; or they may cause negative effects; i.e., loss of miR-29 causing adverse fibrosis in the post-infarcted heart [24]. Examples involving microRNA demonstrate how the same communication transfer mechanism can provide both healing and killing functions depending on the changes of intercellular fluxes of vital components, and emphasises the regulatory importance of such a mechanism.

In contrast to gap junctions which provide an electrical continuum between cells, there is another type of cell communication which is organised to provide a cytosolic continuum of adjacent cells joined by different tiny cell membrane extensions. The first observation of organisation of the cell-to-cell channelling was made using a scanning electron microscope which showed that PC12 cells communicate by extended cellular formations coined tunnelling nanotubes (TNTs) [25]. Transmission electron microscopy showed that these extensions are organised by plasma membranes of neighbouring cells with two cytosolic contents being organised as a continuum without any structures inside which could limit exchange between cells, aside from the diameter of the nanotube itself. Sequentially, two contacting cells have not only an aqueous but also membranous continuum allowing the exchange with water soluble agents and lipid-soluble material through lateral diffusion along membranes. The transmitting chemical signal or a cargo (lipid droplets [26], vesicles or organelles [27]) are thought to be transported either passively by diffusion or as in case of a cargo transportation, by an active transport machinery. The last one often involves cytoskeletal elements such as F-actin in TNTs smaller than 100 µm in diameter and both F-actin and

microtubules in TNTs whose diameter exceeds 100 µm [25,28,29]. Drugs which cause F-actin depolymerisation prevent formation of TNTs [30]. Tunnelling nanotubes seem to be a very secure and directed way of transporting signalling molecules between cells organised without the leak of signalling molecules into the extracellular space. The diameter of TNTs reportedly varies from 20 to 200 nm, with the length far exceeding cellular dimensions [31]. Some TNTs do not touch the substrate, thus making them highly flexible and mobile. Tunnelling nanotubes have no known unique biochemical markers but can be detected by microscopic methods such as electron (see above) and light [32] microscopy.

Lipid components have been shown to participate in the mechanism of communication between contacting cells (mostly organised by TNTs) [25,33]. It is known that in the lateral transport of molecules along the cell surface, lipid rafts play a key role in transmitting signals from receptors and EVs [34]. Participation of lipid rafts in intercellular communication is evident in mesothelioma cells contacting through TNTs that contain more lipid rafts than non-contacting cells [35].

The data on intercellular communication in the cardiovascular system are very scarce, particularly concerning the role of lipid rafts in this process. Later in more detail we will discuss the cross-talk between cardiac fibroblasts and contractile cells of the heart, which determines normal and pathological functioning of a heart [36]. In addition to this type of interaction the *in vitro* communication organised by TNTs between cardiac myocytes and stem cells has been shown, the importance of which lies in the possibility of stem cell differentiation into cardiomyocytes [32]. The lipid component may be one of many critical factors of cell commuting devices at least based on the fact that sites of contacts with TNTs are enriched with lipid rafts [37]. B-cells forming TNT-like cytoneme, (filipodia-like tubular extension of plasma membrane with parallel actin filaments inside the thin tube that can project to other cells conveying signalling proteins), contain a significant portion of lipid domains essential for rafts [38]. Besides the role of rafts in a cell communication organised by TNTs, the rafts are important factors in the process of uptake of EVs by a tissue including myocardium. The numerous mechanisms for EVs uptake have been documented and lipid rafts were found to be involved in both clathrin- and caveolin-mediated endocytosis as a significant part of EVs absorption by a target cell [39]. In general, lipids (particularly, cholesterol) and lipid rafts are essential components necessary for normal myocardial contractile function and ischaemic tolerance. Depletion of cholesterol aggravates both cardiac performance and cardioprotective mechanisms [40]. Later, we will describe this issue in more detail when endothelial cell – contractile cell axis will be discussed.

Thus although intercellular communication processes are likely to be highly complex due to the cellular heterogeneity of tissues and organs, the diverse modes of intercellular communication

confers specificity, clarity of signal and compartmentalisation of signal. In the remaining sections of this review, we consider the various cell communication modes discussed above according to function, and we consider examples of processes in other cell types which may have mechanistic parallels within cardiovascular cells.

To Kill: Intercellular Communication Lessons From Tumours and the Immune System

Heart failure with preserved ejection fraction may include inflammation in its aetiology underlying its distinct structural and functional changes [41]. Pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α and profibrotic TGFβ, are augmented in the myocardium of such patients [42]. Inflammatory cells expressing CD3, CD11a and CD45 have been detected that are associated with oxidative stress in cardiomyocytes and endothelial cells due to pro-inflammatory cytokines [43]. The subsequent transdifferentiation of cardiac fibroblasts to myofibroblasts that produces more collagen together with lower activity of metalloproteases yields fibrosis that may thus promote diastolic dysfunction in these heart failure patients [43].

This as well as other data compels us to discuss the role of communication with and among immune cells in cardiovascular pathologies.

The *communication of immune with non-immune cells* is organised by T-cells and antigen-presenting cells (APC). T-cell activation occurs as a result of a complex process which requires the interaction of a T-cell with major histocompatibility complex (MHC) proteins and further secretion of regulatory or cytolytic factors [44]. Analogous to cell communication in the nervous system this was called the “immunological synapse”. Cell surface structures (e.g., T-cell receptor) regulating contact between the membranes of two cells are the bases of this type of communication yielding the transduction of the signal to the interior of a cell. T-cell activation consists of mostly three phases. The first phase is the T-cell polarisation when non-stimulated rounded, low motile T-cells with integrin adhesion molecules are held in an inactive state [45] after exposure to chemokines rapidly performs polarisation with formation of a front end, or lamellopodium, and a back end, or uropod [46]. The second phase is the initial adhesion organised by activated integrin triggering formation of actin-based cell protrusions enriched by T-cell receptors which form sensory contacts, subsequently immunological synapse signalling starts, and is sustained with immunological synapse maturation [47]. Interestingly, phenotypic changes in T-cells after their activation are associated with dramatic changes in mitochondrial function [48]. The pathological impact of leukocytes infiltrated in the tissue and relocated to future inflammation sites is well known. These cells cross the walls of the blood vessel starting from a layer of endothelial cells forming a first barrier for penetration [49]. The

transport of white blood cells through the endothelial barrier is a critical step for inflammatory processes driven by elevated cytokines and chemokines. Taken up from the blood stream, leucocytes first interact with receptors in the surface of endothelial cells causing leucocyte arrest and adhesion, and subsequent migration (diapedesis) across the pericyte sheath and basement membrane [50,51]. Every step of this pathway is organised by multiple factors providing cellular docking and *cross-talk of leucocytes and endothelial cells*. There are many reviews on mechanisms underlying this transfer (e.g., see [49]).

Exchange of molecular signals *by smooth muscle cells and monocytes/macrophages* may be an important step in atherogenesis. The cell dialogue between these cells results in modification of extracellular matrix composition and angiogenesis. Such communication may cause changes in the pattern of secretion of matrix proteins by smooth muscle cells which, in turn, may induce secretion by monocytes of some inflammatory angiogenic factors (such as VEGF and IL-1β). This cross-talk in later stages may sequentially activate some extracellular metalloproteases and induce rupture of the plaque causing atherothrombosis [52].

Cell death triggering may be a result of concerted communication *between smooth muscle cells and endothelial cells* with key vasoactive players such as NO and endothelin-1 [53]. Under pathological conditions, such cellular dialogue may be altered leading to a sustained increase of vascular contractility and abnormal vascular proliferation. The communication between smooth muscle cells and endothelial cells is not limited by paracrine signalling but may also include communication via myoendothelial junctions and EVs [54,55].

Intercellular communication during carcinogenesis includes pathogenic stimulus and chronic inflammation, similar to many cardiac pathologies. The surface proteoglycan layer (glycocalyx) plays the main role in receiving primary information on the stimulus in cancer cells [56]; similarly in the heart it regulates a vascular endothelium response to physiological or pathological signals [57]. The transmission of the information involves extracellular matrix, gap junctions and other adhesion systems (reviewed in [58,59]). Cellular communications in the cancer cells environment is another example of cellular cross-talks [60].

Among numerous relations between cells which surround cancer cells, thus forming a malignant tumour, we can recall the cross-talk when one talking partner is a fibroblast. Fibroblasts are relatively undifferentiated cells with a plastic phenotype [61,62]. Apparently, their potency to be converted into different phenotypes is determined by their microenvironment. Similar to the heart, the key process of tumorogenesis is the fibroblast activation in response to tissue injury and some stimuli yielding formation of a damage-associating phenotype. In this aspect, the parallelism between tumour and heart seems obvious since while activation of fibroblasts in a tumour results in

formation of the cancer stroma (plus inflammation), in a damaged heart it causes the cardiac remodelling as a result of fibrosis (plus inflammation) in an infarct zone and both events can be considered as deleterious for humans [63].

In a cell communication “vocabulary” which includes numerous chemical factors such as reactive oxygen species, cytokines, etc., another crucial chemical term which cells can “speak” with is mitochondrial DNA (mtDNA). It has been demonstrated that horizontal transfer of mtDNA from cell to cell may compromise respiratory function [64]. Since mtDNA is able to leave the cell [65], and this nucleic acid is known to be a component of the innate immune response, it is tantalising to suggest that mitochondrial DNA may constitute another novel mode or component of intercellular communication. Besides, transfer of mtDNA can contribute to the beneficial cardioprotective effects of mitochondrial transplantation demonstrated recently [66].

Some elements of communication through EVs and membrane lipid rafts are involved in *viruses-host cell interactions*. Viral infections are known to be associated with cardiac pathologies, such as myocarditis, pericarditis, and arrhythmias after infection with a dengue [67], West Nile [68] viruses and other arboviruses [69]. Viral particles may, via similar communication mechanisms to EV, interact with a host cell. For instance, HIV carries a shell made of a lipid bilayer with entrapped proteins and RNA, with a size of viral particle ranging from 100 to 120 nm. The infection with HIV is highly dependent on lipid rafts on the cellular membrane and, specifically, on the cholesterol contained in the rafts [70]. In addition, lipid rafts determine HIV internalisation and also affect the progression of the infection, particularly the release of viral particles from endosomes and permeation to the cytosol. Thus it seems tentative to suggest that lipid rafts may also play a role in the intracellular sorting of exosomes, not unlike cholesterol-sequestering agents that promote the transport of exosomes toward the apical membrane of a trophoblast facilitating their release in maternal circulation instead of equivalent process toward a fetal circulation [70]. Similar data on the role of lipid rafts in the internalisation of coxsackie virus have been reported [71].

To Heal: Stem Cell Interactions

As discussed above, the interaction of stem cells with other cell types may underlie potential mechanistic roles underlying cell therapy. On the one hand, the interaction of stem cells, (both exogenous and intrinsic) with specific cells within "niches" [72] may determine the fate of stem cells, the path of differentiation, proliferative potential, and, ultimately, the regenerative efficiency. Impaired perception of stem cell signals from the cell environment may lead to unpredictable consequences, including malignancy [73,74] due to formation of teratomas.

On the other hand, a growing number of recent studies address paracrine action (in the broadest meaning) of stem cells on the surrounding tissue. In this case, the signals of different origin can be transferred from stem cells to the cells of the organ, stimulating its regeneration, protecting it from damage or normalising the metabolism. In the framework of this concept, the stem cells were regarded as "cytokine factories". Indeed, it is known that they produce a significant number of biologically active molecules, such as TGFβ, VEGF, EGF, SDF-1, prostaglandin E, nitric oxide and many others [75]. These factors are released by a stem cell in the extracellular space and after binding to corresponding receptors of surrounding cells, they exert their biological effects while many of them may enter the bloodstream, causing systemic effects.

A significant portion of protective and regulatory effects of stem cells are associated with the microvesicles or exosomes released from them [76]. Such structures can contain various cytokines, and many other physiologically active components of cells, such as microRNAs, signal proteins and even organelles [14]. A great number of reviews with descriptions of the mechanics of these processes are available elsewhere including itemisation of signalling from stem cells, implemented via EVs(e.g., see [14,77-79].

Importantly, entrapment of an active compound within the vesicle solves the problem of signal dilution in the extracellular environment and it allows accurately directed delivery of signal to the targeted cells, since the surface of the exosomes can carry ligands, providing the affinity of the vesicles to specific cell types [80].

However, the greater specificity and efficiency of signal transfer between stem cells and differentiated tissue cells is provided by direct contact organised by TNTs. Tunnelling nanotubes were discovered in haematopoietic stem cells [81], between endothelial progenitor cells and cardiomyocytes [82], between mesenchymal stromal cells and cardiomyocytes [32], as well as between epithelial cells of the renal tubules and neurons [83]. To date, the structure referred to as TNTs, is described for many types of intercellular interactions, but in most cases, at least one of the partners is a stem cell [84]. Tunnelling nanotubes are a discrete cellular extension of cytoplasm, bounded by a plasma membrane which connects two cells delivering substances and signalling molecules that are transmitted through a medium or via EVs, but with far greater speed and efficiency than in the ways outlined above. However, the most intriguing result of such contact between stem and differentiated cells is the possibility that TNTs may transport cytosolic organelles, including mitochondria [25,84], which may change the metabolism of the recipient cell [66]. Evidence supports that such mitochondrial transfer within nanotubes [32,82], is distinct to each nanotube in that mitochondria can move only in one direction from cells which formed the TNT, to the cell which received the nanotube, but not vice versa [25]. In the case of stem cells, stem cells are

shown to be donors, rather than recipients of mitochondria, particularly in experimental models associated with cell damage. For example, transport of mitochondria from the multipotent mesenchymal stem cells (MMSC) into the epithelial cells of the lungs to protect them from endotoxin-induced death, maintained normal levels of ATP production and prevented lung injury *in vivo* [85]. Recently, the mechanism of mitochondria transport from stem cells into damaged epitheliocytes was partially resolved [86]. Finally, a recent study demonstrated that MMSC derived from induced pluripotent cells (iPS) were capable of transferring mitochondria to epithelial cells of the lungs, and could reduce the damage caused by a cigarette smoke [87]. However, although the majority of studies indicate positive effects of mitochondrial transport, sometimes donor mitochondria can have toxic effects [88]. Contact of stem and differentiated cells by TNTs has also a reciprocal effect on the stem cells. Thus, in some cases the contacts via TNTs elicited the differentiation of stem cells [32,83]. In other work, the transport of mitochondria via TNTs from smooth muscle cells have been reported to be the cause of increased proliferation of MMSC, whereas blocking the formation of TNTs abolished this effect [89]. The opposite effect was demonstrated when mature cardiomyocytes were co-cultivated with stem cells, extracted from fat or bone marrow. In this case, the transfer of mitochondria to cardiomyocytes caused their partial dedifferentiation [90]. Thus although conceptually and practically in its infancy, mitochondrial transplantation may afford rescue of cellular function [66].

To Regulate: Communication in Heart, Brain, Vasculature and Others

In the heart, *cardiac myocytes* and *cardiac fibroblasts* are roughly in equal proportion meaning that every myocyte borders one or more fibroblasts [91]. The heart is known to frequently undergo so-called cardiac remodelling as a result of disease and ageing which is associated with structural and electrical changes in both types of cells [92,93] and strongly depends on the cells' communication. First of all, cross-talk between these cells is organised through exchange by paracrine signals (such as TNF, TGFβ, IL family, VEGF, ANG-2, endothelin-1 and others [2,94-96]). This kind of signalling can be deleterious for the heart tissue resulting in cardiac fibrosis [97]. At the same time, some excreted paracrine factors such as IL-33 and ST2 can be beneficial for the heart [98,99]. Also, paracrine factors excreted by cardiac fibroblasts can regulate electrical properties of myocytes through both direct and paracrine interaction [100-102]. One of the pathways involved in paracrine communication between cardiac myocytes and cardiac fibroblasts was suggested to involve pannexins-formed channels in the cellular membranes of these two types of cells [103,104].

It is still under debate whether cardiac myocytes and fibroblasts can communicate through gap junctions in the heart *in vivo*, but under *in vitro* co-culturing conditions they do form this kind of junction [105]. This junctional communication is reportedly deleterious, resulting in arrhythmogeneity of fibrotic myocardial cultures due to expression of connexin43 in cardiac fibroblasts [106]. Junctional coupling of myocytes and fibroblasts has been demonstrated to modulate calcium fluxes which can also contribute to incidence of arrhythmias in fibrotic heart tissue [107]. Figure 1 schematically illustrates the deleterious outcome of interaction of cardiac myocyte with cardiac fibroblast organised by electrical, biochemical and biomechanical communication, in comparison to some beneficial effects of cardiac myocyte-stem cell interactions. More detailed mechanisms of the cell-to cell communication in heart are described elsewhere [59].

Neuron-glial interactions are also important in cellular cross-talking in the developing heart and in communication between cardiac ganglia and cardiac cells of the adult heart [108]. To emphasise the importance of communication between neuronal and non-neuronal cells (basically microglia and astroglia) within the entire cellular network in CNS, the term “Neurovascular unit” has been coined [109,110]. The unit consists of the brain major cell types, namely endothelial cells, astrocytes, neurons and their axons, and other supporting cells to integrate incoming information with further release of a proper response [111].

Although in the brain, astrocytes can protect neurons from a pathological impact [112], in contrast, impaired astrocytes can release molecular factors that selectively damage neurons [113]. Interestingly, mitochondria have been reported to be involved in the cross-talk between astrocytes and neurons when neurons release impaired mitochondria with their subsequent degradation in adjacent astrocytes [114]. This implies the importance of mitochondrial transfer between neuronal and non-neuronal cells. In addition, recent work has demonstrated that neurons and astrocytes exchange with healthy mitochondria in a unidirectional way: from astrocytes to neurons [115]. This phenomenon was observed under conditions of tissue ischaemia or ischaemia-simulated conditions causing cell damage and apparently the transfer of mitochondria to these neurons fulfilled a rescuing mission in overall neuron salvage process. This result is comparable to the beneficial process of mitochondrial transplant injection to heal the damaged heart mentioned above [116,117]. There is also ultrastructural evidence for the presence of EVs containing mitochondria in the astrocytes’ cultivation media [118] potentially being the source of release of mitochondria from astrocytes that may, via the bloodstream, reach target organs such as the heart.

Thus, in addition to the cross-talk of neural cells by neuromediators and chemokines, neural cells can also communicate through establishing direct contacts. In these cases, gap junctions are involved by mediating the rapid diffusion and distribution of ions and transmitters to neighbouring

cells [119,120]. A principle component of gap junctions is connexin 43 (Cx43), but they also may contain Cx30, Cx26, Cx40, Cx45 and Pannexin1 providing direct contact-based cellular cross-talks [121-124].

Another important cellular partnership we observe is between *endothelial cells and other cells of the tissue*. A very good example for such partnership is a cross-talk between glomerular endothelial cells and *podocytes* and *mesangial cells* which is very important in aetiology of diabetic kidney disease [125]. In patients with macroalbuminuria, both podocytes damage and endothelial cells injury were observed [126] . The endothelium injury is at least partially caused by a diabetes-induced oxidative stress which activates production of heparinase, ultimately resulting in increased glomerular permeability [127]. Thus, diabetes compromises normal functioning of endothelial cells. Endothelial cells, podocytes and mesangial cells share the glomerular basement membrane on which they all sit. In normal kidney, endothelial cells transmit insulin-like growth factor (IGF) and hepatocyte growth factor (HGF) to podocytes and platelet-derived growth factor B (PDGFB) to mesangial cells, while mesangial cells send back to endothelial cells, TGFβ and integrin. In the diabetic kidney, these cross-talks are dramatically changed. The endothelial cells – podocytes vascular endothelial growth factor (VEGF) signalling, which is essential for normal kidney functioning, becomes altered [128,129]. New elements or old elements in enhanced levels, such as endothelin-1 (ET-1) [130], angiopoietins (Ang-1, Ang-2) [131] and TNF-α [132,133], are all implicated in renal injury. eNOS, another essential component of the renal cells cross-talk, when ablated, causes heavy albuminuria associated with podocytes injury [134]. Other factors such as prostanoids derived from activated cyclooxygenase also play a paracrine role in mediated podocytes injury [135]. Recent findings point to microRNAs (mir-143 and mir-145) as factors regulating interaction of endothelial cells with smooth muscle cells [136].

In the heart, besides earlier described communication between cardiac myocytes and fibroblasts, one of highest importance is the *endothelial cell – contractile cell* axis. The cardiac endothelial system is organised by a monolayer of cells covering cardiac cavities (endocardial endothelial cells) and the internal surface of the myocardial vascular system (vascular endothelial cells). Some of the factors providing communication between endocardial endothelial cells, vascular endothelial cells and cardiac myocytes are identical to those indicated for renal cellular communication. Significant attention in these links has been attracted to eNOS and its product NO, which is mostly formed by endothelial cells [137] but in some, although at much lower levels, by cardiac myocytes [138]. Expression of eNOS is modulated by numerous factors such as TGFβ, protein kinase C, TNF-α, HSP and others. NO is an essential factor necessary for normal cardiac functioning [139], however at high levels NO can cause pathological activation of guanylate cyclase yielding

cGMP which desensitises cardiac contractile elements to calcium ions [140]. NO activates G proteins (G_s and G_i) stimulating Ca-channels [141]. General targets for this second messenger are proteins which can undergo nitrosylation. Critical proteins involved in excitation-contraction, such as ryanodine receptor, can be directly phosphorylated by NO resulting in myocardial contractile activation [142]. Important to this regulatory signalling are lipid rafts with their uneven distribution among planar and invaginated (caveolae) parts of the plasma membrane. Ion channel activities critical for shaping the cardiac action potential were found to be strongly dependent on the location: either being in caveolae or outside of it [143]. Importantly, there is an intracellular cross-talk between caveolae and mitochondria [144] which represents intracellular communication between the cell membrane and cellular organelles which is highly organised and proceeds with participation of G-proteins [145]. Ischaemic and pharmacologic preconditioning causes translocation of principle caveolae proteins, caveolin-1 and 3 from a cell surface to mitochondria affording a protection from ischaemia-reperfusion injury [146,147] (note, that among all caveolins caveolin-3 (Cav-3) is specific for striated muscle and certain smooth muscle cells). Caveolins regulate multiple cellular processes including cell transduction apparently through housing of numerous signalling molecules, e.g., G-protein coupled receptors (GPCRs), thus regulating multiple associated proteins such as G_i, adenylate cyclase, and effector kinases [148]. It has been found that cardiac-specific caveolin 3 expression mimics protective ischaemic preconditioning via activation of GPCR/G_i signalling pathway [149]. The described picture outlines the main components participating in the communication pathway from one cell to the interior of another cell (e.g., to mitochondria with their important role in collecting survival signals [150]) to afford protection.

As we have already mentioned, depletion of cholesterol aggravates pathological changes in cardiac performance and protective stress signalling including ischaemic tolerance. Gradual depletion of sarcolemmal cholesterol content results in significant changes in myocardial function and tolerance to ischaemia/reperfusion whereas disruption of caveolae (through deletion of caveolin 3) specifically modifies ischaemic tolerance without direct effect on basic cardiac performance [40]. In parallel, ischaemic preconditioning of the heart causes translocation to mitochondria of another principal component of caveolae, connexin-43 which also affords protection not observed in inactive connexin-43 systems [151]. The role of caveolae in NO signalling is critical since endothelial NO synthase activity is blocked by binding to caveolin-1 and activation of NO synthase is associated with the release from the inhibitory clamp of caveolin-1 [152]. Besides NO, endothelial cells and cardiomyocytes communicate by ET-1, angiotensin II, prostaglandin, peptide growth factors, neuregulin (reviewed in [153]) . While for normal modulation of contractile cells by endothelial cells, specific levels of such second messengers are optional, a significant

alteration of these levels may augment pathologies like myocardial infarction, ischaemia, hypertension, arrhythmias, congestive heart failure, and atherosclerosis [154-157].

In addition to gap and tight junctions, endothelial cells communicate with their neighbours through adherens junctions. In this type of junction their cytoplasmic surface is linked to the actin cytoskeleton. They are expressed as bands forming a circle around the cell (zonula adherens) or as loci of joints to the extracellular matrix (adhesion plaques). Similar cell junctions (fascia adherence) were found in cardiac myocyte which form on the surface of cardiac myocyte a ribbon-like structure not long enough to completely circle the cell. Adherent junctions contain cadherins, α-catenin, β-catenin, p120 (δ-catenin), γ-catenin (reviewed in [158]).

To Rejuvenate: Cross-Talk Between Organs and Organisms

Cross-talk between organs is well illustrated by the data in studies on protection of the brain or heart (damaged during a stroke or infarct correspondingly) by a remote preconditioning of the kidney or limbs [159-163]. The concept of remote preconditioning has evolved into 'remote conditioning', a term that encompasses a number of related endogenous cardioprotective strategies, applied to remote organs before (remote ischaemic preconditioning), during (preconditioning), or after (postconditioning) acute myocardial infarction [164,165]. Remote organ-heart neuronal and humoral communications can afford protection to the heart against stresses (i.e., by erythropoietin synthesised in kidney and liver [166,167] or adenosine, bradykinin, stromal derived factor-1α and others (for review see [165])). In contrast, considering pathophysiological aspects, heart failure is often accompanied by a number of comorbidities of the kidney [168,169], liver [170,171] or other organs [172,173], and thus adverse communication may be involved.

In the hierarchy of the biological communicational systems, the *cross-talk between organisms* joined together either artificially (such as in parabiosis [174]) or naturally (such as at pregnancy [175]) with at least partial unification of the blood systems, further demonstrate the potency of cross-talk between organs. Parabiosis is an example of a remote communication whereby humoral factors circulate and transfer from one parabiotic subject to another, i.e., when only one parabiotic partner was exposed to low pO_2, erythropoiesis was observed in both partners [176] due to induced synthesis of erythropoietin in both. In general, the parabiotic interaction has common features to the junctional connection of two cells. Both interactions can result in functional changes in both partners thus playing an either deleterious or healing/rejuvenating role (See Figure 2). In recent studies, the regenerative (possibly rejuvenating) effect of parabiosis on, skeletal muscles [177], liver [178] and brain [179-181] has been demonstrated. The study on rejuvenation of the ageing heart by using the parabiotic model is most intriguing [182]. It was shown that after four

weeks of exposure to the circulation of young mice, the aged heart showed significantly regressed cardiac hypertrophy and molecular remodelling while growth factor 11 (GDF11) simulated the positive outcome reached by parabiosis. In the parabiotic model, the organisms do not communicate through large vessels, although they are united by small vessels, mostly capillaries (by the way, young capillaries have been considered a rejuvenation factor [183]) which were suggested to serve a root for trafficking of rejuvenating factors including GDF11 from young parabionts. Recombinant GDF11 was shown to induce inhibition of phenylephrine-mediated hypertrophy in cardiac myocytes supporting the idea that cardiac myocytes are primary targets for GDF11 [182]. In addition, GDF11 reversed impairments in aged muscle stem cells (satellite cells) [184] showing the high potential of this rejuvenating factor to regenerative therapy leading to improvements in cardiac performance [185]. However, due to methodological controversies [186] full experimental evidence supporting the role of GDF11 as a rejuvenating factor is currently incomplete. Similar to the many studies that have examined the multiple components of conditioned media for factors involved in stimulating stem cells, vascular or myocardial cells, or other cell types, communicating beneficial and adaptive intercellular signalling, such factors in parabiotic communication also remain a focus of research [187-189].

Conclusion

In the present review we have highlighted the importance of intercellular cross-talk mechanistic processes for homeostatic maintenance between differing neighbouring and distant cells during adaptation and survival as a tissue and organ. Such processes are highly diverse and are still being studied at a rudimentary level, mainly in experimental models and require considerable further research in order to fully determine their specific roles in normal physiology and pathology. Continued research in these basic processes will afford greater mechanistic insights into targeting disease aetiology and potential future therapeutic targets.

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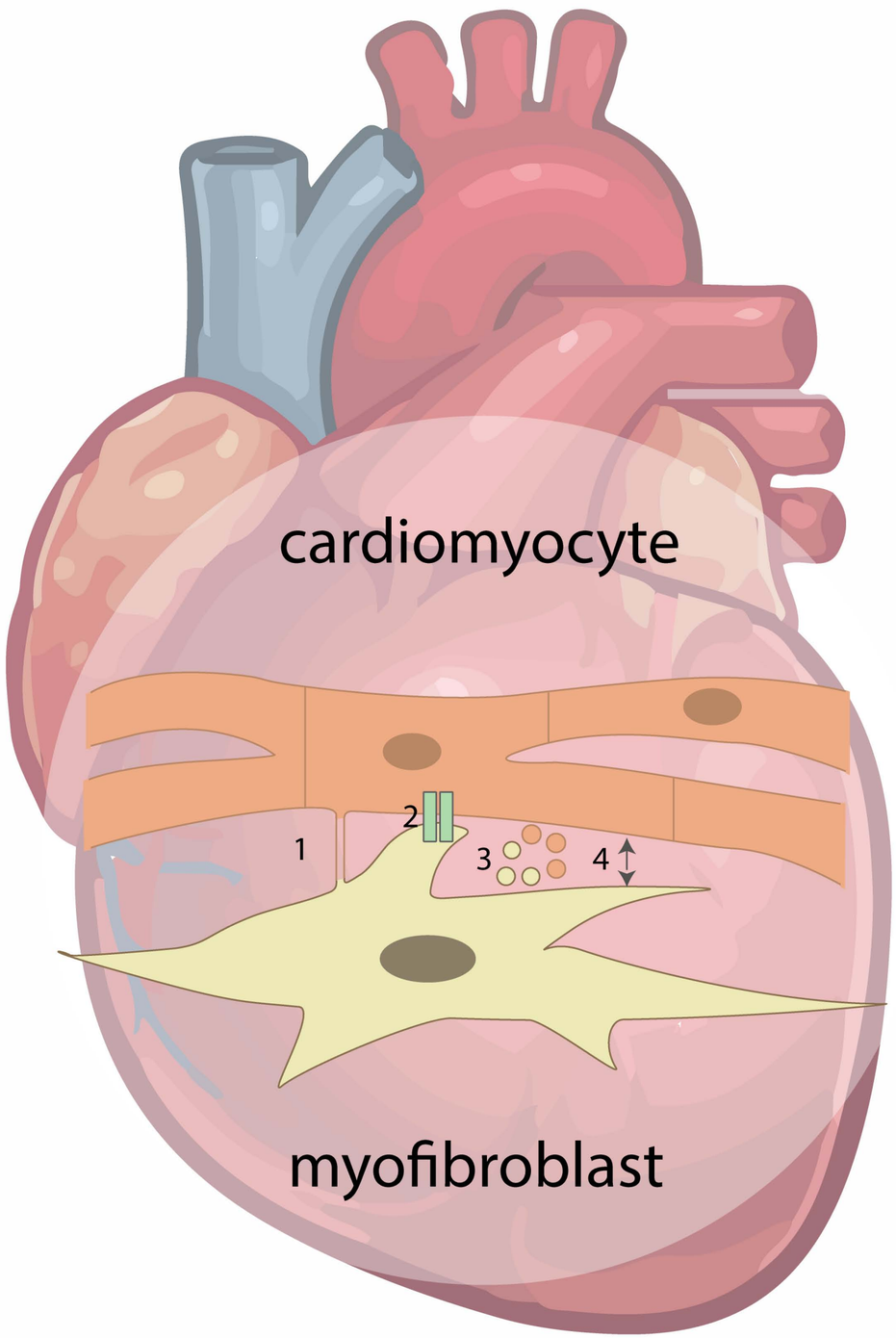
Figures legends

Figure 1. Cardiac myocyte–fibroblast (left) and cardiac myocyte-stem cell (right) interaction in the heart. This includes electrical communication (through: 1, TNTs and 2, gap/adherence junctions); biochemical communication (through 3, EVs) and biomechanical communication (through 4, extracellular matrix). Some details can be found in [36]. While heart hypertrophy, arrhythmias and tissue fibrosis may result from interaction of cardiac myocyte with fibroblast, the interaction with stem cell can yield the healing effect through restoration of cellular bioenergetics and normalisation of electrical communication of cardiac myocytes along the tissue.

Figure 2. Parabiotic (left) and paracytotic (right) interactions. First is organised by unified circulation and second is organised by TNTs connecting neighbouring cells.

TO KILL

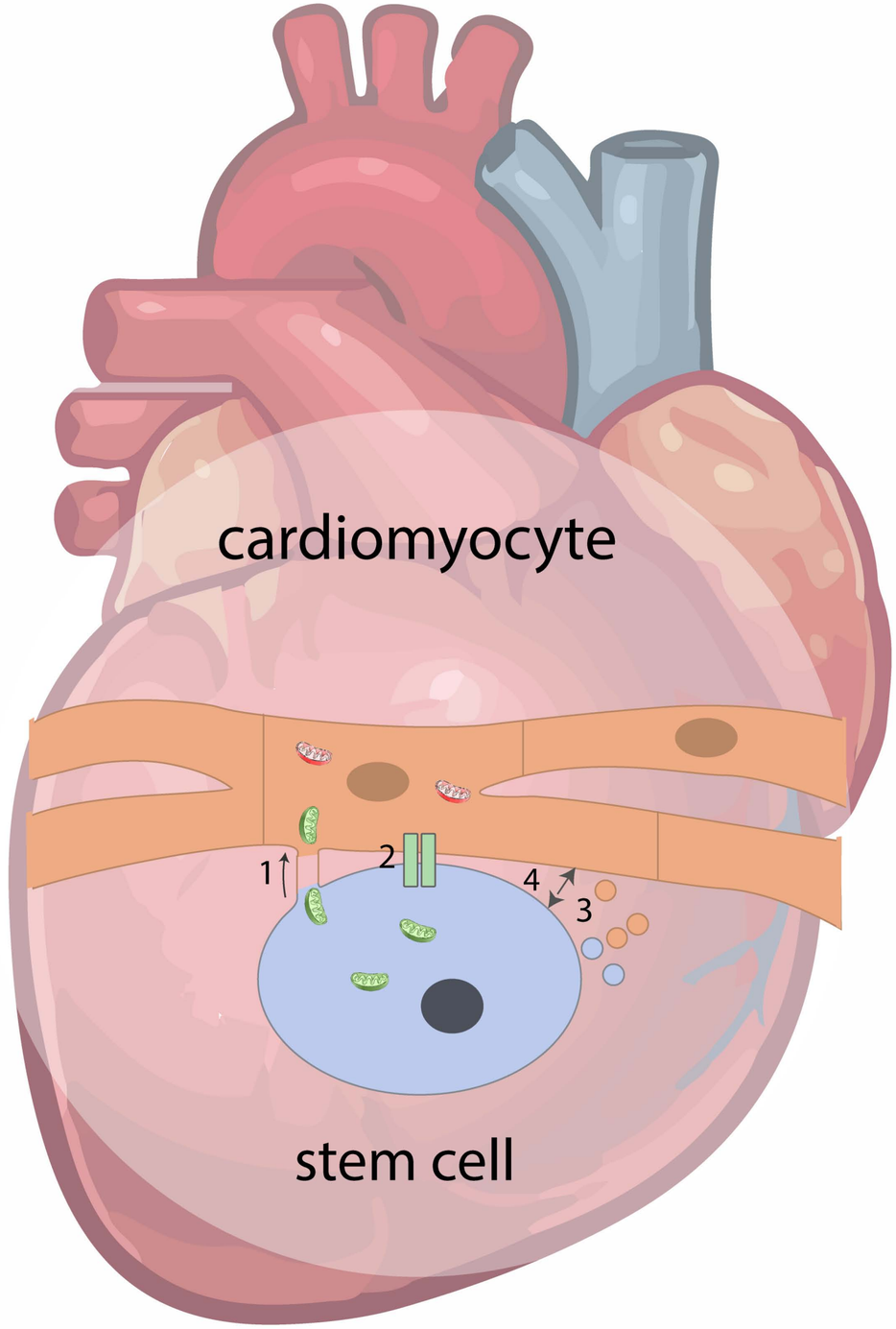


hypertrophy

arrhythmias

fibrosis

TO HEAL



bioenergetic restoration

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conductance