Neural Regulation of Cardiac Repair and Regeneration: Mechanisms and Emerging Therapeutic Strategies

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A myocardial infarction, also known as a heart attack, is the sudden ischemic death of myocardial tissue, due to plaque rupture and results in fibrous scar tissue formation and irreversible heart damage. Current treatments aim to reduce symptoms and prevent further damage rather than addressing the issue at hand: the heart's limited regenerative capacity. This paper examines emerging evidence suggesting that neuromodulatory mechanisms may influence cardiac repair and regenerative processes. A targeted, narrative literature review of primary research studies was conducted using PubMed, supplemented by foundational studies on neuro-cardiac mechanisms. The reviewed studies, largely derived from animal models and early-stage investigations, highlight the potential of neuromodulation to affect cardiac repair due to findings that suggest it may affect cardiomyocyte survival, angiogenesis, and cellular proliferation through components of the neuro-cardiac axis. This includes proteins such as neuregulin-1, nerve growth factor, and brain derived neurotrophic factor, and the autonomic nervous system. Innovative technologies also contribute to this field, with vagus nerve stimulation being a prominent example, helping promote angiogenesis and promoting cardiomyocyte survival. Another approach is by creating a favorable environment for the growth of heart tissue, through the use of proteins and pathways that lead to a better regenerative environment. However, current findings remain preliminary and largely indirect, with limited translational evidence in humans. Further studies and clinical investigations are required to determine the safety and clinical relevance of neuromodulation-based approaches for cardiac regeneration following myocardial infarctions.

Keywords: myocardial infarction, neuromodulation, vagus nerve stimulation, cardiomyocyte proliferation, cardiac regeneration

Introduction

A myocardial infarction (MI), also known as a heart attack, refers to the sudden ischemic death of myocardial tissue, often due to occlusion of a coronary vessel following the rupture of a plaque. Sustained ischemia results in cardiomyocyte (CM) death due to the restricted blood flow in the heart, and initiates a cascade of inflammatory and fibrotic responses[1]. Despite the fact that MI can be life-threatening, it occurs frequently, with 3.8% of the population under 60 years of age and 9.5% of individuals over 60 experiencing MI[2]. While advancements in medicine have reduced the number of MI-related deaths, millions still die each year, making it a pressing concern.

In a heart attack, the death of CMs in the myocardium followed by necrosis of tissue remains the biggest issue. Over the course of the following weeks, the necrosed tissue is gradually replaced by fibrotic scar tissue, primarily through the activity of fibroblasts[3]. However, the resulting scar is non-contractile and becomes mechanically passive within minutes of infarction, which directly compromises the heart's ability to pump blood effectively[4]. Furthermore, the walls of the ventricles in the heart thin significantly, leading to structural weakening and eventual heart failure due to the heart's inability to handle the load[5]. In addition to mechanical impairment, the scar tissue can cause disruption in electrical signals, increasing the risk of arrhythmias[4]. Since scar tissue neither contracts nor conducts electrical signals, it cannot be functionally reintegrated into the heart, causing further complications post-MI. These changes are permanent and pose a significant issue in the heart's function and patient's recovery.

An inability to contract or conduct in long-term function underscores the critical constraint of the heart's limited ability to regenerate dead tissue. Less than 1% of CMs are renewed in a 20-year-old adult, and this number only decreases with age to 0.3% at age 75[6]. With elderly individuals experiencing the most incidents of MI, it is crucial to be able to handle complications of an MI, including scarring due to an inability to regenerate.

Cardiac regeneration has been a long-standing goal in cardiovascular research with numerous strategies being explored over the years. However, these investigations have produced limited success most likely due to biological constraints and

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technical barriers. For example, a human clinical investigation of autologous bone-marrow mononuclear cell (BMC) infusion after acute MI showed that the BMCs had a modest effect on left ventricular ejection fraction (LVEF) and was not uniformly significant when compared to controls, despite improvements in infarct size and slight improvements in wall motion. Overall, the investigation showed that there are associations between cell therapy and favorable trends in function and LV remodeling, but these associations are not large [7]. Another attempt at regeneration was done by attempting to differentiate induced pluripotent stem cells into CMs *in vitro* before transplantation into damaged heart tissue. However, experimental findings indicated limited long-term engraftment and an increased risk of arrythmias [8,9]. Collectively, these findings suggest that the limited success of prior regenerative strategies reflects not an absence of regenerative attempts, but the presence of persistent biological constraints that restrict their effectiveness in the adult injured heart.

Neuromodulation (NM) is the process of stimulation, modification, regulation, or alteration of activity in the nervous system, through electrical, chemical, and mechanical means. Physiologically, NM often regulates autonomic nervous system balance and influences neurotransmitter and signal release. It is a global regulatory framework that coordinates responses across organs and systems through the nervous system, which plays a key role in every aspect of human function [10]. Nerves from the sympathetic nervous system densely innervate the heart, which remains under constant neural regulation [11]. NM may influence cardiac regeneration through extrinsic regulators that shape regenerative outcomes.

NM offers a targeted approach through a higher spatiotemporal precision than medication, and is advantageous because it can be reversible. One significant challenge is identifying the myriads of physiological effects elicited when intervening in the nervous system [12]. Furthermore, there are numerous types of NMs that exist today and each have their own challenges and opportunities. The two major categories of NM are invasive and non-invasive. Invasive strategies include deep brain stimulation (DBS) and intracranial cortical stimulation (ICS), which require surgical implantation of electrodes into the brain, and transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) are non-invasive requiring only external scalp electrodes. DBS is an intracranial electrical therapy that sends continuous pulses into subcortical brain nuclei or tracts and aims to treat disorders such as Parkinson's and ICS uses surgically implanted electrode arrays placed epidurally or subdurally over or into the cortex to targets epilepsy, tinnitus, pain, and depression. tDCS uses scalp electrodes over targeted regions and TMS is administered over the scalp for cortical areas. Common risks vary by type but include infection, hardware failure, or bleeding for invasive methods. Other risks include mild headache, discomfort, or transient fatigue, with rare seizures in non-invasive methods. DBS and ICS provide continuous long-term stimulation and tDCS sessions last 10-20 minutes with effects persisting hours to days due to weak scalp currents and TMS uses repetitive pulses over multiple sessions [12]. Despite these various types of NM, high-quality evidence for the impact of NM on the heart remain limited and largely preclinical.

CMs have a distinct lifecycle that is characterized by a short window of proliferative capacity during early development and neonatal stages. Shortly after birth, mammalian CMs exit the cell cycle, creating the biological barrier that prevents cardiac regeneration. The CM cell cycle is tightly regulated by various molecular mechanisms involving transcription factors, noncoding RNAs, along with other pathways. The CM cell cycle is activated when cyclins bind to cyclin-dependent kinase, leading to continuous CM proliferation in utero and during the neonatal window. After this short developmental period, CMs undergo a major metabolic shift from anaerobic glycolysis to mitochondrial oxidative phosphorylation to meet higher energy needs. This transition increases production of reactive oxygen species, which cause DNA damage, triggering cell cycle arrest through activation of molecular checkpoints to mitigate propagation of further damage [13,14].

This paper will discuss the mechanisms in which neuromodulation can be utilized for cardiac repair. This includes the complex innervation of the sympathetic nervous system in the heart, and neural proteins such as neuregulin-1. An emerging medical intervention known as vagus nerve stimulation will also be discussed for its contributions for cardiac regeneration. Finally, cardiac repair cannot be successfully stimulated unless it has a favorable environment for growth and the mechanisms that achieve this will also be discussed. MI is a significant issue that affects a large portion of the population and causes irreversible damage. By understanding MI and the limitations of the heart, more effective treatments can be developed that can potentially restore cardiac function after injury.

Existing studies examining neuromodulation in the context of cardiac repair differ substantially in the type of evidence they provide for regeneration. Some investigations offer direct evidence of CM proliferation and cell-cycle re-entry through cytokinesis markers, genetic lineage tracing of cells, and multi-marker cell cycle analyses, thereby providing considerable evidence for myocardial regeneration. Other studies show improved CM survival, reduced apoptosis, and antifibrotic effects; this category of evidence represents the most prevalent form of published investigations in this area. Additional studies reported increased angiogenesis and microenvironment conditioning without demonstrable new CM formation, but may still support cardiac repair indirectly by creating favorable conditions for regeneration. These categories have different biological and translational implications and should

not be interpreted equivalently. Accordingly, this review differentiates among these forms of evidence to provide an accurate assessment of how NM supports cardiac regeneration.

The studies reviewed employ a range of cardiac injury models that differ in their applicability and translatability towards humans. Neonatal and zebrafish models demonstrate that cardiac regeneration is biologically achievable, but their species-specific and time-specific contexts limit direct translation to adult humans. Adult rodent models offer greater relevance to mammalian injury responses, although important physiological differences remain. *In vitro and ex vivo* systems are useful for understanding specific biological mechanisms but lack systemic complexity. In contrast, clinical studies are more relevant to humans, however they often provide less detail about the underling biological mechanisms.

This review aims to synthesize and critically evaluate existing evidence to examine the potential implications of NM for cardiac repair and regenerative processes.

Methods

A narrative literature review was conducted using the online database PubMed, as the primary and sole literature database to source peer-reviewed literature with a focus on primary research papers relevant to neuromodulation and cardiac regeneration. Primary research was defined as original experimental or clinical studies, rather than reviews of such investigations. The initial search for papers was done using keyword-based searches and relevant Medical Subject Headings (MeSH) including, "neuromodulation", "cardiac regeneration", "myocardial infarction", and "Cardiomyocytes". Articles were screened based on relevance to neuromodulatory mechanisms in cardiac injury and repair and those published in the last 10 years were prioritized, however earlier studies were included when necessary for underlying key mechanisms. Approximately 130 articles were screened in detail, of which 62 were included in the final synthesis. Study quality was assessed based on experimental design and the strength of evidence supporting regeneration versus indirect cardioprotective effects. To mitigate selection bias, studies were screened consistently based on relevance to neuromodulatory mechanisms in cardiac injury and repair, rather than on reported outcomes. Reference lists of relevant articles were also reviewed to identify additional studies in Table 1.

Mechanisms of Neuromodulation in the Heart

Although the adult human heart is remarkably resilient, its capacity to regenerate after injury is extremely limited. After an MI, affected tissue begins to undergo apoptosis as the blood supply to it is restricted. This results in a non-contractile, fibrotic scar that poses a serious risk to patients following a heart attack [3]. Current treatments focus on preserving function and delaying further damage, essentially just managing symptoms rather than addressing the core issue at hand: the lack of CM regeneration in the heart [15]. This lack of regeneration is caused by withdrawal from the cell cycle after birth [16]. The cardiovascular system is controlled by divisions of the central nervous system (CNS), which exerts widespread influence over cardiac function. Understanding this neurocardiac-axis opens the door to therapeutic strategies that go beyond targeting only symptoms.

Sympathetic Innervation

On a broader scale, neuromodulation is done through targeting the autonomic nervous system (ANS). These therapies seek to control the ANS by utilizing the structures that make it up, such as sympathetic nerves and ganglia [17]. Sympathetic nerves densely innervate the heart, regulating myocardial contractility, heart rate, and blood pressure [11]. An experiment conducted by White et al. in 2015 illustrated the importance of sympathetic influence in cardiac regeneration. They used Wnt1-Cre transgenic mice crossed with Tomato reporter mice to trace neural crest-derived cells, including autonomic nerves in the heart. They reported that after removing the left ventricular apex in 2-day-old mice, sympathetic nerves surrounding the heart had a robust regrowth into the regenerating myocardium. To further test their hypothesis, they applied a chemical sympathectomy which inhibited sympathetic regrowth and subsequent cardiac regeneration, leading to an increased scar size than without the sympathectomy [18]. In this preclinical murine model, this study demonstrated that sympathetic nerves may be critical for heart regeneration and after injury, suggesting that these nerves may be associated with cardiomyocyte proliferation and functional recovery.

The sympathetic nervous system also mediates norepinephrine release, which activates β-adrenergic receptors (β-AR) [19]. To evaluate the role of this pathway in cardiac regeneration, Sakabe et al inhibited β-AR signaling in juvenile mouse heart's using metoprolol, a selective beta-blocker for β1-adrenergic receptors, to evaluate its role in heart regeneration in postnatal mice after MI. The researchers concluded that CM proliferation was strengthened and cardiac regeneration was improved post MI resulting in reduced scar formation and improved cardiac function through the use of metoprolol in the juvenile mouse heart [20]. Persistent sympathetic overactivation, and the resultant β-AR stimulation leads to endoplasmic reticulum stress and apoptosis in CMs [21], which may be why metoprolol induced the observed effect on Sakabe et al's experiment. Thus, the sympathetic nervous system may exert a dual influence when introduced into a mature human heart: supportive during neonatal regeneration, but inhibitory when chronically activated in the matured heart.

The Role of the Parasympathetic Nervous System

The complement to the sympathetic nervous system, the parasympathetic nervous system also plays a significant role in cardiac repair through the use of cholinergic pathways in the heart. Parasympathetic nerves, primarily via the vagus nerve, release acetylcholine (ACh) into the myocardium, where it acts on muscarinic and nicotinic receptors for maintenance of heart rate and contractility[22,23]. To test its importance in the heart, researchers inhibited ACh secretion from CMs in neonatal mice and they found that lack of cardiomyocyte-secreted ACh disturbed regulation of cardiac activity, adverse effects such as CM remodeling, hypertrophy and oxidative stress. These results in neonatal mice suggest CM derived ACh contributes to maintenance of cardiac homeostasis, and modulation of its activity in injured heart tissue may influence myocardial responses, suggesting a potential neuromodulatory role that warrants further investigation in human models[23].

Experimental evidence robustly demonstrates the necessity of cholinergic input for effective cardiac regeneration. Through atropine, pharmacological inhibition of cholinergic nerve function in injured zebrafish and mice heart tissue reduced CM proliferation and impaired the regenerative process. However, in zebrafish tissue treated with beta-adrenergic antagonist propranolol, CM production was significantly greater as opposed to the ones treated with atropine[24]. The experiment demonstrates that effective cardiac regeneration requires intact parasympathetic input. To apply this clinically, the cholinergic pathway should be enhanced after injury, perhaps through vagus nerve stimulation or other technologies, to promote cardiac repair.

The nervous system, particularly the ANS, plays a critical role in maintaining cardiovascular homeostasis and has been recognized as a potential mediator of cardiac regeneration. By leveraging the close anatomical and functional relationship between the ANS and the heart, researchers are exploring how neural inputs can influence processes such as cardiomyocyte survival, proliferation, and repair after injury. Beyond autonomic modulation, another technique that can be suggested is the use of neural pathways and proteins that play key roles in the cardiovascular system.

Proteins for Cardiac Neuromodulation: Neuregulin-1

One such neural factor that has been implicated in CM regeneration is neuregulin-1 (NRG-1). Originally characterized for its role in nervous system development, NRG-1 has also emerged as a key regulator of cardiac development and repair. NRG-1 binds to the extracellular domain of ErbB receptor tyrosine kinases in CM and acts by means of paracrine signaling[25] to induce cell proliferation, differentiation and other processes[26]. It has also been implicated in an antifibrotic effect, which can be useful in clearing the fibrotic scar after an MI[27]. The NRG-1/ErbB2/ErbB4 complex controls CM survival and myofibril disarray according to *in vitro* and *in vivo* studies, which have tested whether stimulation of these receptors can induce CM proliferation. In the paper, *Neuregulin1/ErbB4 Signaling Induces Cardiomyocyte Proliferation and Repair of Heart Injury*, primary adult rat ventricular CM were isolated and exposed to various extracellular factors to test for induction of DNA synthesis and cell proliferation. When NRG-1 was applied in increasing concentrations to determine dose-response, DNA synthesis and proliferation of CM increased at each dose, resulting in improved cardiac function and structure following MI. *In vivo*, genetic manipulation of ErbB4, a main receptor for NRG-1, in neonatal mice confirmed that ErbB4 expression is essential for normal postnatal CM proliferation. Moreover, injecting recombinant NRG-1 into adult mice showed significantly increased bromodeoxyuridine, which is a thymidine analog that marks DNA synthesis and cell proliferation[16]. This study provides direct evidence that NRG can induce adult, differentiated CM via ErbB2/ErbB4 signaling and promote reentrance of the cell cycle and cell division in mice, although the extent to which such responses translate to regeneration in the adult huma heart remains to be established.

Further studies on NRG-1 and its receptor have revealed similar results. In one experiment, neonatal mouse heart injury and *ex vivo* cultured human infant myocardia were treated with recombinant NRG-1 (rNRG-1) at various developmental stages to assess CM proliferation and heart function. Both late and early exposure of rNRG-1 showed an increase in CM cycling, resulting in significant cardiac regeneration and improved heart function[28]. Another key study showed that NRG-1 receptor ErbB2 is downregulated at the time that CMs stop proliferating, suggesting a correlation between NRG-1 and CM proliferation. When ErbB2 expression was inhibited through genetic manipulation, normal developmental CM proliferation and cardiac function were diminished, leading to severe heart failure and early postnatal death in murine models. Researchers then transiently overexpressed ErbB2 in neonatal mice and found that the regenerative capacity of the heart is increased due to CM proliferation, dedifferentiation, and redifferentiation. These experiments show that higher ErbB2 levels increase the heart's responsiveness to NRG1 and the ability of cardiomyocytes to proliferate[29]. These studies prove the relevance of NRG-1 and ErbB2 in mice and how upregulating both may prove an effective neuromodulatory avenue for CM proliferation in humans as well.

Cardiac Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) is a neuromodulatory strategy under active study for MI and heart failure because it rebalances autonomic tone and dampens pathologic inflammation,

two barriers to cardiac repair[30]. It achieves these results by electrically stimulating the vagus nerve, one of the 12 cranial nerves[31]. The vagus nerve, part of the parasympathetic division of the ANS, helps regulate cardiovascular function through control of heart rate, rhythm, contractility, and blood pressure. It does this through the innervation of fibers in CMs that control these functions[32]. Stimulation of the vagus nerve is a novel approach to treating cardiovascular disease and holds great promise for the future of CM regeneration. Traditionally, VNS has been used to reduce inflammation; however, a targeted approach can lead to cardiac regeneration[33].

VNS exerts powerful anti-inflammatory effects through the cholinergic anti-inflammatory pathway (CAP). This is achieved when the efferent branch of the vagus nerve releases ACh, activating a specific immune cell receptor, 7nAChR, which in turn changes expression of cytokines associated with inflammation[30]. This important function has been utilized many times to treat inflammation in a variety of disorders, such as rheumatoid arthritis, sepsis and systemic inflammatory response syndrome, and cardiovascular diseases, including MI[34].

Vagal innervation is required for an optimal cardiac environment and so provides a viable avenue for cardiac regeneration. To test this theory, a foundational study performed a surgical vagotomy on neonatal mice, where the vagus nerve was cut. The result was a significant decrease in the CM cell-cycle markers, Cyclin D2 and Cdk4, suggesting that the vagus nerve aids in the life cycle of a CM. To further test the impact of the vagotomy on cell regeneration, it was paired with a heart apical resection or MI, which resulted in a lower level of proliferating CMs[24]. Lack of vagal nerve innervation led to these adverse effects, proving the importance of the vagus nerve in CM proliferation in mice, and its potential as a therapeutic target in human models.

There are many forms of vagus nerve stimulation but most commonly it is done by implanting a pulse generator device subcutaneously in the upper left chest. An electrode lead is then connected to the vagus nerve through an incision in the neck and attached to the generator[35]. Another approach of VNS is transcutaneous auricular VNS (taVNS) which is a non-invasive means of VNS which stimulates the auricular branch of the vagus nerve via the ear[36]. Both forms of VNS send electrical impulses from the pulse generator, through the electrode, to the vagus nerve[37]. When stimulated, the vagus nerve can impact the cardiovascular system through activation of afferent and efferent pathways. Refer to Figure 1 for the comparison of subcutaneous VNS and taVNS. Vagal efferent fibers release acetylcholine, which binds to receptors in the heart, leading to reduced heart rate and improved electrical stability. Afferent fibers activate brainstem nuclei that help rebalance autonomic tone, reduce sympathetic overdrive, and enhance parasympathetic output[17].

Researchers conducted a study to test the effect of a novel kind of VNS to test the rate of CM proliferation. They used an adeno-associated virus to deliver ChR2, a light-sensitive protein to part of the vagus nerve in mice, enabling precise optical control of cardiac vagal activity after MI. This technique is known as optogenetics, where cells are controlled by light. Optogenetic stimulation increased CM proliferation and myocardial regeneration *in vivo*, leading to improved cardiac function. Despite not being a traditional VNS method, optogenetic stimulation of the vagus nerve holds a compelling promise of CM proliferation[38].

VNS has also been found to have a pro-angiogenic effect. VNS was applied to a murine MI model to increase acetylcholine release and reduce inflammation, after which angiogenesis was assessed through immunostaining methods. It was found that stromal cell-derived factor-l alpha (SDF-1α), a chemokine involved in homing and migration of stem and progenitor cells, was upregulated. By recruiting stem and progenitor cells, SDF-1α helped form new blood vessels in the injured myocardium and thus promoting angiogenesis[39,40]. Another example of VNS's angiogenic effect was illustrated in a study where VNS induced upregulation of VEGF, a critical molecule of angiogenesis. Sarcomere organization, energy metabolism, and expression of CM phenotypes were also improved, leading to a healthier heart after MI[41].

In a clinical study done by Stavrakis et al in 2017, low level VNS (LLVNS) was used in cardiac post-operative patients to assess its efficacy in suppressing atrial fibrillation and inflammatory cytokines. They concluded that post-operative atrial fibrillation occurred far less often with LLVNS and also an enhanced decline of post-op cytokines, creating an exemplified anti-inflammatory trend as opposed to control models[42]. Another study done by Zhao et al aimed to study the effect of VNS in heart attack with reperfusion; researchers induced VNS in adult rats before coronary ischemia and through reperfusion, and then tested heart injury and function. The result was that VNS reduced infarct size and improved cardiac function after reperfusion. There was a decrease in inflammation, preserved vasoconstriction/ vasodilation, and pro-cholinergic signaling. These studies show the potential benefits of VNS in improving cardiac function after injury.

VNS also has some limitations that need to be addressed to make it a more safe and effective treatment for cardiovascular diseases. There is still a lack of understanding behind the biology of the mechanisms involved in VNS, making it hard to create settings and plans without a clear vagus nerve-organ roadmap. Since these parameters are not yet defined, there is no standard dose or consensus on the "right" stimulation parameters. There are also some hardware limits; most current systems lack functional and spatial selectivity to achieve targeted neuromodulation in a complex fasciculate nerve, such as the vagus nerve. This can lead to unintended side effects

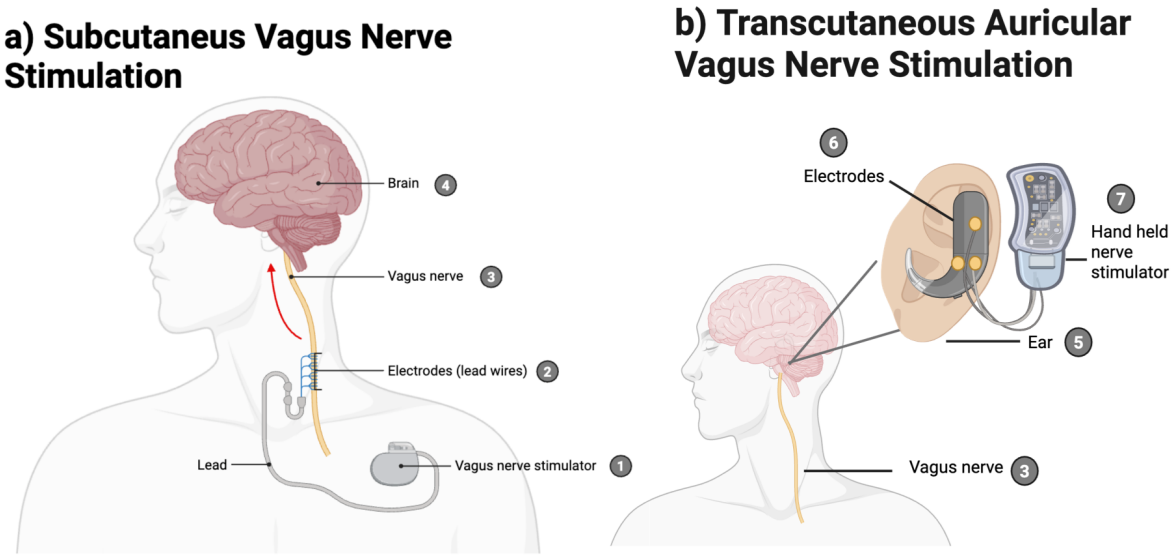

Fig. 1 Types of VagusNerve Stimulation (VNS): a) Subcutaneous VNS is an invasive procedure where the vagusnerve stimulator (1) is surgically implanted in the chest and connected by a lead to electrode (2) wrapped around the cervical vagusnerve (3) where electrical impulses travel from the stimulator via the lead to the vagusnerve where electrical impulses travel from the stimulator via the lead to the vagusnerve until it reaches the brain (4). B) Transcutaneous auricular vagusnerve stimulation is a non-invasive procedure in which electrodes (6) are placed on the auricle (5) of the ear to stimulate the auricular branch of the vagusnerve (3). Stimulation is delivered through impulses sent from the hand-held stimulator (7). Both approaches activate afferent and efferent vagal pathways, leading to reduced heart rate, enhanced electrical stability, suppression of inflammation, and promotion of cardiomyocyte survival and regeneration. While VNS has demonstrated anti-inflammatory and pro-angiogenic effects in preclinical and clinical studies, taVNSoffers a less invasive strategy with the potential for broader clinical application.

such as hoarseness, difficulty swallowing, nausea, chest and abdominal pain, bradycardia, and more, from the inadvertent stimulation of somatic branches[31].

Setting the Stage for Heart Regeneration

Efforts to regenerate damaged myocardium hinge not only on activating CM proliferation but also on the cardiac tissue context in which these interventions occur. Previous sections have shown how neuromodulation can lead to direct CM regeneration, but there are other ways to achieve this effect. One such way is by creating the ideal environment for regeneration, utilizing an approach in which neuromodulation sets the stage for CMs to proliferate. This is done through the use of proteins and pathways that lead to a better regenerative and homeostatic environment in heart tissue after injury.

The environment of heart tissue is essential to the success of CM, ensuring their fate and function are normal. For example, pliable matrices of the heart can promote CM proliferation and dedifferentiation[43]. Concentrations of cell types such as immune and neuronal cells all play a role in creating a homeostatic environment in which CMs have the stability to grow[44]. Increasing blood supply through promotion of angiogenic factors can also create a favorable environment for new cells and tissue, allowing them to get desired nutrients. Lack of a supportive environment can instead push for adverse effects where CMs and the myocardium can't thrive, so by ensuring the presence of one, regenerative therapies have the most optimal outlook.

Emerging evidence suggests that neurotrophins play a compelling part in the vascular and cellular components of regeneration. Neurotrophins are a family of peptides that include nerve growth factors (NGFs), brain-derived neurotrophic factor (BDNF), and more dimeric peptides. While they have neuronal functions such as synaptic plasticity and axonal growth, they also aid in the formation of the heart during development and the control of cardiac cells and regulation of angiogenesis and vasculogenesis postnatally[45]. Modulation of neurotrophins serves as an outlet for cardiac regeneration through promotion of angiogenesis and cellular remodeling.

NGF contributes to maintenance and regeneration of the nervous system but has also been found to promote angiogenesis and cardiomyocyte survival. An experiment to investigate the roles of NGF and its receptor tropomyosin-related recep-

tor A (TrkA) in inducing cardiac repair after MI using heart tissue from zebrafish and neonatal mice showed higher levels of NGF and TrkA in infarcted heart tissue than without MI. This suggests that the expression of NGF and TrkA were upregulated to perform cardiac repair. To further test this theory, vectors carrying NGF were injected into murine heart muscle in an area surrounding the infarct. This resulted in increased cardiac function post-MI; Left ventricular (LV) pressure was increased, indicating improved contractile force, and improvements in relaxation and remodeling were also detected. Moreover, fewer apoptotic endothelial cells and CMs were present in NGF vector injected animals as opposed to those with a null vector injection. There was also an increase in capillary and small arteriole density, as well as a 152% improvement in blood flow compared to the control[46]. These findings suggest that NGF delivery after MI is associated with significantly improved angiogenesis and helped prevent apoptosis of surrounding cells, altogether creating a favorable regenerative environment in animal models, and has the potential to induce a similar effect in human models if translated over.

Another neurotrophin with potential for cardiac repair is BDNF, which plays an active role in the cardiovascular system through stabilization of capillaries and arterioles, increased cell survival, and cardiac function. BDNF and its receptors are expressed in numerous critical places in the heart, from cardiac cells such as CMs, endothelial cells, and vascular smooth muscle cells to the coronary vessels[47]. Using *in vivo* assays, researchers tested angiogenic activity by injecting BDNF into mice. This experiment concluded that BDNF is associated with improved angiogenesis in mice.

As discussed earlier, VNS is beneficial for cardiac repair through its promotion of CM proliferation, but also its cardioprotective effects that create a homeostatic environment favorable for regeneration. VNS has been proven to reduce infarct sizes, promote angiogenesis and anti-inflammatory effects, and slow cardiac remodeling[31]. These processes help to create an ideal cardiac environment by helping to halt post-MI problems that create life-long issues. When utilized with other neuromodulation techniques that make an effective environment and promote CM proliferation, VNS has another powerful benefit in terms of cardiac regeneration.

Discussion

While the heart's inability to regenerate lost tissue has traditionally been seen as a fixed limitation, emerging research points to the nervous system as a key modulator of cardiac healing. Neural factors, proteins, and pathways can be used to induce CM proliferation, and promote an optimal regenerative environment through promotion of angiogenesis, vasculogenesis, and extracellular matrix remodeling. Neuromodulators such NRG-1, NGF, and BDF are proteins in the neurocardiac-axis that aid these processes (Figure 2) Technologies like VNS further aid these processes in a clinical setting and can be used as a viable treatment. Evidence from preclinical and translational studies highlights several converging mechanisms that can be used to model neuromodulation in cardiac regeneration as a key treatment for MI.

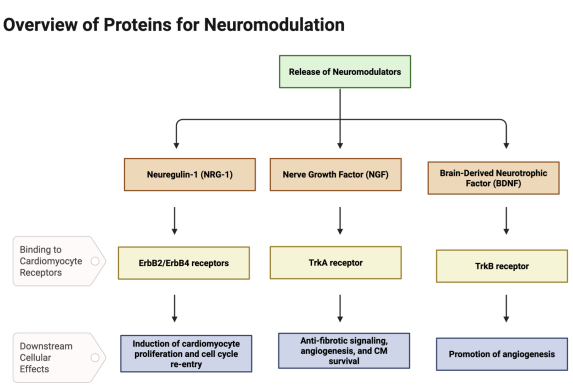

Fig. 2 Overview of proteins for neuromodulation: Neuromodulators such as neuregulin-1 (NRG-1), nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF) are released into the cardiac environment and act on specific surface receptors expressed by cardiomyocytes (CMs). NRG-1 binds to ErbB2/ErbB4 receptors, leading to cardiomyocyte proliferation and entry into the cell cycle. NGF binds to TrkA receptors and produces anti-fibrotic effects while promoting angiogenesis and cardiomyocyte survival. BDNF binds to TrkB receptors and leads to promotion of angiogenesis.

These findings position neuromodulation as both a regenerative trigger and a modulator of post-injury remodeling, but there are limitations to this field. One such being the models being used to collect data. Many of the murine models used by researchers are only a few days old, when regenerative capacity is still high, right before it diminishes in the following weeks of life. This does not account for age-related diseases such as MI, where potential pathways used for neuromodulation change with age. By using aging models to recapitulate age-related pathologies, we can better understand the efficacy of cardiac regeneration through neuromodulation in different age groups of patients. Furthermore, many regenerative strategies effective in small animals remain unproven in humans due to lack of clinical research. By the inclusion of more research done in patients of MI or larger mammals, a more accurate and clearer picture is available and allows for more effective therapies to be developed.

While several studies report positive CM proliferation or cardiac remodeling, other investigations have shown limited, inconsistent, or context-dependent outcomes, depending on factors such as model, timing, or intervention parameters. Rather than undermining the potential relevance of NM, these mixed results underscore the need for careful interpretation.

Weighing both supportive and null findings is therefore essential for accurately assessing the translational potential of NM-based strategies.

It is important to note that the majority of mechanistic evidence linking NM to cardiac regeneration is derived from preclinical animal models, in which physiology and post-injury responses differ substantially from those of the adult human heart. This translational gao may limit direct extrapolation to human cardiac regeneration after MI.

As a new and emerging field, not many research and clinical trials have been conducted in using neuromodulation for cardiac regeneration, posing as a significant limitation. Clinical trials provide critical data on whether an intervention is safe and effective in humans. Without them, proposed therapies remain theoretical, restricting the evidence base for future reference and treatment. Further research into an innovative therapy also creates uncertainty about the safety and efficacy, making it difficult to be used for patients who need it. Through addressing this issue by advancing and increasing research in this field, the translation of neuromodulation into a safe and effective therapeutic option for cardiac regeneration can be accelerated. This creates numerous benefits such as refinement of techniques and treatment protocols, increased knowledge on safety and risks, and guide clinical practice.

Despite limitations that exist in this emerging field, the future of neuromodulation in cardiac regeneration is bright. By stimulating CM proliferation and the creation of healthy heart tissue, research in many cardiovascular diseases that impair the tissue beyond MI are positively affected, as this is a field with many clinical uses. For example, the heart's regenerative ability is already researched in young animal models, which can be seen as a limitation of MI research, but is also a positive trait for the treatment of pediatric and neonatal patients suffering from congenital heart defects. These disorders require multiple surgeries throughout a child's lifetime, increasing scar tissue and inducing significant physical strain. This issue is the same in MI, prompting neuromodulation as a therapeutic. The use of this research is expansive in a clinical setting, from minimizing post-cardiac surgery complications to a variety of cardiovascular diseases and disorders. Other future directions also include advancements in the technology that can make this possible, such as non-invasive bioelectronic devices that are able to aid in regenerative processes in the heart and multi-target approaches that seek to utilize the nervous system to aid heart regeneration.

One proposed research avenue for cardiac neuromodulation is the use of zebrafish as a model. Zebrafish are widely used as models in regenerative medicine for their high capacity to regenerate their organs, including the heart. By studying how the nervous system impacts cardiac regeneration in this species, and others that have similar capabilities, new and innovative therapeutics can be developed that are much more effective at addressing cardiac injury and repair[48].

Neuromodulation is an expanding field, and there are many advances being made today, such as ongoing clinical trials, experiments, and innovative technologies. One such study conducted at the University of Oklahoma used tVNS in heart failure patients with preserved ejection fraction to study the effect on diastolic dysfunction, exercise capacity, and inflammatory cytokines in a sham-controlled, double-blind study. They concluded that tVNS significantly improved quality of life and heart function; there was a significant improvement on global longitudinal strain, a measure of how well the heart muscle contracts, and decreased tumor necrosis factor-alpha (TNF-α), a serum inflammatory cytokine[49]. Beyond this study, not many other clinical trials have been performed or completed, highlighting the need for further research to be done.

New VNS devices are being developed and tested to overcome limitations discussed earlier and are a bright step in future directions of this technology. The CardioFit system is one such technology that consists of an implantable, closed-loop VNS system that delivers right-cervical vagal stimulation via a specialized cuff and right ventricle sensing lead. In canine heart-failure models, CardioFit improved left ventricle function, reduced TNF-α and IL-6 levels, two markers of inflammation, normalized nitric-oxide synthase expression, and restored connexin-43, a protein that forms gap junctions. These results indicate that improved heart function and anti-inflammatory and anti-remodeling effects can be associated with CardioFit[50]. The CardioFit system was also tested in a multinational, randomized trial with heart failure patients, where it produced similar results to the canine trial with an improved quality of life in patients, but did not improve the risk of death or heart failure events, leading to its termination. This highlights the need for better identifying target patient populations and optimizing dosing in future VNS trials to ensure optimal outcomes in patients[51].

Overall, neuromodulation represents a promising frontier in cardiac regenerative medicine, bridging neuroscience, cardiology, and bioengineering. While current evidence supports its potential to enhance repair and recovery following myocardial injury, the field remains in an early translational phase. By addressing its limitations, neuromodulation provides a positive outlook in cardiac regenerative medicine.

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Table 1 Summary of studies included in this review

Title	Study authors	Year	Sample size (N)	Study Type	Key Findings	Adverse event rates
Evidence for cardiomyocyte renewal in humans	Bergmann, O., Bhardwaj, R. D., Bernard, S., Zdunek, S., Barnabé-Heider, F., Walsh, S., Zupicich, J., Alkass, K., Buchholz, B. A., Druid, H., Jovinge, S., & FriséN, J.	2009		Primary human tissue study / observational investigation	• Adult human cardiomyocytes do renew but very slowly: about 1% of cardiomyocytes are replaced per year at age ∼20, falling to roughly 0.4–0.5% per year by age ∼75.	Not applicable
Neuregulin1/ERBB4 signaling induces cardiomyocyte proliferation and repair of heart injury	Bersell, K., Arab, S., Haring, B., & Kühn, B.	2009		Primary preclinical experimental study in adult mice	• Neuregulin-1 acting through ErbB4 induces cell-cycle re-entry and division in mononucleated adult cardiomyocytes, but not binucleated cells, indicating that at least a subset of differentiated cardiomyocytes can be driven to proliferate.	Not applicable
Changes in cardiomyocyte cell cycle and hypertrophic growth during fetal to adult in mammals	Bishop, S. P., Zhou, Y., Nakada, Y., & Zhang, J.	2021		Primary experimental study	• Cardiomyocyte proliferation is robust in feral and neonatal stages but declines sharply afterwards • After this short window of proliferation, growth is dominated by hypertrophy rather than cell division.	Not applicable
Identification of the prosurvival activity of nerve growth factor on cardiac myocytes	Caporali, A., Sala-Newby, G. B., Meloni, M., Graiani, G., Pani, E., Cristofaro, B., Newby, A. C., Madeddu, P., & Emanueli, C.	2007		Primary mechanistic experimental study	• NGF is a pro-survival factor for CMs and blocking endogenous NGF or TrkA signaling increases cardiomyocyte apoptosis,	Not applicable
Role of the stromal cell derived factor-1 in the biological functions of endothelial progenitor cells and its underlying mechanisms	Cun, Y., Diao, B., Zhang, Z., Wang, G., Yu, J., Ma, L., & Rao, Z.	2020		Primary in vitro experimental study	• SDF-1 significantly enhanced EPC proliferation, migration, and tube formation in vitro, mediated via CXCR4 receptor activation of Akt and ERK signaling pathways.	Not applicable

Title	Study authors	Year	Sample size (N)	Study Type	Key Findings	Adverse event rates
ERBB2 triggers mammalian heart regeneration by promoting cardiomyocyte dedifferentiation and proliferation	D'Uva, G., Aharonov, A., Lauriola, M., Kain, D., Yahalom-Ronen, Y., Carvalho, S., Weisinger, K., Bassat, E., Rajchman, D., Yifa, O., Lysenko, M., Konfino, T., Hegesh, J., Brenner, O., Neeman, M., Yarden, Y., Leor, J., Sarig, R., Harvey, R. P., & Tzahor, E.	2015		Primary experimental study in transgenic mice	• Constitutively active ERBB2 induces cardiomyocyte dedifferentiation, proliferation, and transient cardiomegaly in postnatal mice • Post-ischemic ERBB2 activation drives redifferentiation resulting in anatomical and functional heart regeneration with reduced scarring in juvenile/adult mice	Not applicable
Specialized fibroblast differentiated states underlie scar formation in the infarcted mouse heart	Fu, X., Khalil, H., Kanisicak, O., Boyer, J. G., Vagnozzi, R. J., Maliken, B. D., Sargent, M. A., Prasad, V., Valiente-Alandi, I., Blaxall, B. C., & Molkentin, J. D.	2018		Primary experimental study	• Cardiac fibroblasts rapidly proliferate after heart attack, and turn into myofibroblasts that make scar tissue for support	Not applicable
Vagus nerve stimulation for the treatment of heart failure	Gold, M. R., Van Veldhuisen, D. J., Hauptman, P. J., Borggrefe, M., Kubo, S. H., Lieberman, R. A., Milasinovic, G., Berman, B. J., Djordjevic, S., Neelagaru, S., Schwartz, P. J., Starling, R. C., & Mann, D. L.	2016	707 patients with chronic HFrEF	Multicenter, randomized, open-label Phase III clinical trial (INOVATE-HF; NCT01303718).	• VNS did not reduce death or heart failure hospitalizations (30% vs 26% control). • Improved quality of life and exercise capacity, but no change in heart size.	Serious procedure/device-related AEs: 11% in VNS group (mostly implant complications, dyspnea, pneumonia); annual mortality 9.3% VNS vs 7.1% control (p=0.19).
Epidermal growth factor receptor–dependent maintenance of cardiac contractility	Guo, S., Okyere, A. D., McEachern, E., Strong, J. L., Carter, R. L., Patwa, V. C., Thomas, T. P., Landy, M., Song, J., Lucchese, A. M., Martin, T. G., Gao, E., Rajan, S., Kirk, J. A., Koch, W. J., Cheung, J. Y., & Tilley, D. G.	2021		Primary experimental study in conditional knockout mice.	• EGFR in heart muscle cells maintains normal pumping strength. Deleting EGFR causes weak heart contractions and eventual heart failure. Restoring EGFR fixes the problem.	Not applicable
Optogenetic Stimulation of the Cardiac Vagus Nerve to Promote Heart Regenerative Repair after Myocardial Infarction	Han, Y., Wei, X., Chen, G., Shao, E., Zhou, Y., Li, Y., Xiao, Z., Shi, X., Zheng, H., Huang, S., Chen, Y., Wang, Y., Zhang, Y., Liao, Y., Liao, W., Bin, J., Wang, Y., & Li, X.	2024		Primary experimental study in adult mice post-MI.	• Optogenetic cardiac vagal stimulation increased cardiomyocyte proliferation, angiogenesis, and reduced scar size post-MI, with improved ejection fraction and ventricular function vs controls.	Not applicable

Title	Study authors	Year	Sample size (N)	Study Type	Key Findings	Adverse event rates
Neurotrophins promote revascularization by local recruitment of TrkB+ endothelial cells and systemic mobilization of hematopoietic progenitors.	Kermani, P., Rafii, D., Jin, D. K., Whitlock, P., Schaffer, W., Chiang, A., Vincent, L., Friedrich, M., Shido, K., Hackett, N. R., Crystal, R. G., Rafii, S., & Hempstead, B. L.	2005		Primary experimental study in adult mice (ischemia and angiogenesis models	• BDNF and NT-4 induce neoangiogenesis comparable to VEGF, acting directly on TrkB+ endothelial cells in muscle	Not applicable
Nerve growth factor stimulates cardiac regeneration via cardiomyocyte proliferation in experimental heart failure	Lam, N. T., Currie, P. D., Lieschke, G. J., Rosenthal, N. A., & Kaye, D. M.	2012		Primary experimental study in larval zebrafish	• Heart failure reduced cardiomyocyte proliferation 6-fold and total cardiomyocyte numbers by 63%; NGF treatment rescued proliferation 4.8-fold and restored cardiomyocyte counts by 142% without anti-apoptotic effects.	Not applicable
Vagus nerve stimulation optimized cardiomyocyte phenotype, sarcomere organization and energy metabolism in infarcted heart through FoxO3A-VEGF signaling	Luo, B., Wu, Y., Liu, S., Li, X., Zhu, H., Zhang, L., Zheng, F., Liu, X., Guo, L., Wang, L., Song, H., Lv, Y., Cheng, Z., Chen, S., Wang, J., & Tang, J.	2020		Primary experimental study in adult rats post-myocardial infarction.	• VNS improved ejection fraction (+15%), reduced infarct size (↓28%), and enhanced cardiomyocyte sarcomere organization and mitochondrial ATP production post-MI.	Not applicable
Nerves regulate cardiomyocyte proliferation and heart regeneration.	Mahmoud, A. I., O'Meara, C. C., Gemberling, M., Zhao, L., Bryant, D. M., Zheng, R., Gannon, J. B., Cai, L., Choi, W., Egnaczyk, G. F., Burns, C. E., Burns, C. G., MacRae, C. A., Poss, K. D., & Lee, R. T.	2015		Primary experimental study in zebrafish and neonatal mice post-injury.	• Reducing cardiac innervation (genetic or surgical) decreases cardiomyocyte proliferation and blocks heart regeneration in both zebrafish and neonatal mice. • Nerve-derived factors like NRG1 and NGF partially rescue proliferation/repair when nerves are disrupted, showing nerves actively regulate the regenerative response.	Not applicable

Title	Study authors	Year	Sample size (N)	Study Type	Key Findings	Adverse event rates
Nerve Growth Factor Promotes Cardiac Repair following Myocardial Infarction	Meloni, M., Caporali, A., Graiani, G., Lagrasta, C., Katare, R., Van Linthout, S., Spillmann, F., Campesi, I., Madeddu, P., Quaini, F., & Costanza Emanueli.	2010		Primary experimental study in adult mice post-myocardial infarction.	• Blocking endogenous NGF worsened apoptosis, reduced angiogenesis, and impaired LV function post-MI. • NGF gene therapy improved survival of ECs/cardiomyocytes, increased capillary/arteriolar density, boosted myocardial blood flow, and enhanced LV function (↑LVEF, ↓EDP)	Not applicable
Intracoronary Bone Marrow Cell Transfer after Myocardial Infarction	Meyer, G. P., Wollert, K. C., Lotz, J., Steffens, J., Lippolt, P., Fichtner, S., … Drexler, H.	2006	60 patients with acute MI randomized 1:1 to control vs intracoronary BMC transfer.	Randomized controlled clinical trial	• Intracoronary infusion of autologous bone marrow cells after acute MI produced a modest, early rise in left ventricular function, but this advantage was no longer evident on longer-term follow-up compared with standard care.	No clear excess of serious cardiac complications or arrhythmias was observed in the bone marrow cell group; the intervention appeared clinically acceptable from a safety standpoint.
B-AR blockers suppresses ER stress in cardiac hypertrophy and heart failure.	Ni, L., Zhou, C., Duan, Q., Lv, J., Fu, X., Xia, Y., & Wang, D. W.	2011		Primary experimental study (human tissue + rat hypertrophy/HF models).	• ER stress markers (GRP78, CHOP, p-PERK, p-eIF2α) are elevated in human failing hearts and rat hypertrophy models. • β-blockers (metoprolol) reduced ER stress, apoptosis, hypertrophy markers, and improved cardiac function by inhibiting CaMKII overactivation.	Not applicable
The local microenvironment limits the regenerative potential of the mouse neonatal heart	Notari, M., Ventura-Rubio, A., Bedford-Guaus, S. J., Jorba, I., Mulero, L., Navajas, D., Martí, M., & Raya, Á.	2018		Primary experimental study in neonatal mice (P1-P3)	• Mouse hearts lose regenerative ability between P1 and P2 due to rapid stiffening of ECM.	Not applicable

Title	Study authors	Year	Sample size (N)	Study Type	Key Findings	Adverse event rates
Transient regenerative potential of the neonatal mouse heart	Porrello, E. R., Mahmoud, A. I., Simpson, E., Hill, J. A., Richardson, J. A., Olson, E. N., & Sadek, H. A.	2011		Primary experimental study in neonatal mice	• P1 mouse hearts fully regenerate after 20% resection via CM proliferation • Regenerative capacity is lost by P7. These older hearts form scar tissue rather than new tissue.	Not applicable
Cardiomyocyte-secreted acetylcholine is required for maintenance of homeostasis in the heart.	Roy, A., Fields, W. C., Rocha-Resende, C., Resende, R. R., Guatimosim, S., Prado, V. F., Gros, R., & Prado, M. a. M.	2013		Primary experimental study in conditional knockout mice.	• CM-secreted Ach helps maintain heart health and regulates critical signaling pathways.	Not applicable
Biomechanical assessment of remote and postinfarction scar remodeling following myocardial infarction.	Rusu, M., Hilse, K., Schuh, A., Martin, L., Slabu, I., Stoppe, C., & Liehn, E. A.	2019		Primary experimental study in adult mice post-myocardial infarction.	• Infarct scar gets 10 times stiffer from day 3 to 28 while remote myocardium stiffened only by 2 times. • The scar stiffens according to a gradient with the early scar being compliant and the late-stage scar being more rigid.	Not applicable
Inhibition of β1-AR/Gαs signaling promotes cardiomyocyte proliferation in juvenile mice through activation of RhoA-YAP axis.	Sakabe, M., Thompson, M., Chen, N., Verba, M., Hassan, A., Lu, R., & Xin, M.	2022		Primary experimental study in juvenile mice.	• β1-AR/Gαs signaling increases CM proliferation and improved heart regeneration after injury.	Not applicable
Allogeneic Transplantation of iPS Cell-Derived Cardiomyocytes Regenerates Primate Hearts	Shiba, Y., Gomibuchi, T., Seto, T., Wada, Y., Ichimura, H., Tanaka, Y., … Ikeda, U.	2016		Preclinical experimental study of allogeneic, MHC-matched human iPSC-derived cardiomyocyte transplantation after MI with immunosuppression	• Allogeneic iPSC-derived cardiomyocyte transplantation in primates achieves graft survival, partial scar remuscularization, and improved LV function at 12 weeks post-MI.	High incidence of early post-transplant ventricular arrhythmias that decrease over time; no acute rejection under immunosuppression

Title	Study authors	Year	Sample size (N)	Study Type	Key Findings	Adverse event rates
Low-Level vagus nerve stimulation suppresses Post-Operative atrial fibrillation and inflammation.	Stavrakis, S., Humphrey, M. B., Scherlag, B., Iftikhar, O., Parwani, P., Abbas, M., Filiberti, A., Fleming, C., Hu, Y., Garabelli, P., McUnu, A., Peyton, M., & Po, S. S.	2017	29 patients undergoing cardiac surgery randomized to low-level tragus stimulation	Randomized controlled clinical trial in post-cardiac surgery patients	• LLTS reduced post-operative atrial fibrillation incidence (20% vs 54% sham, p=0.04) and duration.	No serious procedure-related AEs; minor skin irritation in 2 patients (7%); all resolved spontaneously.
Microenvironment stiffness amplifies post-ischemia heart regeneration in response to exogenous extracellular matrix proteins in neonatal mice.	Wang, X., Pierre, V., Senapati, S., Park, P. S., & Senyo, S. E.	2021		Primary experimental study in neonatal mice post-ischemia.	• A softer cardiac environment helped preserve cardiac function and increase CM proliferation after injury, making ECM therapy more effective. Conversely, stiffness can worsen ischemic damage	Not applicable
Vagus nerve stimulation-induced stromal cell-derived factor-l alpha participates in angiogenesis and repair of infarcted hearts.	Wang, Y., Liu, Y., Li, X., Yao, L., Mbadhi, M., Chen, S., Lv, Y., Bao, X., Chen, L., Chen, S., Zhang, J., Wu, Y., Lv, J., Shi, L., & Tang, J.	2023		Primary experimental study in adult rats post-myocardial infarction.	• VNS promoted angiogenesis by inducing SDF-1α expression and redistribution to repair the infarcted heart during angiogenesis.	Not applicable
Sympathetic reinnervation is required for mammalian cardiac regeneration.	White, I. A., Gordon, J., Balkan, W., & Hare, J. M.	2015		Primary experimental study in neonatal mice.	• Sympathetic nerves reinnervate the injured neonatal mouse heart during regeneration, restoring normal density/patterning by day 21. • Chemically ablating the sympathetic nerves prevents the neonatal heart from regenerating	Not applicable
Reduced matrix rigidity promotes neonatal cardiomyocyte dedifferentiation, proliferation and clonal expansion	Yahalom-Ronen, Y., Rajchman, D., Sarig, R., Geiger, B., & Tzahor, E.	2015		Primary experimental study in neonatal mice	• Soft, compliant ECM promotes neonatal CM dedifferentiation and re-entry into to the cell cycle, leading to cell proliferation, while a stiff matric inhibits division	Not applicable

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