Advances in Biology & Earth Sciences
Vol.9, Special Issue, 2024, pp.58-80
https://doi.org/10.62476/abes9s58

CARDIOVASCULAR DISEASE, SIGNALING, GENE/CELL THERAPY AND ADVANCED NANOBIOMATERIALS

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Abstract. Cardiovascular biomaterials (also known as CB) are the most common type of biomaterials, both in terms of investments and demand. This review article compiles information on the CB and categorizes it into three primary categories: metals, polymers, and biological materials. Blood compatibility is one of the primary parameters that restricts the use of biomaterials for cardiovascular applications. Within the scope of this study, a number of significant figures concerning blood compatibility are investigated. There were a variety of surface modification techniques that were being utilized at the moment in order to enhance the compatibility of the CB. For the purpose of gaining a deeper comprehension, a number of contemporary applications of surface modification techniques on materials for cardiovascular devices were also discussed. Last but not least, the utilization of induced human pluripotent stem cells, the endothelization of cardiac implants, and the current trend of CB. As a result of the rapid expansion of the field of CB, a significant number of new researchers and academics are developing an interest in it. This overview will serve as a one-stop shop for quickly gaining an understanding of the fundamental studies that have been conducted in the field of CB.

Keywords: *Nanomedicine, drug delivery, cancer, cancer metabolism, cell signaling, drug development.*

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Received: *18 November 2023;* ***Accepted:*** *29 March 2024;* ***Published:*** *8 April 2024.*

1. Introduction

Globally, one of the biggest health burdens is cardiovascular disease. The "No.1 killer", cardiovascular disease, accounts for around 40% of all fatalities globally, taking the lives of almost 17 million people annually (Dagenais *et al*., 2020). The tremendous amount of effort that has been put forth to continue improving the prognosis of cardiovascular disorders has resulted in a steady decline in the incidence of chronic heart failure, which is the final stage of the majority of cardiovascular illnesses. But in a population-based research including four million people in the UK, almost three out of every thousand patients experienced heart failure annually (Conradet *et al*., 2018).

Despite recent advancements, the prognosis for chronic heart failure remains relatively poor. At 1, 5, 10 and 15 years following the diagnosis of chronic heart failure, the survival rates were 75.9%, 45.5%, 24.5% and 12.7%, respectively, (Taylor *et al*., 2019) which completely altered the survival rate among those patients. To exacerbate

How to cite (APA):
Erdil, N. (2024). Cardiovascular disease, signaling, gene/cell therapy and advanced nanobiomaterials. *Advances in Biology & Earth Sciences*, 9(Special Issue), 58-80 https://doi.org/10.62476/abes9s58

the situation, repeated and worsening episodes are a common feature of chronic heart failure. Hospital stays and ER visits on a regular basis raise the financial burden considerably. Hospitalizations for heart failure were projected to have cost the US economy 11 billion dollars in 2014 (Jackson *et al*., 2018).

Patients with chronic heart failure in Denmark must pay an average of 17,039 euros annually for their condition, which is over three times more than what a control person in the same age, gender, marital status and municipality would have to pay (Bundgaard *et al*., 2019). As a result, increasing the survival rate of people with chronic heart failure is crucial for both the economy and worldwide public health. Because of innovations in genetic tools, we now have a much better understanding of the signaling cascades that are associated with chronic heart failure. Translational work, on the other hand, is still a little bit behind schedule. In the treatment of chronic heart failure, beta-blockers, aldosterone receptor antagonists and angiotensin II-converting enzyme inhibitors/angiotensin II receptor blockers were initially developed as the primary treatment. This was more than ten years ago (Cohn *et al*., 2022).

The neutral endopeptidase neprilysin was further inhibited by sacubitril–valsartan, which resulted in an improvement in the chances of survival for patients who were suffering from chronic heart failure (McMurray *et al*., 2014). The remarkable effectiveness of sodium-glucose cotransporter 2 inhibitors in the treatment of chronic heart failure An unexpected discovery that the risk of heart failure was lower in diabetic therapeutic trials was the impetus for the discoveries made in (McMurray *et al*., 2019; Packer *et al*., 2020; Zelniker *et al*., 2019).

2. Signal Pathways

Thanks to the progress that has been made in molecular research, we will have a great deal more therapeutic targets and opportunities for heart failure medications. As a result of the fact that myocardial infarction and ischemic cardiomyopathy are the most common causes of chronic heart failure, there is a direct connection between heart failure and the processes that are responsible for these disorders, in addition to the healing of myocardial tissue. Recent research has shown that immune cells, microvascular endothelial cells, lymphatic endothelial cells, cardiomyocytes and fibroblasts play a significant role in the maintenance of normal cardiac function as well as the pathogenesis of chronic heart failure among other cell types. In the event that the heart fails, we will discuss the signal transduction processes of each cell in turn. In recent times, there has been an increase in the amount of attention paid to the condition associated with heart failure with left ventricular ejection fraction or HFpEF. When it comes to epidemiology, pathophysiology and most importantly, how each kind of heart failure responds to heart failure medication, there are significant differences between heart failure with decreased ejection fraction (HFpEF) and heart failure with HFpEF syndrome (HFrEF). As a result, a concise summary of the research that has been conducted on the molecular mechanism of this particular subtype of chronic heart failure will be presented.

Calcineurin-nuclear factor of activated T cells (NFAT) signaling

A serine/threonine protein phosphatase that is reliant on calcium and calmodulin, calcineurin is a heterodimer made up of the catalytic subunit calcineurin A (CnA) and the regulatory subunit calcineurin B. (CnB). Under baseline circumstances, the

autoinhibitory domain at CnA's C-terminus generates α-helices to block the upstream catalytic site. A rise in intracellular Ca2+ concentration causes Ca2+ to occupy low-affinity binding sites in CnB, which causes CnA to undergo a conformational shift. This alteration promotes Ca2+-calmodulin binding. The interaction between CnA and Ca2+ results in the release of the catalytic site from the autoinhibitory domain, which ultimately leads to the full activation of the calcineurin complex (Roy & Cyert, 2020). Through this mechanism, calcium signaling is connected to the dephosphorylation of calcineurin, which occurs in a wide variety of downstream substrates, including NFAT. The subcellular location of NFAT is precisely determined by the degree of phosphorylation it possesses. After being dephosphorylated by calcineurin, NFAT functions as a transcription factor to initiate the transcription of a wide variety of genes, including those that are responsible for pathological cardiomyocyte hypertrophy. During the year 1988, Molkentin and colleagues created a transgenic animal that was capable of overexpressing a constitutively active version of CnA in cardiomyocytes. However, this version was missing the C-terminal autoinhibitory region (Molkentin *et al*., 1998). Despite the fact that all transgenic mice developed significant cardiac hypertrophy on their own, the calcineurin inhibitor cyclosporin A was able to prevent it from occurring. In vitro, calcineurin inhibition was found to be effective in reducing pathological cardiomyocyte hypertrophy that was induced by either phenylephrine (PE) or angiotensin II (Ang II). NFAT3, which is constitutively active in cardiomyocytes, was also produced in a transgenic animal. This is given that NFAT3 is the predominant NFAT isoform in the heart. The hypertrophic phenotype of CnA transgenic mice was well reproduced in NFAT3 transgenic mice. Since then, calcinurin inhibition has been used to treat heart hypertrophy with great success. Calcineurin signaling was downregulated in transgenic mice that overexpressed inhibitory proteins or dominant-negative calcineurin mutants. These animals were shielded from myocardial hypertrophy brought on by isoproterenol infusion or pressure overload (Zou *et al*., 2001; Rothermel *et al*., 2001; De Windt *et al*., 2001). In addition, the decreased activity of calcineurin was caused by the deletion of the integrin-binding protein-1 (CIB1) and the calcineurin partner Ca2+ through genetic deletion. The pathological hypertrophy that was brought on by pressure overload was less severe in CIB1-KO mice when compared to control mice. Physiologic hypertrophy that was induced by swimming, on the other hand, did not experience any consequences (Heineke *et al*., 2010) Furthermore, calcineurin inhibition was a cause for concern for a number of investigations, despite the fact that these findings were encouraging. Overexpressing the endogenous calcineurin inhibitor ZAKI-4 beta resulted in a reduction of the pressure overload-induced cardiac hypertrophy; however, this was accompanied by an increase in the severity of diastolic dysfunction (Gelpi *et al*., 2009).

Signaling through the interactions of G protein-coupled receptors

Endothelin-1 (ET-1) and catecholamines are significant inducers of chronic heart failure and cardiac hypertrophy. Catecholamines are also a significant inducer of Ang II. These extracellular signals are primarily transmitted to intracellular effectors by means of G protein-coupled receptors from the extracellular environment (Frey & Olson, 2003). The intracellular domain of these transmembrane proteins, also known as receptors, contains a site that is capable of binding to G proteins. In response to the binding of a ligand, a G protein-coupled receptor undergoes a conformational change and performs the role of a guanine nucleotide exchange factor. This allows for the

substitution of GTP for GDP on a G protein. Activation of the G protein is achieved through this mechanism, which involves the release of the α subunit (Gα) from the β and γ subunits (Gβγ) (Thal *et al*., 2018). Different downstream signaling pathways are activated by the activated protein G and these pathways vary depending on the type of Gα molecules. There is a connection between Gq/11 and the receptors for α-adrenergic, ET-1 and angiotensin II. This interaction between activated Gq/11 and phospholipase Cβ (PLCβ) results in the production of diacyl glycerol (DAG) and inositol-1,4,5-trisphosphate during the process (IP3). Protein kinase C is activated by the latter, while the former causes an increase in the amount of Ca2+ that is found inside the cell (PKC). Both the calcineurin-NFAT signaling pathway and the calmodulin-dependent kinase pathway can be activated by an increase in Ca2+ within the body (CamK). It is through the phosphorylation of histone deacetylases (HDACs) that CamK facilitates the movement of histones from the nucleus to the cytoplasm (Wu *et al*., 2006).

ERK signaling

Of the five subtypes of ERK, the most extensively researched are ERK1 and ERK2. MEK1/2 are the corresponding MAPKKs upstream of ERK1/2. A tiny G protein belonging to the Ras family activates the MAPKKK RAF1, which is located upstream of MEK1/2. After activation, cAMP-responsive element-binding protein (CREB) and ELK1 are among the transcription factors that ERK1/2 phosphorylates after translocating to the nucleus. In the end, activation of the ERK1/2 MAPK cascade results in a transcriptome alteration that promotes cell proliferation. Spontaneous cardiac hypertrophy was seen in 50 transgenic mice with activated MEK1 overexpression specific to cardiomyocytes. MEK1 selectively turned on ERK1/2, but not JNK or p38. It's interesting to note that these mice's heart performance grew over time without showing any symptoms of decompensation. Both in vitro and in vivo, cardiomyocytes with MEK1 overexpression exhibited resistance to apoptotic stimuli. These findings suggested that concentric healthy hypertrophy, as opposed to pathologic hypertrophy, was linked to the ERK1/2 pathway (Bueno *et al*., 2002). ERK1/2 can integrate signals from various pathways in addition to the traditional RAF1-MEK1/2 pathway. Thr183 and Tyr185 in murine ERK2 (Ferrell & Bhatt, 1997) are the threonine and tyrosine in the threonine-glutamate-tyrosine (TEY) motif inside the activation loop that MEK1/2 phosphorylates to activate ERK1/2. A research revealed that ERK2 might interact with Gβηq in order for it to be autophosphorylated at Thr188. Pressure overload-induced ventricular hypertrophy was enhanced by a gain-of-function mutation in ERK2 that mimics phosphorylation, but this phenotype was inhibited by a loss-of-function mutation. A mechanistic analysis revealed that the ERK2 Thr188 mutation significantly affected the phosphorylation of its nuclear targets but had no effect on the phosphorylation of ERK1/2's cytosolic substrates. This suggests that autophosphorylation at Thr188 promotes ERK2 nuclear translocation (Lorenz *et al*., 2009).

p38 signaling

Numerous inflammatory and stressful events, including cytokines, infections and oxidative stress, can trigger p38 signaling. The two major activators of p38 are MEK3 and MEK6, while TGF-beta activated kinase is a kind of MAPKKK that may activate p38 (TAK). It has been demonstrated that p38 activation occurs in models of cardiac hypertrophy that are caused by pressure overload, ET-1 or PE. Phosphorylation of a

number of dystrophic gene transcription, including MEF2, is facilitated by activated p38 signalingTAK1 (Takeishi *et al*., 2001; Clerk, 1998). Dual-specificity protein phosphatases, also known as DUSPs, are a class of specialized phosphatases that have the ability to dephosphorylate and inactivate MAPKs (Dickinson & Keyse, 2006). Primarily acting on p38 are DUSP1 and DUSP4, among them. Pharmacological suppression of p38 was able to restore mice with severe dilated cardiomyopathy and cardiac hypertrophy caused by twofold deficiency in DUSP1 and DUSP4 (Auger-Messier *et al*., 2013). There is ongoing debate on MEK3/6's role in cardiac hypertrophy. Increased ANP expression, sarcomere reconfiguration and cell expansion were among the hypertrophic responses brought on through the production of MEK3/6 in cardiomyocytes through in vitro overexpression (Wang *et al*., 1998). At the same time that MEK6 overexpression only resulted in mild cellular hypertrophy, heart cross-sections demonstrated that MEK3 overexpression led to sporadic hypertrophy and heterogeneous myocyte atrophy (Liao *et al*., 2001). According to the findings of another study, the results were inconsistent. Ang II, isoproterenol, pressure overload and PE all caused more severe cardiac hypertrophy in mice that expressed dominant-negative MEK3 and MEK6 than control mice did. This hypertrophy was brought on by pressure overload.

Phosphoinositide 3-kinases (PI3K)

PI3K is an essential molecule that plays a role in the transmission of signals that indicate cell growth and proliferation. There are four different classes of PI3Ks, with Class I being further subdivided into different subsets known as IA and IB. It is possible for PI3Ks to be controlled by tyrosine kinase receptors, such as the IGF-1 receptor and G protein-coupled receptors, such as the α- and β-adrenergic receptors (Zhu *et al*., 2001; Schlüter *et al*., 1998; Chesley *et al*., 2000). A catalytic p110γ and a regulatory p101 subunit are the components that make up Class IB PI3K. On the other hand, Class IA PI3K is composed of a p110 catalytic subunit (with α, β or δ isoforms) and a p85 regulatory subunit. GRCPs are responsible for the regulation of Class IB PI3K, whereas tyrosine kinase receptors are responsible for the regulation of Class IA PI3K. After being activated, phosphatidylinositol-3,4,5-triphosphate (PI3K) is the product of the conversion of phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-triphosphate (PIP3). PIP3 has the ability to directly bind to phosphoinositide-dependent kinase-1 as well as protein kinase B (PKB)/AKT (PDK1). Due to the fact that PIP3 is membrane-restricted, binding attracts and facilitates the interaction between AKT and PDK1 at the membrane. The phosphorylation and activation of AKT are both brought about by the interaction that takes place between PDK1 and AKT. Downstream effectors such as mTOR and glycogen synthase kinase 3β (GSK3β) are phosphorylated by activated AKT, which continues the process.

MicroRNAs: MicroRNAs are the little noncoding RNAs that have been researched the most (miRNAs). These single-stranded RNAs, which are used in the process of RNA silencing, have a length of 22 nucleotides or less. With the help of complementary sequences, microRNAs are able to bind to mRNA molecules, primarily in the 3' non - coding region (UTR).Translational repression or mRNA degradation results from the binding of a miRNA. It has been demonstrated that many miRNAs control cardiac hypertrophy. The in vivo suppression of miR-133 through the use of chemically modified antisense oligonucleotides was responsible for the development of sustained cardiac hypertrophy (ASOs). It is possible that the mechanism behind the

antihypertrophic effect of miR-133 is the downregulation of its targets, which include cell replication cycle 42 (Cdc42), negative protein complex detailed member A and ras transcription factors family member A (RhoA) (NELFA) (Carè *et al*., 2007). MiR-133, which targets adenylate cyclase VI and the downstream cAMP-dependent pathway, was shown to reduce myocardial hypertrophy and apoptosis that were brought on by pressure overload or β-adrenergic stimulation, according to a different research study (Castaldi *et al*., 2014). microRNA-378 was able to inhibit cardiac hypertrophy by concentrating on a considerable number of components of the MAPK pathway. These components included MAPK1, the IGF-1 receptor, growth factor receptor-bound protein 2 and kinase suppressor of ras 1 (Ganesan *et al*., 2013).

LncRNAs: Other lncRNAs are involved in the process of heart hypertrophy as well. Unlike microRNAs, long noncoding RNAs (lncRNAs) in cardiomyocytes are involved in a wide variety of molecular functions. Mhrts, which stand for myosin heavy chain-associated RNA transcripts, are a collection of antisense transcripts that are located at the Myh7 gene locus. In the event that pressure overload leads to hypertrophy of the heart, Mhrts are downregulated. Following TAC surgery, there was a correlation between the restoration of one Mhrt's expression and an increase in cardiac function as well as a decrease in hypertrophy (Mhrt799). For the purpose of controlling hypertrophy in a mechanistic manner, Mhrt and Brg1 established a feedback loop. One of the chromatin remodeling factors known as Brg1 is responsible for facilitating the transcriptome changes that are associated with hypertrophy. When the cells were subjected to stress, the chromatin repressor component Brg1 was able to inhibit Mhrt transcription. When Mhrt joined to the helicase domain of Brg1, it successfully separated itself from its genomic DNA targets, which resulted in the cessation of subsequent chromatin remodeling (Han *et al*., 2014).

Platelet - derived growth factor β (TGF-β)

The cytokine that has been linked to fibrosis in multiple organs has been the subject of the most extensive research study (Bissell & George, 2001; Meng *et al*., 2016; Saika *et al*., 2008). Within the heart of mammalian organisms, the TGF-β family is comprised of three isoforms, namely TGF-β1, -β2 and -β3 (MacLellan *et al*., 1993). Transforming growth factor-beta 1 (TGF-β1) is a protein that is found in all tissues and appears to be the most powerful regulator of fibrosis (Kim *et al*., 2018). The transforming growth factor-beta (TGF-β) is located in the extracellular matrix (ECM) and is released as a latent complex along with its binding proteins. In order for mature TGF-β to be released, numerous activation processes are required (Robertson *et al*., 2016). The latent TGF-β complex functions as a sensor and it is sensitive to signals from a wide variety of activators, such as reactive oxygen species (ROS), integrin and proteases (Annes *et al*., 2003; Shi *et al*., 2011).

Five type II receptors, also known as TβRII and seven type I receptors, also known as TβRI and also referred to as activin-like receptor kinase (ALK) 1–7, are present in mammals. These are all serine/threonine kinases that are transmembrane in nature (Rahimi *et al*., 2007). Following the binding of TGF-β to TβRII, a heterotetrameric complex is formed, consisting of two TβRI units and two TβRII units. This complex phosphorylates and activates the cytoplasmic domain of TβRI, thereby initiating a cascade that manifests further downstream (Heldin *et al*., 2016; Shi *et al*., 2003).

Wnt signaling

The presence of the Wnt1 gene in breast tumors was an important finding that was made in 1982 (Nusse & Varmus, 1982). The first explanation of the connection between diseases and the Wnt signaling pathway was presented in the year 1991. There is a class of secretory proteins known as (Kinzler *et al*., 1991; Nishisho *et al*., 1991). Wnts that can be found in a wide variety of organs and animals. Among the vertebrates, it has been demonstrated that 19 Wnt genes function as ligands and these ligands are capable of interacting with at least 15 receptors in order to undergo signal transduction. Among the three pathways involved in (Hu *et al*., 2020) Wnt signaling are: The planar cell polarity, the calcium route and the canonical β-catenin-dependent pathway are the three pathways that are commonly used (Tao *et al*., 2016).

A heterodimeric receptor complex consisting of one LRP5/6 and one FZD is what extracellular Wnt binds to so that it can function. Axin is recruited through the recruitment of DVL by FZD, which provokes another of the receptors to phosphorylate LRP5/6 by GSK3 and CK1α. Additionally, this causes Axin to recruit in the process. The subsequent process involves the separation of the β-catenin destruction complex, which results in nuclear translocation and the accumulation of β-catenin. Both β-catenin and T-cell factor (TCF) are responsible for activating Wnt-responsive genes within the nucleus (MacDonald *et al*., 2009; Nusse & Clevers, 2017).

Wnt/β-catenin signaling

Extracellular vesicles have been shown to be capable of transporting Wnt ligands to cardiac fibroblasts, which then have the ability to activate the Wnt/β-catenin pathway, as demonstrated by an observation made *in vitro* (Dzialo *et al*., 2019). Moreover, the expression of Wnt1 was increased when acute myocardial ischemia damage occurred. The expression of profibrotic genes was induced by Wnt1, which also led to an increase in the number of cardiac fibroblasts observed. In the aftermath of an acute ischemic insult, the disruption of Wnt/β-catenin in cardiac fibroblasts had a detrimental impact on both the healing of wounds and the functioning of the heart function (Duan *et al*., 2012).

Wnt/β-catenin signaling pathway

Patients who were diagnosed with atrial fibrillation (AF) had significantly lower levels of miR-27b-3p in their peripheral blood. The findings of this study revealed that miR-27b-3p had the ability to specifically target Wnt3a and decrease its expression. As a result, atrial fibrosis was alleviated and the signaling between Wnt and β-catenin was blocked (Lv *et al*., 2019). Desmoglein-2 (DSG2) (AC) is one of the genes that is associated with arrhythmogenic cardiomyopathy that is altered in a pathogenically altered manner the most frequently). AC pathogenesis was observed in mice that had overexpressed the human DSG2 mutant specifically in cardiomyocytes. This pathogenesis included ventricular fibrosis and necrosis of cardiomyocytes. Within the context of this AC model, it was discovered that miR-708-5p, miR-217-5p and miR-499-5p were highly dysregulated. One hypothesis proposed that the dysregulated microRNAs would have the ability to regulate the Wnt/β-catenin signaling pathway. The inhibition of fibrosis by (Calore *et al*., 2019) miR-29 has been demonstrated in a variety of organs (Qin *et al*., 2011; Xiao *et al*., 2012). AntimiR-29 treatment, global miR-29 deletion and cardiomyocyte-specific miR-29 loss have all been shown to stop pressure overload-induced cardiac hypertrophy and fibrosis.

Wnt/calcium signaling pathway

One of the most important downstream effectors of the Wnt/calcium pathway (Sheldahl *et al*., 2003) is called CaMKII and it is involved in the remodeling of the heart. The transgenic overexpression of DVL-1, which activated wnt signaling, was responsible for the cardiac enlargement and fibrosis that was observed, in addition to the severe heart failure that was observed. Every single one of the three downstream Wnt pathways was operational in transgenic mice (Malekar *et al*., 2010). Following the removal of CaMKIIδγ, the cardiac phenotype of mice exhibiting DVL-1 overexpression returned to its normal state. The absence of CaMKII did not have any impact on the activation of JNK or β-catenin that was produced by Dvl-1. This indicates that CaMKII was the primary mediator of the cardiomyopathy that was induced by Dvl-1 overexpression. CaMKII established a mechanistic connection between Wnt signals and the activity of HDAC4 and MEF2 (Nirenberg & Leder, 1975). Global genetic modification, on the other hand, was not successful in determining the function of CaMKII in a number of different types of cardiac cells.

Plasmid-based gene therapy

DNA fragments of a significant size can be packaged using plasmids, which are not only easy to work with but also simple to store. The uncommon genomic incorporation that occurs in plasmids is a significant factor that contributes to their low carcinogenicity (Laitinen *et al*., 1992). Plasmid-mediated gene therapy was first applied to rabbits in 1996, marking the first time that this technique was used. phVEGF165, which is cDNA encoding the 165-amino acid variant of VEGF and was put into the pUC118 vector, improved tissue perfusion and collateral circulation after it was injected into the hindlimb muscles of rabbits that were suffering from ischemia (Tsurumi *et al*., 1996). The clinical application of PhVEGF165 was evaluated in a timely manner in patients who were suffering from ischemia in their limbs. A balloon used for angioplasty was used to inject 2000 micrograms of phVEGF165 into the popliteal artery, which resulted in the induction of angiogenesis (Isner *et al*., 1996). The results of clinical trials that utilized plasmid-mediated gene therapy for the treatment of peripheral artery disease were significantly encouraging (Williams & Kingston, 2011). 1998 saw the implementation of phVEGF165 gene therapy for the purpose of promoting myocardial angiogenesis in patients who were experiencing symptoms of myocardial ischemia. In the course of this investigation, a small thoracotomy was performed on the left anterior side in order to inject a moderate quantity of 125 micrograms of phVEGF165 directly into the myocardium that was ischemic. In addition to this, myocardial perfusion was considerably improved (Losordo *et al*., 1998).

Virus-based gene therapy

The delivery of genes through plasmid vectors, which have a low delivery efficiency, is less successful and less efficient than the delivery of genes through adenoviruses and AAV vectors. It is possible for viral vectors, which are composed of a lipid envelope or a protein capsid, to enter the nucleus of the target cell. These vectors are responsible for transporting the target cDNA (Kay, 2011).

Oligonucleotide-based gene therapy

In the past, it has been established that gene therapy is a method that targets illnesses by utilizing the protective function of genes that are overexpressed. Through

the utilization of microRNAs, it is possible that certain disorders could potentially benefit from the downregulation of specific genes. Furthermore, despite the fact that AAV-delivered small hairpin RNAs have the potential to silence genes, (Grund *et al*., 2019) this method is currently only useful for fundamental research. Gene silencing can also be accomplished through the systematic administration of synthetic RNAs or antisense oligonucleotides (ASOs). Significant improvements can be made to the potency, stability, distribution and cellular absorption of these drugs through the application of the appropriate chemical modifications (Crooke *et al*., 2018). There is no comparison between RNA therapy and traditional pharmacological treatment when it comes to the significant benefits it offers. To begin, certain proteins are difficult to target with inhibitory compounds due to their distinctive conformation, whereas oligonucleotides are easy to target; this is in contrast to the situation with mRNAs. On top of that, noncoding RNAs, which are typically considered to be unhackable, have the potential to be the focus of RNA intervention. In the second place, off-target impacts can be avoided by carefully designing the order first. Modifications such as phosphorothioate, 2′-O-methyl and 2′-fluoro nucleotide are added to the siRNA in order to increase the stability of the molecule. When it comes to improving patient compliance, the ability of Inclisiran to reduce LDL-C over an extended period of time is a significant advantage. The results of this study lend credence to the viability and efficacy of oligonucleotides as a treatment for cardiovascular disease. However, current investigation has shown order to encourage findings, despite the fact that clinical trials were not yet conducted to investigate the potential of antisense technology to cure cardiomyopathy. An example of this would be the administration of an ASO targeting PLN through subcutaneous injection, which prevented Ca2+ from being mishandled and improved heart function in mice models of dilated cardiomyopathy (Grote Beverborg *et al*., 2021). In addition to targeting genes that code for proteins, targeting noncoding RNAs is a viable strategy that can be utilized. It is a long noncoding RNA (lncRNA) that is abundant in cardiac fibroblasts and is known as Wisp2 superenhancer–associated RNA (Wisper). Wisper is responsible for positively regulating cardiac fibrosis after damage has occurred. Following a myocardial infarction, the reduction of cardiac fibrosis and the improvement of heart function were both achieved through the downregulation of Wisper on the part of ASO. Using (Micheletti *et al*., 2017) miRNA mimics is yet another method that can be utilized for the purpose of gene silencing. When compared to siRNAs or ASOs, miRNA mimics have a greater number of targets but are less selective.

Utilizing stem cell therapy as a foundation for therapeutic strategies

In the initial attempt to produce myocytes that were generated exogenously, skeletal myoblasts were utilized. The implantation of autologous skeletal myoblasts into the infarcted region of animal models of myocardial infarction slowed the remodeling of the ventricles and partially restored cardiac function (He *et al*., 2005; Taylor *et al*., 1998; Ye *et al*., 2007). Skeletal myoblast transplantation improved the left ventricular ejection fraction (LVEF) and the New York Heart Association (NYHA) class while simultaneously reducing the likelihood of hospitalization for heart failure, according to a phase I clinical study that included ten patients who had been diagnosed with ischemic cardiomyopathy (Menasche *et al*., 2003). Nevertheless, a multicenter, completely random, placebo-controlled, double-blind phase II study was conducted with 94 patients who had myocardial infarction and left ventricular dysfunction. The results of this study

showed that myoblast transplantation did not improve heart function as determined by echocardiography at six months. In patients who were undergoing myoblast transplantation, the likelihood of suffering arrhythmic episodes was significantly increased (Menasché *et al*., 2008).

Myoblasts, despite the fact that they possess contractile properties, are unable to establish an electromechanical link with cardiomyocytes that are adjacent to them. This may be the reason why myoblasts are unable to enhance coordinated cardiac contraction. Additionally, disconnected myoblasts have the potential to take on the role of ectopic arrhythmia triggers. These deficiencies limit the extent to which this strategy can be translated into other contexts (Durrani *et al*., 2010).

Biological Materials

Regarding the functionality of biological tissues, metallic and polymeric materials are superior substitutes for heart tissues during repair and replacement. However, when it comes to the functionality of biological tissues, these materials fall short. Biological tissues can originate from either human beings or xenografts (allograft). Porcine valves, bovine pericardial valves and allograft or homograft valves are the three types of bioprosthetic valves that are currently available on the market (Izadifar *et al*., 2018). Porcine valves are the most common type. Homografts are the name given to the whole aortic or pulmonary roots that have been cryopreserved as though they were whole human valves. After implantation, it undergoes additional modifications and revisions to conform to the recipient's dimensions and shape (Stoica *et al*., 2017). In order to create the porcine xenograft valve, the aortic valve of a pig is directly maintained in a glutaraldehyde solution that has a low concentration. Porcine valves, in contrast to mechanical valves, which require senior citizens to have a prescription for an anticoagulant, are appropriate for elderly patients.

When it comes to replacing valves from cattle or pigs, calcification and valve deterioration are two of the most common problems that arise. Additional chemical agents are applied to both types of tissues in order to address these issues. The goal of these applications is to decrease the likelihood that the tissues will calcify during the implantation process and to increase the lifetime of the tissues. The utilization of these organic biomaterials for the purpose of bioprosthetic valves and vascular grafts has typically involved a pretreatment, which can be either chemical or physical in nature. The objective of this pretreatment is to maintain and strengthen the material's resistance to degradation or degradation. The immunogenicity of the materials has been reduced as a result of this, which has improved their compatibility.

Naturally derived biomaterials for cardiovascular tissue engineering

Naturally produced scaffolds have been utilized to promote heart regenerative medicine (Dar *et al*., 2002; Ceccaldi *et al*., 2014; Sun *et al*., 2018). This has been accomplished by producing biomimetic organ scaffolds at clinically relevant scales. These types of materials are scaffolds that are widely used for the purpose of integrating cells in order to create an organ analog that is functional. Natural biomaterials include well-characterized biopolymers such as chitosan, collagen, gelatin, Matrigel, chitosan, alginate, and decellularized extracellular matrix (dECM) (Leor *et al*., 2005; Huyer *et al*., 2015). These biomaterials are used for cardiac tissue engineering. Moreover, some newly discovered biomaterials, such as silk and other conductive materials like carbon nanotubes and graphene, have been evaluated in recent times (Keane & Badylak, 2014).

The crosslinking of these scaffolds can be accomplished through a variety of methods, including enzymatic, UV/vis light-initiated and ionic-based approaches, depending on the specific application (Dar *et al*., 2002; Di Felice *et al*., 2015). It is possible for alginate to form very porous structures, which makes it possible to seed relatively high densities of cells into the tissue construct. This makes alginate an attractive hydrogel for cardiac bioengineering. Through the utilization of such methods, it is possible to produce tissue scaffolds that possess physiologically relevant cell densities in a straightforward and consistent manner (Dar *et al*., 2002). It is also possible to combine chitosan and alginate in order to produce polyelectrolyte complexes (PECs) with extremely porous lattices. These PECs are suitable for three-dimensional cell culture because they maintain the paracrine profile of the target cells. Enhanced vascularization, decreased fibrosis and successful integration of host tissue have been observed during the application of PEC patches in models of myocardial infarction (Stoica *et al*., 2017).

As a result of their biocompatibility and the fact that they can be reabsorbed, collagen and gelatin are among the natural biomaterials that are utilized the most frequently in the field of cardiac tissue engineering (Lee *et al*., 2017; Serpooshan *et al*., 2017). The production of cardiac patches and in vitro tissue models could be accomplished with the help of these materials. As an illustration, in mouse and pig models of myocardial infarction, acellular type I collagen gel scaffolds seeded with cardiogenic follistatin-like 1 protein demonstrated a remarkable function as a cardiac patch in the process of rebuilding damaged heart tissue (Wei *et al*., 2015; Lee *et al*., 2017).

An alternative investigation was conducted using a rat model of myocardial infarction. In this study, childish rat cardiomyocytes (CMs) had been embedded into thick elastin patches, formed in vitro prior to being inserted and then maintained. An infarcted region was prevented from dilatation through the use of cellular grafts, which also resulted in a thickening of the systolic wall and revealed very little sourced arrhythmia (Zimmermann *et al*., 2006). Additional naturally occurring biopolymer, fibrin, has also been utilized in the field of heart tissue engineering (Serpooshan *et al*., 2017; Li *et al*., 2015). Rat neonatal CMs, endothelial cells (ECs) and fibroblasts, for instance, have been effectively added to fibrin-based patches, crosslinked with thrombin enzymatically and aligned mechanically during culture networks (Ye *et al*., 2011; Thomson *et al*., 2013). Under these circumstances, cardiac cells rebuilt the fibrin hydrogel, reacted to electrical pacing by contracting and were incredibly viable. Furthermore, it has been demonstrated that within the fibrin tissue constructions, ECs and fibroblasts self-assemble into vascular networks (Ye *et al*., 2011; Thomson *et al*., 2013). Silk fibroin scaffolds are a family of natural biomaterials that are highly amenable to chemical modification. This allows for the expression of a wide variety of small molecules and attachment factors, which can be easily customized to resemble the environment of the cardiac niche. According to one example, over the course of twenty-one days, rat cardiac When it comes to the field of cardiac tissue engineering, fibrin is a leading contender due to the fact that it can be injected and that it can generate scaffolds that are completely and entirely autologous (Li *et al*., 2015). In addition to these two significant advantages, fibrin also possesses the following. It has been demonstrated that fibroblasts, endothelial cells (ECs) and rat neonatal CMs can be successfully added to fibrin-based patches, crosslinked with thrombin through enzymatic processes and aligned mechanically while the cells are being cultured (Ye *et al*., 2011; Thomson *et al*., 2013). This has been accomplished with great success. Under these circumstances, the

fibrin hydrogel was reconstructed by cardiac cells and the cells responded to the electrical pacing by contracting. Additionally, the cells exhibited a high degree of viability. In addition to this, it has been demonstrated that extracellular vesicles (ECs) and fibroblasts are capable of self-assembling into vascular networks within the constructions of fibrin tissuprogenitor cells. These cells were cultured on porous electrospun semialigned scaffolds and during this time, the cells produced noticeably increased quantities of sarcomeric proteins such as titin, as well as improved native extracellular matrix (ECM) deposition onto and within the silk fibers (Di Felice *et al*., 2015).

Synthetic scaffolds

However, the majority of scaffolding materials that are used for cardiovascular tissue engineering are naturally produced (Lee *et al*., 2014; Ge *et al*., 2006; Bhattarai *et al*., 2018). The primary reason that synthetic biomaterials are utilized is due to the fact that they possess superior mechanical stability, variety, tunability and ideal degradation rates. In addition, synthetic polymers, in contrast to natural biopolymers, are more versatile and can be utilized in a wide range of manufacturing processes. Some examples of these processes include electrospinning, solvent casting and three-dimensional printing. This makes it possible to manipulate the material with ease while maintaining or improving its intended properties, such as the structure and properties of the scaffolding (Ji & Guvendiren, 2017). Polyglycolic acid (PGA) and polylactic acid (PLA) are two examples of bioresorbable polymers that have been extensively researched for their potential use as scaffold materials for cardiovascular applications. A significant amount of PGA has been utilized by researchers as a biodegradable synthetic material for the purposes of tissue engineering and surgical procedures (Freed *et al*., 1994; Huang *et al*., 2014; Gao *et al*., 1998). Dacron® and polytetrafluoroethylene (PTFE), both of which are nonbiodegradable materials, are used in the production of the vast majority of synthetic grafts manufactured today (Matsuzaki *et al*., 2019). Utilizing graft alternatives with a diameter greater than 6 millimeters has proven to be successful for the majority of these grafts (Matsuzaki *et al*., 2019). When synthetic vascular grafts are placed in blood arteries with a small diameter, early thrombosis induces a reduction in the graft's patency (Hoenig *et al*., 2005). In addition to poly(\-caprolactone) (PCL) (Lee *et al*., 2019) other synthetic materials have also been investigated for their potential use as biomaterials in the creation of vascular grafts. PCL vascular grafts were shown to facilitate faster endothelialization and the creation of extracellular matrix when compared to PTFE grafts, as demonstrated by (Pektok *et al*., 2008)

In addition to application in synthetic vascular grafts, PCL has also been employed in heart valve tissue engineering along with polymers such as PLA and PGA due to their appropriate degradation rates and FDA acceptance (Fallahiarezoudar *et al*., 2015; Del Gaudio *et al*., 2008). In tissue engineering heart valve research, polyglycerol sebacate (PGS) shown good biocompatibility and rapid breakdown rates between 4–6 weeks (Masoumi *et al*., 2013). Developed by Langer et al., PGS displays elastomeric qualities while being suited for a range of biologic and ECM-like material (Wang *et al*., 2002; 2003). Additionally, it has been discovered that PGS promotes collagen fiber alignment in native heart valves and exhibits superior stiffness and cell adhesion when compared to PGA scaffolds (Masoumi *et al*., 2013). Within 14 days of EC culture, PGS scaffolds sustained endothelization under flow conditions.

Although synthetic-based, bioresorbable polymer scaffolds offer superior mechanical strength, integrity and processability, natural materials typically promote

cellular interactions and tissue remodeling more effectively than synthetic materials do. For this reason, multifunctional scaffolds that incorporate both synthetic and natural components are frequently sought after (Lee *et al*., 2019; Xue *et al*., 2013). This is because these scaffolds are able to achieve both mechanical integrity and biological activity successfully. It is highly likely that these hybrid scaffolding systems will become the standard for cardiovascular biomaterials that are utilized in clinical settings in the years to come.

Composite (hybrid) scaffolds

Composite scaffolds, also known as hybrid scaffolds, are constructed by combining natural and synthetic biomaterial components in order to boost the desired cellular and tissue responses in a synergistic manner (Shapira *et al*., 2016). In particular, these hybrid materials have the potential to give engineers access to a wide variety of mechanical, electrical and biochemical properties that are necessary for biocompatibility and proper functioning in cardiovascular tissues (Shapira *et al*., 2016). Especially when it comes to the design of cardiovascular scaffolds, the utilization of these adjustable features has the potential to identify the optimal performance of biomaterials. Because the three primary characteristics of composite biomaterials—biochemical, mechanical and electrical capabilities—can be altered individually or in combination to provide a wide range of functions, these scaffolds are useful in the clinical setting as well as in the field of regenerative medicine. It is common for hybrid scaffold biochemistry to have the goal of modulating biodegradability, biocompatibility, angiogenesis and cell adhesion, proliferation and differentiation (Nandakumar *et al*., 2013). Natural materials such as collagen, gelatin, elastin, alginate, fibrinogen and related peptide biomolecules are combined with synthetic materials such as poly(lactic-co-glycolic acid) (PLGA), poly(lactic-co-glycolic acid) (PCL), polyglycolic acid (PGS) and its derivatives (Sapir *et al*., 2011; Rai *et al*., 2013; Ravichandran *et al*., 2013; Li *et al*., 2006; Feiner *et al*., 2016). These hybrid combinations have shown to be more effective in terms of cardiac gene expression and metabolic activity when compared to each material on its own (Park *et al*., 2005). The two primary challenges that are encountered in cardiac patches can be successfully addressed by hybrid biomaterials. These challenges are maintaining scaffold placement and cell adherence to the host (Feiner *et al*., 2016).

3D printing and bioprinting

Three-dimensional printing, which is an additive manufacturing technique that is gaining popularity, encompasses a variety of processes that make use of computer-aided models to enable the creation of 3D scaffolds that can be customized through the deposition of material in three layers) (Serpooshan *et al*., 2017). In the field of cardiovascular medicine, these are frequently patient-specific heart models that are utilized for anatomical investigations, surgical planning and educational purposes. When it comes to three-dimensional printing, the term "bioprinting" refers to the process of using biopolymers, cells or other biomaterials. The process of 3D bioprinting is frequently utilized for the purpose of recreating intricate and varied structural characteristics and mechanical qualities. This is due to the fact that it enables the very accurate and precise deposition of numerous biomaterials within a single build. The process of bioprinting can also be accomplished through other methods; extrusion-based, inkjet and stereolithography methods are among the most popular forms of bioprinting (Duan, 2017).

Electrospinning

A further method of fabrication that is frequently used in conjunction with additive manufacturing techniques is known as electrospinning. CTVE has a number of primary goals, one of which is to develop graft materials that have the capacity to integrate with living tissue and remain potent over an extended period of time, all while exhibiting characteristics that are comparable to those of the original organ. Electrospinning is frequently used to produce nano- and micrometer-scale fibers that have a high volume and consistency (Sill *et al*., 2008). Doing so allows for the achievement of this goal. During this procedure, a polymer solution is loaded into a syringe pump and a conductive needle is used to extrude fibers or microbeads while a high voltage is applied to the syringe pump. Once that is complete, a standard system is grounded at the metal mandrel that is utilized for the purpose of gathering the electrospun fibers (Bhardwaj & Kundu, 2010). During the electrospinning process, a number of factors influence the formation of the fibers as well as their shape. By adjusting these parameters, it is possible to achieve fiber alignment and widths that range from 100 nanometers to 5 micrometers (Goh *et al*., 2013). The syringe needle is used in conjunction with a syringe pump to ensure that the polymer solution is dispensed at a controlled rate (Goh *et al*., 2013; Sell *et al*., 2009). The electrospinning method can be utilized to produce bioresorbable grafts that allow for the modification of the structure to take place in situ. As a result of their ability to replicate the shape and size of the original extracellular matrix, electrospun fibers have been utilized in the production of a wide range of tissue scaffolds (Goh *et al*., 2013; Kyle *et al*., 2009). In the fields of vascular, bone, neuron and tendon and ligament tissue engineering, this technology has proven to be particularly useful on a broad scale.

3. Conclusion

This will open up the possibility of developing regenerative therapeutic alternatives that are tailored to individual patients or injury types, which will propel the field of cardiovascular tissue engineering forward. The advancement of biomaterials and the best manufacturing processes will be the driving force behind this. The construction of biomaterial scaffolds that are capable of housing functionalized groups that are necessary for cell adhesion, proliferation, differentiation and function is a potential bioengineering method that is being utilized more and more commonly in translational and fundamental research applications. Providing patients with safer and potentially more effective regenerative medicines, as well as tissue engineering techniques that more closely resemble the original tissue milieu, is possible through the combination of these scaffolding materials with autologous cell sources. In spite of the fact that the field of cardiac biomaterials has a bright future ahead of it, there are still a number of problems and restrictions that need to be investigated further. Vascularization is an essential component for clinical translation, but the majority of in vitro methods are unable to achieve it despite attempts. In order to achieve the highest possible level of survival and functionality of synthetic tissues in vivo, it is necessary to incorporate a sufficient amount of vascularization into the scaffold construction prior to the implantation process. This requires the utilization of angiogenic growth factors in conjunction with the formation of intricate cocultures of cardiac and vascular cells within the three-dimensional artificial tissue for the cardiovascular system.

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