Conductive Polymers in Infarction Repair

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The function of the heart pump may be impaired by events such as myocardial infarction, the consequence of coronary artery thrombosis due to blood clots or plaques. A whole heart transplant remains the gold standard so far and the current pharmacological approaches tend to stop further myocardium deterioration, but this is not a long-term solution. Electrically conductive, scaffold-based cardiac tissue engineering provides a promising solution to repair the injured myocardium. The non-conductive component of the scaffold provides a biocompatible microenvironment to the cultured cells while the conductive component improves intercellular coupling as well as electrical signal propagation through the scar tissue when implanted at the infarcted site. The in vivo electrical coupling of the cells leads to a better regeneration of the infarcted myocardium, reducing arrhythmias, QRS/QT intervals, and scar size and promoting cardiac cell maturation.

conductive polymers | striated muscle cell electrical coupling | cardiac tissue engineering | cardiac muscle repair | electrical signals | biomimetic material constructs

1. Introduction

Myocardial infarction (MI) is one of the clusters of numerous other cardiovascular diseases and occurs due to the blockage of the coronary artery delivering blood (ischemia) to the ventricle with consequent oxygen shortage to the contractile cells (cardiomyocytes) [1]. The final result is that, after MI, billions of cardiomyocytes (CMs) with limited proliferation capacity are lost and substituted by heterogeneous collagen-rich fibrotic scar tissue [2][3]. Among others, the fibrotic scar does not display contractile capabilities and does not appropriately conduct electric currents, thus generating myocardial arrhythmias and asynchronous beating, contributing to determine heart failure in the worst-case scenario [2]. The current pharmacological approaches are palliative [4] and finalized to prevent intra-coronary blood clotting (thrombolytics, antiplatelet agents, such as aspirin, etc.) and post-ischemic ventricular dilation (ACE-inhibitors, β-blockers, etc.), but do not induce regeneration of the injured cardiac tissue. So far, the heart transplant is the gold standard in post-MI end-stage heart failure, but the lack of organ donors and the possibility of immune rejection makes this approach elusive [5].

In recent years, the parallel progresses in cell biology, materials science, and advanced nano-manufacturing procedures have allowed us to envision the possibility to set up novel strategies (collectively dubbed “tissue engineering”) to combine cells and biomaterials to fabricate myocardium-like structures in vitro to be engrafted into the heart to repair the damaged parts. This approach is characterized by an extreme level of complexity and, as a

matter of fact, after more than two decades of extensive efforts, many issues remain to be answered before tissue engineering products can be used at the bedside.

Natural or synthetic biomaterials, such as cardiac patches [6], injectable hydrogels [7], nanofiber composites [8], nanoparticles [9], and 3D hydrogel constructs [10], have been scrutinized to produce structures that mimic the mechanical properties of the extracellular matrix of the myocardium and potentially restoring the cardiac functions [11][12]. However, the issues related to arrhythmias and asynchronous beating of the injured myocardium are not resolved due to the non-conductive nature of most of the polymers used so far. The solution to this issue has been envisioned in conveying electric signals through scaffolds with embedded polymers displaying electroconductive characteristics comparable to the biological tissues (**Figure 1**) and this has already been demonstrated to enhance cell differentiation to mature CMs [13].

Electrically inert biomaterials can be blended with conductive polymers, such as polyaniline (PANI), polypyrrole (PPy), and Poly(3,4-ethylenedioxythiphene)/PEDOT, which belong to the family of intrinsically conductive organic materials [14]. The resulting electroconductive scaffold would harness the biocompatibility and the mechanical properties of the inert biomaterial and the electrical nature of the conductive component to drive the differentiation of the cultured stem/progenitor cells to cardiomyocyte-like cells with synchronous beating patterns, and enhance the expression of cardiac-specific genes.

GATA4 and Nkx2.5 are cardiac-specific transcription factors that play a fundamental role in myocardial differentiation and cardiac hypertrophy in the early stages of cardiogenesis in a developing embryo, while cardiac troponins are expressed in the cardiac muscles of the mammalian and avian species [15][16][17]. Connexin 43 is the principal gap junction protein of the heart which mediates action potential propagation between cells to synchronise cardiac contraction. In addition to this canonical role, it may act as a transcription regulator [18]. This cell-laden conductive scaffold improves the electrical signal propagation through the scar tissue, when implanted in vivo, and results in repair/regeneration of the injured myocardium with elevated ventricular wall thickness, improved blood pumping ability, reduced scar size, shorter QRS/QT intervals, and lower risk of arrhythmias, as shown in **Figure 2** [19].

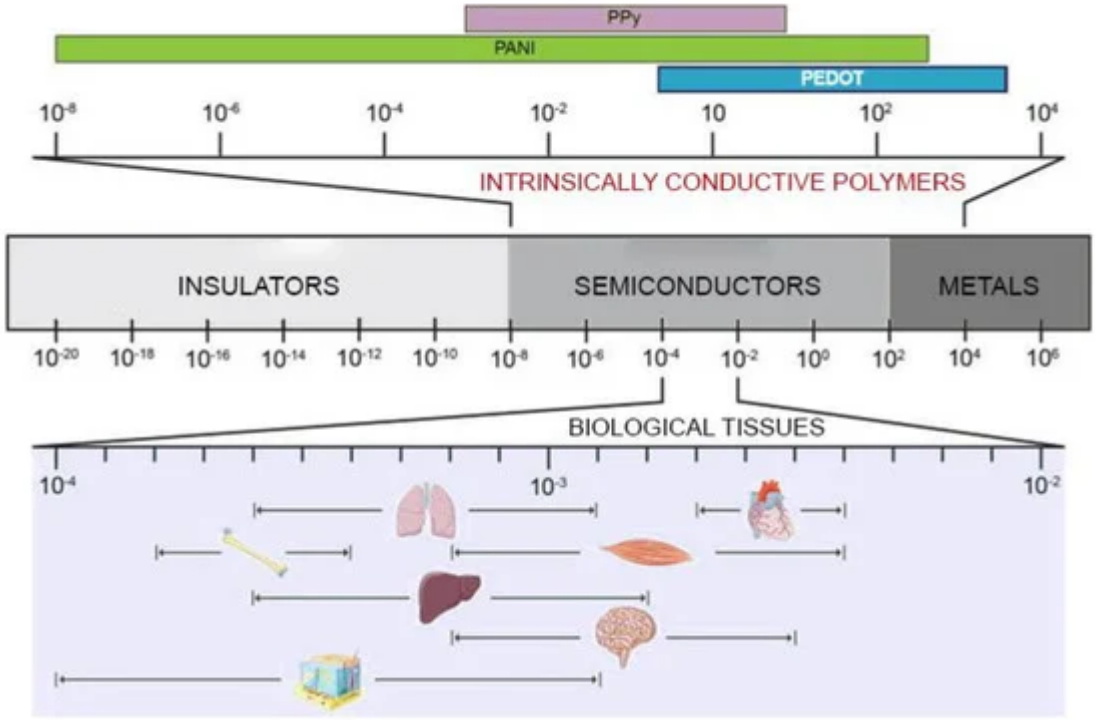

Figure 1. Electrical conductivity of common materials and biological tissues. The typical electrical conductivity values of intrinsically conductive polymers (top) are compared to those of common materials (centre) and biological tissues (bottom). Values are expressed in S/cm. Adapted with permission from [13].

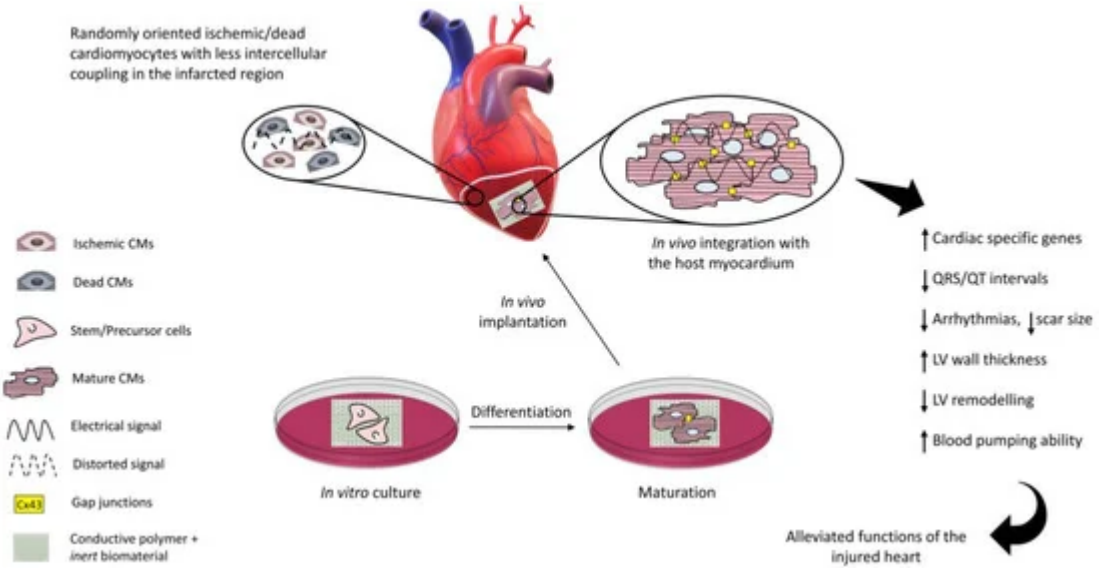

Figure 2. Conductive scaffold-based cardiac tissue engineering. After MI, damaged and dead cardiomyocytes (CMs) compromise the electrical conduction of the myocardium. The in vitro cell-laden construct can be transplanted at the infarction site to restore the electrical functions and to repair the damaged myocardium.

2. Conductive Polymer-Based Scaffolds in Cardiac Tissue Engineering

2.1. Polyaniline

Polyaniline (PANI) is a widely used material in tissue engineering and biomedical applications (**Table 1**) due to its intrinsic ability to conduct electric currents and good biocompatibility [20][21][22][23]. The polymer's conductivity can be tuned by chemical or electrochemical doping (p-doping (oxidation) or n-doping (reduction)) [24]. However, the powdered form of the PANI does not dissolve in its doped form in any common organic solvents and the electro-mechanical properties of the blends and composites depend on the uniform dispersion of the PANI particle in the polymer matrix. PANI particles can be prepared previously and then added to the matrix. Alternatively, aniline is polymerised to polyaniline in the polymer matrix (in situ chemical polymerisation method) [25]. Different PANI blends and composites have been created using various synthesis methods and combining PANI with diverse biomaterials to manufacture suitable conductive constructs for cardiac repair.

Table 1. Polyaniline based conductive constructs for cardiac tissue engineering.

Conductive Substrate	Mechanical Properties	Electrical Properties	Cell Line or Tissue	Biological Response
Poly-l-Lysine-PANI nanotubes membranes [26]			Rat CMs	Better CMs proliferation
PLCL, PANI electrospun membranes [27]	E = 50 MPa, εr = 207.85%, UTS = 0.69 MPa	Four-probe technique, σ = 13.8 mS/cm	Human fibroblasts, NIH-3T3, C2C12	Improved cell adhesion and metabolic activity
PGLD, PANI nanotubes membranes [28]			Cho cells, neonatal rat CMs	Good biocompatibility
PU-AP/PCL porous scaffold [29]	Ec = 4.1 MPa, C.S = 1.3 MPa	Four-probe technique, σ = 10^{-5} S/cm	Neonatal rat CMs	Enhanced Actn4, Cx43, and cTnT2 expressions.
PANI/PCL patch [30]		Two-probe technique, σ = 80 µS/cm	hMSCs	Differentiation of hMSCs to CM-like cells
PDLA/PANI electrospun membranes [31]		σ = 44 mS/cm	primary rat muscle cells	Improved cell adhesion and proliferation
Gelatin/PANI electrospun membranes [32]	E = 1384 MPa, UTS = 10.49 MPa, εr = 9%	Four-probe technique, σ = 17 mS/cm	H9c2	Smooth muscle-like morphology rich in microfilaments
Gelatin/PANI hydrogels [33]	G' = 5 Pa, G" = 26 Pa	Pocket conductivity	C2C12, BM-MSCs	Improved cell-cell signalling and proliferation

Conductive Substrate	Mechanical Properties	Electrical Properties	Cell Line or Tissue	Biological Response
		meter, σ = 0.45 mS/cm		
PU-AP/PCL films [34]	E' = 10 MPa at 37 °C	Four-probe technique, σ = 10^{-5} S/cm	L929, HUVECs	Improved cytocompatibility, good antioxidant properties
PLGA, PANI electrospun meshes [35]	E = 91.7 MPa	Four-point probe, σ = 3.1 mS/cm	Neonatal rat CMs	Enhanced Cx43 and cTnI expressions
PGS/PANI composites [36]	E = 6 MPa, UTS = 9.2 MPa, εr = 40%	Four-probe technique, σ = 18 mS/cm	C2C12	Good cell retention, growth, and proliferation
PCL, amino capped AT films [37]	E = 31.2 MPa, UTS = 48.3 MPa, εr = 646%	-	C2C12	Spindle like morphology, myotube formation
PCL, PANI electrospun membranes [38]	E = 55.2 MPa, UTS = 10.5 MPa, εr = 38.0%	Four-point probe, σ = 63.6 mS/cm	C2C12	Myotube formation
PANI, E-PANI films [39]		Z > 10 MΩ/sqr for PANI Z = 6 MΩ/sqr for E-PANI	H9c2	Improved proliferation and cell attachment on E-PANI
PLA/PANI electrospun membranes [40]		Four-probe technique, σ = 21 μS/m	H9c2, rat CMs	Myotube formation from H9c2 cells, enhanced Cx43 and α-actinin expression, improved Ca^{2+} transients for CMs
PCL/SF/PANI hydrogels [41]	εr = 107%		C2C12	Excellent cell alignment, myotube formation
Chitosan-AT/PEG-DA hydrogels [42]	G' = 7 kPa	Pocket conductivity meter, σ = 2.42 mS/cm	C2C12, H9c2	Improved cell viability

Conductive Substrate	Mechanical Properties	Electrical Properties	Cell Line or Tissue	Biological Response
PGS-AT elastomers [43]	E = 2.2 MPa, UTS = 2.0 MPa, εr = 141%	-	H9c2, rat CMs	Synchronous CM beating with improved Ca^{2+} transients, H9c2 showed good orientation, enhanced Cx43 and α-actinin expression
PANI, Collagen, HA electrospun mats [44]	E = 0.02 MPa, UTS= 4 MPa, εr = 78%	Four-probe technique, σ = 2 mS/cm	Neonatal rat CMs, hiPSCs	Synchronous beating of CMs derived from hiPSCs. Enhanced Cx43 and cTnI expression
AP, PLA films [45]		Four-point probe, σ = 10^{-6} to 10^{-5} S/cm	H9c2	Pseudopodia like morphology, improved Ca^{2+} transients
Chitosan, PANI patch [46]	E = 6.73 MPa, UTS = 5.26 MPa, εr = 79%	Four-probe technique, σ = 0.162 S/cm	Rat MI heart	Improved CV in the infarcted region with healing effects
PA, PANI patch [47]	Elongation = 84%	Digital Avometer, σ = 2.79 S/m	Pork heart	Cardiac ECM mimicking
HPLA/AT films [48]	εr = 42.7%, E = 758 MPa		C2C12	Myotube formation
Dextran-AT/chitosan [49]	G' = 620 Pa at t = 50 min	Four-probe technique, σ = 0.03 mS/cm	L929, C2C12	high proliferation rate, good in vivo degradation, generation of new myofibers

Abbreviations: PANI: Polyaniline, PLCL: poly(l-lactide-co-ε-caprolactone), E: elastic modulus, εr: strain at rupture, UTS: ultimate tensile strength, Ec: compressive modulus, C.S: compressive strength, G': shear storage modulus, G": shear loss modulus, E': tensile storage modulus σ: electrical conductivity, CMs: cardiomyocytes, PU: polyurethane, AP: aniline pentamer, PCL: polycaprolactone, hMSCs: human mesenchymal stem cells, hiPSCs: human induced pluripotent stem cells, PDLA: poly (d-lactic acid), BM-MSCs: bone marrow-derived mesenchymal stem cells, PGS: polyglycerol sebacate, AT: aniline tetramer, E-PANI: polyaniline-emeraldine base, PLA: polylactic acid, SF: silk fibroin, PEG-DA: dibenzaldehyde-terminated poly(ethylene glycol), HA: hyaluronic acid, PA: polyamide, HPLA: hyperbranched polylactide, CV: conduction velocity

2.2. Polypyrrole

Polypyrrole (PPy) is another intrinsically conductive polymer that has been extensively studied in the field of biomedical and tissue engineering, as shown in **Table 2** [50][51][52][53][54][55]. It has been reported that polypyrrole offers more favourable biological properties than polyaniline. However, under similar experimental conditions, cells cultured on these two polymeric substrates have demonstrated comparable biological responses [56]. PPy can be chemically modified and combined with other polymers to provide a biocompatible electrical microenvironment to the cells. This way, cell viability, proliferation rate, and intercellular coupling can be increased appreciably with a high potential to direct their differentiation toward cardiomyocyte-like phenotype. Poly(L-lactide-co-glycolic acid)/PPy conductive 3D electrospun scaffolds exhibited good biocompatibility when cultured with mouse cardiac progenitor cells and human-induced pluripotent stem cells (hiPSCs). Induced pluripotent stem cells proliferated along the conductive fibre lengths without severe apoptosis up to ten days post-culture [57]. Likewise, PPy-chitosan hydrogels offered no cytotoxicity to rat smooth muscle cells and promoted their proliferation, morphology, and metabolism. These conductive hydrogels significantly enhanced the intracellular Ca^{2+} transient propagation in cultured neonatal rat CMs and improved myocardial electrical signal conduction with elevated cardiac functions in the rat MI model [58]. Human-induced pluripotent stem cells derived CMs demonstrated a sarcomeric length of 1.86 µm three weeks post culture on nanopatterned silk fibroin/PPy conductive scaffolds [59] while the average sarcomeric length of human CMs in a relaxed state is about 2.2 µm [60]. This demonstrates the ability of the nanopatterned conductive scaffold to achieve near-physiological sarcomeric lengths owing to nanoscale channels which directed the unidirectional growth and proliferation of cells to achieve cardiac muscle-like striated morphology. Seven days post culture, hiPSCs differentiated to cardiomyocyte-like cells with Nkx2.5 and GATA4 expression elevated by 2 and 3.3-fold, respectively, when cultured on Poly(lactide-co-glycolic acid)/PPy conductive membranes [61].

Table 2. Polypyrrole based conductive constructs in cardiac tissue engineering.

Conductive Substrate	Mechanical Properties	Electrical Properties	Cell Line or Tissue	Biological Response
PCL, PPy films [62]	Nanoindentation test, E = 0.93 GPa	Keithley Parameter Analyzer, ρ = 1.0 kΩ-cm	HL-1 murine CMs	Enhanced Cx43 expression, improved Ca^{2+} transients
Chitosan, PPy porous membranes [63]	E = 486.7 kPa	Three-probe detector, σ = 63 mS/m	NRVMs, rat MI model	Improved cytoskeletal organisation with high beating amplitude, tissue morphogenesis at the MI site
SF, PPy composites [59]	E = 200 MPa, UTS = 7 MPa	Four-probe technique, σ = 1 S/cm	hPSC-CMs	Enhanced expression of Cx43, Myh7, cTnT2, SCN5A genes, elongated Z-band width and sarcomeric length
Chitosan, PPy hydrogels [58]	E = 3 kPa	Four-point probe,	Neonatal rat CMs, rat SMCs	Good proliferation with elevated calcium transients and shorter QRS intervals

Conductive Substrate	Mechanical Properties	Electrical Properties	Cell Line or Tissue	Biological Response
		σ = 0.23 mS/cm		
PLGA, PPy membranes [57]			Mice CPCs, hiPSCs	Good biocompatibility and proliferation rate
PLGA, PPy membranes [61]			hiPSCs	Differentiation of hiPSCs to CMs, enhanced expression of actinin, Nkx2.5, GATA4, and Oct4
PCL, gelatin, PPy electrospun membranes [64]	E = 50.3 MPa, εr = 3.7%	Four-probe technique, σ = 0.37 mS/cm	Rabbit primary CMs	High proliferation rate, enhanced expression of Cx43, cTnT, and α-actinin
PPy, HPAE hydrogels [65]	G' = 35 kPa,	Four-probe technique, σ = 0.65 mS/cm	L929, BMSCs	Enhanced Cx43, α-SMA expressions, excellent cell viability and biocompatibility

Abbreviations: PPy: polypyrrole, E: elastic modulus, εr: strain at rupture, G': shear storage modulus, σ: electrical conductivity, NRVMs: neonatal rat ventricular myocytes, hPSCs-CMs: human pluripotent stem cells derived cardiomyocytes, SF: silk fibroin, CPCs: cardiac progenitor cells, hiPSCs: human induced pluripotent stem cells, PLGA: poly(lactic-co-glycolic acid), HPAE: hyperbranched poly(amino ester), BMSCs: bone marrow-derived mesenchymal stem cells, α-SMA: alpha-smooth muscle actin.

2.3. Poly(3,4-Ethylenedioxythiophene)/PEDOT

PEDOT-based electroconductive scaffolds represent a good electrical interface with biological cells/tissues owing to their intrinsic capability to conduct electrical currents, good stability, mechanical properties and biocompatibility, thus providing promising platforms for tissue engineering applications [66][67][68]. To enhance the poor water solubility, it is combined with Poly(styrenesulfonic acid)/PSS in a polymer blend. A conductive PEDOT:PSS/PEG hydrogel was prepared using two-step sequential polymerisation by in situ synthesis of PEDOT within the pre-crosslinked PEG hydrogel. To promote cell adhesion, RGD peptides were covalently attached to the conductive hydrogel surface. In vitro studies with H9C2 myocytes demonstrated good biocompatibility of this conductive hydrogel. It also supported cell adhesion and proliferation up to five days of culture [69]. Better results to promote cardiomyogenic differentiation have been obtained culturing cardiac cells on more complex conductive structures mimicking the fibrous and porous nature of cardiac ECM. A material mimicking elastomeric mechanical properties of the cardiac ECM was obtained by interpenetrating PEDOT into nitrile butadiene rubber (NBR) and Poly(ethylene glycol) dimethacrylate (PEGDM) crosslinked electrospun mats. PEDOT-embedded mats displayed high flexibility and conductivity, and induced enhanced expression of Cx43 and α-actinin in cardiomyocytes after five days of

incubation, suggesting the presence of contractility and cell maturation [70]. **Table 3** summarizes the applications of PEDOT-based conductive constructs in cardiac tissue engineering and their effect on cellular response.

Table 3. PEDOT based conductive constructs in cardiac tissue engineering.

Conductive Substrate	Mechanical Properties	Electrical Properties	Cell Line	Biological Response
PEG/PEDOT:PSS hydrogels [69]	Ec = 21 kPa	Four-probe technique, σ = 16.9 mS/cm	H9c2	Good cell viability and proliferation
GelMA/PEDOT:PSS hydrogels [71]	E = 10.3 kPa	EIS, Z = 261 kΩ at 1 Hz	C2C12	Good cell viability and proliferation but high polymer concentration was detrimental to cells
Collagen/alginate/ PEDOT:PSS hydrogels [72]	G = 220 Pa, τmax = 41 Pa	Four-probe technique, σ = 3.5 mS/cm	CMs, hiPSCs-CMs	Good cell viability, proliferation, and adhesion, synchronous beating patterns
Alginate/PEDOT hydrogels [73]	Ec = 175 kPa, G' = 100 kPa, G" = 10 kPa	Electrochemical workstation, σ = 61 mS/cm	BADSCs	Differentiation of BADSCs to CMs with enhanced expression of cTnT, α-actinin, Cx43
NBR/PEGDM/PEDOT electrospun membranes [70]	E = 3.8 MPa, εr = 75.1%	Four-probe technique, σ = 5.8 S/cm	Cardiac fibroblasts	Well organised sarcomeres, enhanced expression of α-actinin, Cx43
PCL/PEDOT:PSS microfibrous scaffold [74]	E = 13 MPa		H9c2, primary CMs	Enhanced expression of Cx43 and α-actinin, synchronous beating patterns of CMs

Abbreviations: E: elastic modulus, Ec: compressive modulus, εr: strain at rupture, G: shear modulus, G': shear storage modulus, G": shear loss modulus, τmax: maximum shear stress, σ: electrical conductivity, PEG: polyethylene glycol, EIS: electrochemical impedance spectroscopy, BADSCs: brown adipose-derived stem cells, NBR: nitrile butadiene rubber, PEGDM: poly(ethylene glycol) dimethacrylate, GelMA: gelatin methacrylate

3. The Underlying Mechanisms of the Positive Role of Conductive Substrates in Cardiac Tissue Engineering

Though the electroconductive scaffolds provide better platforms for the tissue engineering of nerve, cardiac, and skeletal muscle tissues, the mechanism by which these constructs influence cellular behaviour is yet to be known [75]. To uncover this, an equivalent circuit model was proposed for two groups of cardiomyocytes seeded on a

conductive substrate. One group was assumed to be active (AG), which could fire spontaneous action potentials, while the other was assumed to be passive (PG), which could not fire spontaneous action potentials, but it was well electrically coupled. AG was considered the only source of ionic current, and the passive group was only affected by the electrical currents from the neighbouring AG. Nano gaps/clefts are formed between the cell membrane of the cultured cardiomyocytes and the substrate surface. Ionic solution filled these clefts during culturing, and it was modelled as seal resistance [76]. Seal resistance is usually generated by the solution between cell-substrate interfacial gaps and has a direct link with the adhesion strength of cells with the substrate [77]. When cells in the active group (AG) fire spontaneous action potentials, the electronic redistribution on the surface of the conductive substrate takes place just beneath the cells. The interfacial clefts between PG cells and substrate fill with more anions due to this electronic redistribution, which depolarises the plasma membrane of cells and could trigger an action potential. Larger seal resistance gives rise to higher excitation potential (Upeak) which indicates a strong electrical coupling between AG and PG. The passive group will fire an action potential once the threshold (Upeak) crosses the resting membrane potential of −90 mV [78][79]. In this way, PG could be stimulated and electrically synchronised to AG under the influence of action potentials generated by the active group, as shown in **Figure 3**.

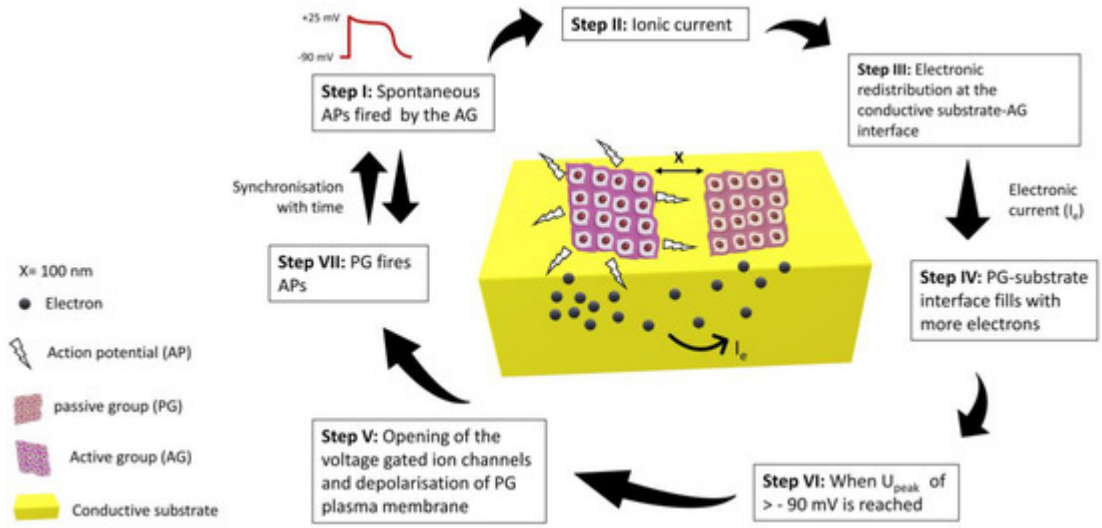

Figure 3. A theoretical model of ionic to electronic current transition for cells cultured on a conductive substrate. The ionic current interacting with electrons could direct their flow in other directions. This electronic current, opening the voltage-gated ion channels, would result in the influx of Na^+, K^+ and Ca^{2+} ions. This influx will depolarise the plasma membrane and the passive group (PG) will eventually fire action potentials.

4. Conductive Substrates for In Vivo Cardiac Repair

Electroconductive scaffolds represent a leap forward in the effort to manufacture supports to properly address cell fate towards a cardiomyocytic phenotype. The scaffold fabrication is a complex endeavour finalised to replicate in vitro the ECM microenvironment to foster proper cell-cell and cell-matrix interactions driving the cardiomyocyte maturation process. An optimal scaffold must be biocompatible (but not necessarily biodegradable, if the constituent materials are immunopermissive), with (i) adequate porosity (to deliver biologically active factors and remove cell waste) and (ii) mechano-structural design (to deliver physical signals, such as stiffness, micro/nano-

topography, etc.), and (iii) with electroconductivity appropriate to mimic the ECM structure and function. Finally, these characteristics must allow the integration of the engineered tissue with the native injured myocardium to restore heart function.

5. Future Research

A biodegradable, intrinsically conductive polymer whose conductivity could be tuned to mimic the electrical features of the myocardium is of great necessity in cardiac tissue engineering. No material has ever been produced which would undergo perpetual contraction and relaxation cycles for an entire span of natural life, like myocardium. To mimic this versatility, future studies should take into consideration the complex biomechanics, anisotropy, micro/nano-architecture, and electrical properties of the myocardium.

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