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The crossroads of inflammation, fibrosis, and arrhythmia following myocardial infarction

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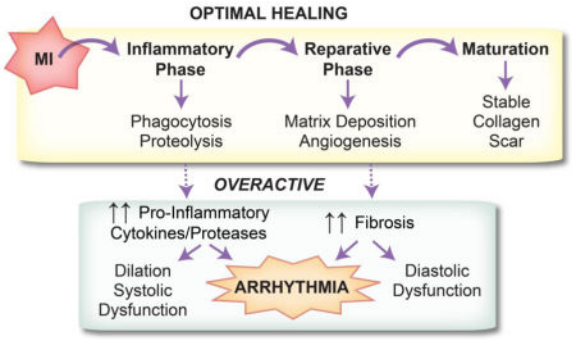
Abstract

Optimal healing of damaged tissue following myocardial infarction (MI) requires a coordinated cellular response that can be divided into three phases: inflammatory, proliferative/reparative, and maturation. The inflammatory phase, characterized by rapid influx of cytokines, chemokines, and immune cells, is critical to the removal of damaged tissue. The onset of the proliferative/reparative phase is marked by increased proliferation of myofibroblasts and secretion of collagen to replace dead tissue. Lastly, crosslinking of collagen fibers and apoptosis of immune cells marks the maturation phase. Excessive inflammation or fibrosis has been linked to increased incidence of arrhythmia and other MI-related pathologies. This review describes the roles of inflammation and fibrosis in arrhythmogenesis and prospective therapies for anti-arrhythmic treatment.

Graphical Abstract



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Disclosures

None.

1. Introduction: Post-MI Healing and Repair

Following myocardial infarction (MI), a coordinated cellular response is required for sufficient wound healing and scar formation. This healing process can be classified into three major phases: inflammatory, proliferative/reparative, and maturation (Figure 1) [1]. The inflammatory phase begins with a rapid influx of neutrophils and monocytes that begins within hours of the ischemic event, particularly in the setting of reperfusion. By day 3, the inflammatory phase is dominated by monocyte-derived macrophages, with pro-inflammatory M1 and anti-inflammatory M2 being the major subtypes. Classically activated M1 macrophages clear dead myocyte debris through phagocytosis and proteolysis. M1 macrophages secrete inflammatory cytokines including interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α as well as proteases including matrix metalloproteinase (MMP)-1, -2, -3, -7, -8, -9, and -12 [2].

Alternatively activated anti-inflammatory M2 macrophages, myofibroblasts, and endothelial cells dominate the proliferative/reparative phase [1]. M2 macrophages secrete the anti-inflammatory cytokine IL-10 and growth factors including transforming growth factor (TGF)-β, which in turn recruit and activate reparative myofibroblasts and vascular cells [2]. Myofibroblasts secrete large amounts of extracellular matrix (ECM) in order to replace lost ventricular tissue with a stable scar. The maturation phase is marked by apoptosis of the majority of the inflammatory and reparative cells and scar maturation and remodeling.

Timely progression and resolution of both the inflammatory and reparative phases is necessary for proper infarct healing. If either phase is overactive or incompletely resolved, adverse LV remodeling occurs. A large body of evidence from mouse MI models supports the concept that impaired resolution of inflammation leads to LV dilation and adverse remodeling [3–5]. At the same time, inflammation is *required* for proper healing, as depleting inflammatory macrophages also leads to impaired healing [6]. An overactive reparative phase is likewise detrimental, promoting fibrosis outside the infarct region and contributing to diastolic dysfunction. A major unanswered question lies in determining which patient populations and which underlying pathologies ultimately contribute to improper resolution of either or both phases.

Importantly, in addition to playing a role in adverse LV remodeling, impaired resolution of either the inflammatory or reparative phase can lead to adverse electrophysiological remodeling, ventricular arrhythmia, and sudden cardiac arrest (Figure 1). Indeed, the mechanisms by which an overactive reparative phase (including interstitial fibrosis and potential myofibroblast-myocyte coupling) may contribute to both triggered and reentrant arrhythmias has been a long-standing area of investigation [7,8]. On the other hand, the mechanisms by which an overactive inflammatory response contributes to ventricular arrhythmias has received less attention. This review focuses on the electrophysiological consequences of both the inflammatory and reparative phases.

2. Post-MI inflammation, electrophysiological remodeling, and arrhythmia

Following ischemia, surviving cardiac myocytes in the infarct border zone (BZ) undergo dramatic electrophysiological remodeling, which, in addition to the fibrotic scar, creates the

substrate for ventricular arrhythmia. Some of the most well documented electrophysiological changes in the infarct BZ include a reduction in repolarizing K^+ currents that may result in a prolonged action potential duration (APD) [9,10], reduced expression or lateralization of connexin 43 (Cx43) which contributes to slowed conduction [11,12], and intracellular Ca^{2+} mishandling that may lead to triggered activity [13,14]. Collectively, these changes provide the trigger and substrate for malignant ventricular arrhythmias.

Despite the rigorous characterization of post-MI electrophysiological remodeling, the upstream mechanisms responsible for these changes are not well understood. Importantly, key cytokines and proteases that are elevated in the myocardium following MI (e.g., TNF-α, IL-1β, IL-6, MMPs) produce electrophysiological changes in cardiac myocytes that mirror those found in the infarct BZ, suggesting that inflammation may be an important contributor to electrophysiological remodeling and arrhythmia. Indeed, a growing body of clinical evidence suggests that post-MI patients with arrhythmia have higher circulating levels of inflammatory cytokines compared to post-MI patients who are arrhythmia free [15,16]. Furthermore, even in the absence of MI or structural heart disease, systemic inflammation is associated with a significantly increased risk for ventricular tachyarrhythmias [17]. The studies described below (Table 1) support these clinical observations and demonstrate mechanistic links between the inflammatory phase and post-MI electrophysiological remodeling.

2.1 TNF-α

TNF-α is significantly elevated in the post-MI heart and is further increased when MI is superimposed on a background of inflammation including atherosclerosis [18], aging [19], or bacterial gingivitis [20]. The electrophysiological effects of TNF-α are well characterized in isolated cardiac myocytes from normal hearts and from those of cardiac-specific TNF-α over-expressing mice. Over-expression of TNF-α prolongs APD and significantly reduces repolarizing K^+ currents (Table 1), whereas L-type Ca^{2+} current (I_{CaL}) remains unchanged [21,22]. Similar results have been observed in normal myocytes treated with exogenous TNF-α. Fernandez-Velasco *et al*. reported a dose-dependent decrease in I_{to} with increasing doses of TNF-α, while I_{CaL} remained unaffected [23]. Decreased I_{to} was also observed in neonatal rat myocytes treated with TNF-α along with decreased KCND2 (Kv4.2: I_{to}) mRNA [24]. TNF-α treatment also prolonged APD and caused a dose-dependent reduction in I_{Kr} in canine myocytes. Here, the reduction in I_{Kr} was not associated with decreased channel (hERG) expression, but rather through increased intracellular reactive oxygen species [25].

TNF-α has negative inotropic effects [26]. Acute treatment of adult rat myocytes with TNF-α leads to rapid decreases in systolic $[Ca^{2+}]$ and reduces the sarcoplasmic reticulum (SR) Ca^{2+} content ($[Ca^{2+}]_{SR}$) [27]. Likewise, TNF-α over-expressing mice also display altered intracellular Ca^{2+} handling, including increased diastolic and suppressed systolic $[Ca^{2+}]$ and prolonged Ca^{2+} transient duration [21]. Wu *et al*. showed that TNF-α treatment of HL-1 cardiomyocytes lead to delayed Ca^{2+} reuptake accompanied by a decrease in SR Ca^{2+} ATPase (SERCA) gene expression [28]. TNF-α and IL-1β have similar effects on intracellular Ca^{2+} handling and, when combined, act synergistically to further decrease

systolic [Ca^{2+}], decrease [Ca^{2+}]$_{SR}$, and increase spontaneous SR Ca^{2+} release events, leading to arrhythmogenic Ca^{2+} waves [29].

TNF-α also impacts gap junction coupling and cell-cell communication. Optical mapping studies in TNF-α over-expressing mice revealed normal ventricular conduction velocity at baseline, but decreased conduction velocity during premature stimuli [21]. Subsequent studies in the atria of the TNF-α mice revealed no change in total Cx43 expression, but a significant increase in Cx43 internalization and lateralization [30]. *In vitro* experiments provided direct evidence that TNF-α reduces activity of the promoter region of the Cx43 gene [31].

2.2 IL-1β

IL-1β is a key regulatory cytokine involved in the post-MI inflammatory response and is required for recruitment of immune cells and subsequent production of other pro-inflammatory cytokines [32,33]. Investigations into the electrophysiological effects of IL-1β have centered on changes in Ca^{2+} handling and cell-cell coupling. Most studies have found a decrease in I_{CaL} by IL-1β [34–36], however Li *et al*. found an increase in I_{CaL} in guinea pig myocytes [37]. Decreased responsiveness of I_{CaL} to β-adrenergic stimulation has also been observed with IL-1β [38,39].

In addition to the synergistic effects of IL-1β and TNF-α [29,40], IL-1β alone appears to have a significant impact on SR Ca^{2+} release and reuptake. Several reports indicate that IL-1β decreases expression (at both the gene and protein level) of important Ca^{2+} handling proteins, including ryanodine receptors (RyR), SERCA, and phospholamban (PLB) (Table 1) [39,41–43].

IL-1β has also been implicated in Cx43 down-regulation. First discovered in astrocytes [44] and later observed in cardiac myocytes from post-MI mouse and canine hearts [45,46], IL-1β produces cell-cell uncoupling, internalization, and reduced expression of Cx43. Our group recently reported similar findings in a mouse model of MI superimposed on atherosclerosis (ApoE$^{-/-}$), which intensifies the inflammatory phase of healing [18,47]. ApoE+MI hearts had a ~3-fold increase in IL-1β expression, a ~2-fold decrease in Cx43 expression, and significant Cx43 internalization and lateralization (Figure 2). The ApoE+MI hearts also had decreased conduction velocity and a significant increase in inducible ventricular arrhythmias. Importantly, the ApoE+MI phenotype could be completely reproduced by acutely increasing post-MI inflammation with lipopolysaccharide (LPS), suggesting that elevated inflammation during healing can produce deleterious electrophysiological consequences [47]. Ongoing work in our laboratory is further defining the role of IL-1β in this process.

2.3 IL-6

IL-6 is also elevated post-MI and may impact cardiomyocyte Ca^{2+} handling. Hagiwara *et al*. reported that IL-6 signaling through gp130 (glycoprotein 130 cytokine receptor) lead to an increase in I_{CaL}, increased systolic [Ca^{2+}] and prolonged APD [48]. IL-6 has also been shown to decrease SERCA gene expression [28,49] and PLB phosphorylation [50], leading

to slowed Ca^{2+} reuptake into the SR [28]. Cytokine signaling through gp130 has also been shown to be a key regulator of remodeling of cardiac sympathetic neurotransmission following MI [51], a known contributor to arrhythmias.

2.4 MMPs

MMPs are important mediators of both the inflammatory and reparative phases of post-MI healing, as they breakdown ECM, a necessary step for proper scar formation. However, these proteinases may also degrade gap junction proteins that are required for proper cell-cell electrical coupling. Lindsey *et al*. demonstrated one of the first mechanistic links between MMP activity and Cx43. They observed that MMP-7 null mice were protected from Cx43 degradation post-MI, had improved conduction velocity, and reduced propensity to arrhythmia [52]. *In vitro* studies demonstrated that MMP-7 directly cleaves Cx43 [52]. Similarly, hypoxia-induced Cx43 reduction is MMP-9 dependent [53]. Investigation into the role of MMP-9 and Cx43 following myocardial injury found that MMP-9 activity corresponded to locations of Cx43 degradation and conduction slowing. However, unlike MMP-7, *in vitro* experiments revealed that Cx43 is not a substrate for MMP-9 [54]. The authors suggest that MMP-9 disrupts normal cell-cell alignment, leading to reduced Cx43 coupling. To date, there are relatively few studies examining the role of MMPs in post-MI Cx43 loss; however, experiments in keratinocytes and epithelial cells support a role for MMPs in Cx43 degradation [55]. Thus, the role of MMP activity and cell-cell electrical communication post-MI remains an important area for future investigation.

3. Post-MI Fibrosis and Arrhythmia

3.1 Mechanisms of Fibrosis Following MI

By days 3–5 post-MI, inflammatory signals start to decline, due to immune cell apoptosis and up-regulation of anti-inflammatory and pro-fibrotic signals, marking the onset of the proliferative/reparative phase of healing (Figure 1). As immune cells retreat, levels of IL-1 and TNF-α decline, while TGF-β and IL-10 increase. TGF-β stimulates the maturation of fibroblasts into myofibroblasts (Mfb), suppresses macrophage activity, and increases expression of both tissue inhibitor of metalloproteinases (TIMPs) and protease inhibitors. Mfbs are characterized by proliferation, increased expression of contractile, focal adhesion, and ECM proteins, and increased collagen synthesis and deposition [56]. Figure 3 shows the time course of collagen deposition and scar maturation following MI wherein the percent of ventricular area and maturity of collagen fibers increases as healing progresses. An overactive reparative phase, however, may lead to fibrosis outside the infarct and contribute to adverse remodeling [1]. When addressing the role of fibrosis and Mfbs in arrhythmogenesis, there are two distinct categories: interstitial fibrosis and Mfb-myocyte coupling.

3.2 Interstitial Fibrosis and Arrhythmia

Following MI, there are distinct patterns of fibrosis, including the compact fibrotic tissue of the scar and varying degrees of interstitial fibrosis adjacent to and outside the infarct. The compact scar is mostly acellular and is electrically non-excitable, although it may serve as an insulated area where reentrant arrhythmia can anchor and convert to sustained ventricular

tachycardia (VT) [57]. We previously showed that the healed compact scar can attract and anchor reentrant VT in the post-MI rabbit heart (Figure 4). In this study, 84% of sustained VTs were found to anchor at the infarct, often stabilizing at the scar following a period of meandering after initiation. Similarly, appropriately timed cardioversion shocks could force detachment and subsequent termination of reentry. These data suggest that compact fibrosis of the scar may be important for maintaining sustained VT and that low-energy methods for detachment of reentry from the scar may be sufficient to terminate VT [57].

Interstitial fibrosis in the BZ and non-infarct tissue is in some ways more arrhythmogenic than the compact scar. Here, myocytes are separated to varying degrees by non-conducting collagenous septa. Depending on the severity, this geometry can favor the escape of focal (ectopic) activity, as well as promote slow conduction and unidirectional conduction block that favor reentrant tachycardia [58,59]. These arrhythmogenic situations are created by conditions of source-sink mismatch and are further exacerbated by electrophysiological remodeling of the surviving BZ myocytes.

The source-sink mismatch typically refers to insufficient depolarizing current generated by an area of excited tissue (i.e., the source) compared to that which is necessary to excite the neighboring quiescent tissue (i.e., the sink). Insufficient source current and subsequent conduction block often occur at sites of expansion (e.g., a depolarizing wavefront traveling from a narrow structure into a larger structure) or when small islands of depolarization are surrounded by quiescent myocardium. The source-sink mismatch likely acts to protect the normal myocardium from ectopic activity. However, interstitial fibrosis can uncouple myocytes from one another by creating small, electrically insulated areas between them. This electrical uncoupling reduces the source-sink mismatch and has been shown to promote the escape of ectopic triggers [60,61]. Morita *et al*. experimentally demonstrated the role of fibrosis in promoting ectopic triggers in hearts of aged rats and rabbits. They showed that the incidence of early afterdepolarizations and triggered activity originated more frequently from the LV base, which had a higher percentage of fibrotic tissue compared to other regions of the heart [62].

Interstitial fibrosis can also have effects on conduction; large areas of fibrosis can force a propagating wavefront to take a ‘zig-zag’ pattern, thus slowing conduction at the macroscopic level. When the activation wavefront is slowed through a fibrotic region, the repolarization wavefront may also be delayed, resulting in an increase in the dispersion of repolarization, another condition that favors reentry. Because interstitial fibrosis often disrupts side-to-side connections between myocytes, the anisotropy of conduction may also be increased. In post-MI swine, Tschabrunn *et al*. showed that deposition of transmural fibrosis, along with preserved borders of subendocardial tissue, contributed to slowed conduction and non-uniform anisotropy, giving rise to reentrant VT [63].

3.3 Myofibroblast-Cardiomyocyte Coupling

Cardiac arrhythmias stemming from fibrosis have traditionally been attributed to the deposition of ECM in the interstitial space. However, a large population of fibroblasts and Mfbs are present during and after MI and play vital roles in the maintenance of ECM [64]. Mfbs may also play a role in post-MI arrhythmogenesis via Mfb-myocyte coupling. For a

more complete discussion of Mfb-myocyte coupling, refer to the accompanying article in this issue by Kohl *et al*., [**JMCC9726**] as well as [8].

When fibroblasts are cultured, they differentiate into Mfbs and upregulate expression of Cx43 and Cx45 [64]. The most compelling evidence for Mfb-myocyte electrical coupling comes from several *in vitro* co-culture studies where coupling was confirmed via direct observation of wavefront propagation through Mfbs, or by changes to myocyte resting membrane potential [65–67]. When cardiomyocytes and Mfbs are well-coupled they are difficult to differentiate electrically, thus evidence of Mfb-myocyte coupling in intact tissue has yet to be unequivocally demonstrated. Immunohistochemical staining of Cx43 in infarcted hearts has, however, demonstrated the potential for coupling [68]. Given the experimental difficulties with differentiating and confirming Mfb-myocyte coupling in the intact post-MI heart, computational modeling has become an important investigational tool in this area.

Using a 2D computational model, Xie *et al*. demonstrated the arrhythmogenic consequences of Mfb-myocyte coupling [69]. Mfbs within the sheet, but not electrically coupled to myocytes act similarly to interstitial fibrosis in that they lead to zig-zag (slowed) conduction. When Mfbs are electrically coupled to myocytes, however, they significantly reduce the conduction velocity (CV) as the ratio of Mfbs to cardiomyocytes increases. The authors attribute this finding to increased electrotonic loading of the myocytes (i.e., increased current sink), reduced myocyte-myocyte coupling, and to differences in resting membrane potential between myocytes and Mfbs (~-80 mV versus ~-50 to -20 mV, respectively) [67]. As Mfb density increases, the resting membrane potential of myocytes becomes more depolarized, inactivating voltage-gated Na^+ channels, which can slow conduction and lead to post-repolarization refractoriness. In this study, only in instances of Mfb-myocyte coupling could reentry be induced by programmed stimulation [69].

McDowell *et al*. demonstrated similar results in the infarct region and peri-infarct zone (PZ) using a 3-dimensional, anatomically accurate model of an infarct rabbit heart. They found that Mfb-myocyte coupling in the PZ only affects reentry at intermediate Mfb:myocyte densities. At higher Mfb densities, reentry is suppressed due to depolarization of myocytes and increased refractoriness; however, this state is also pro-arrhythmic since diastolic depolarization can lower the threshold for ectopic activity. Higher rates of reentry were observed at intermediate Mfb densities wherein coupling of Mfbs to myocytes shortened the APD (because Mfbs act as a current sink when myocytes are depolarized), which lead to increased APD dispersion and enhanced reentry potential [70].

4. Post-MI Arrhythmia Prevention

Prevention of ventricular arrhythmias is primarily achieved through use of implantable devices or anti-arrhythmic drugs. Implantable cardioverter defibrillators (ICDs) are lifesaving, but are highly invasive and impermanent fixes [71]. Ion channel blockers, including flecainide, encainide, and *d*-sotalol, have been used to prevent arrhythmias in the post-MI setting but were discontinued due to dangerous pro-arrhythmic effects. While these drugs decreased incidence of premature ventricular contractions, they increased incidence of

reentrant and fatal arrhythmias [72]. Current therapeutics, such as beta blockers and angiotensin-converting enzyme inhibitors, avoid ion channels and may act indirectly to prevent arrhythmias by altering neurohumoral tone. However, most of these approaches treat the symptom (arrhythmia), rather than the underlying cause (electrophysiological and structural remodeling). Targeting the post-MI inflammatory or reparative phase at the outset might represent a more effective anti-arrhythmic approach.

4.1 Targeting Inflammation

Treatment with non-specific anti-inflammatory steroids following acute MI has resulted in compromised infarct healing, scar tissue thinning, and increased risk of ventricular rupture [73]. However, other studies have reported decreased mortality and no change in rupture risk [74]. Use of non-steroidal anti-inflammatory drugs is associated with worse clinical outcomes and current guidelines advise against their use in MI patients [75]. Thus, more specific targeting of inflammatory signaling is likely required to avoid suppression of beneficial functions.

Given its potentially important role in electrophysiological remodeling (Table 1), TNF-α may represent a novel anti-arrhythmic target. However, anti-TNF-α therapies have been tested for the prevention of heart failure following MI and, although results are somewhat contradictory, the overall consensus is that inhibition of TNF-α yields more detrimental outcomes and should not be used to treat MI [76]. These results underscore the difficulties in targeting post-MI inflammation and are likely due to abatement of the beneficial functions of TNF-α [77].

IL-1 is rapidly upregulated following MI and may play a role in post-MI arrhythmogenesis [45,47]. In the Virginia Commonwealth University Anakinra Remodeling Trial (VCU-ART), Abbate *et al*. demonstrated that administration of anakinra, a human recombinant IL-1 receptor antagonist, following acute MI attenuated LV remodeling without compromising infarct healing [78]. Other therapeutic strategies for modulating IL-1 activity have also been shown to improve LV remodeling and preserve cardiac function [79,80]. Furthermore, the first large, multi-center trial evaluating the efficacy of IL-1 inhibition for limiting the progression of atherosclerosis (*CANTOS*) is currently ongoing [81]. These studies, combined with the role of IL-1 in post-MI Ca^{2+} mishandling and gap junction uncoupling (Table 1), make IL-1 an attractive therapeutic target that warrants further investigation.

4.2 Targeting Fibrosis

TGF-β is central to post-MI scar formation; therefore, TGF-β inhibition may attenuate interstitial fibrosis. Dobaczewski *et al*. demonstrated in mice subject to MI that knockdown of Smad3, a downstream transcription factor for TGF-β, markedly impaired Mfb differentiation, migration, and contractility [82]. Consistent with previous reports [83], they also demonstrated that despite increased Mfb numbers and unchanged infarct size, Mfb inhibition attenuated LV remodeling and ventricular dysfunction [82].

Pirfenidone, a TGF-β inhibitor, was also shown to attenuate TGF-β-mediated fibrosis and reduce arrhythmia following MI [84]. In an ischemia-reperfusion model, Nguyen *et al*. showed that pirfenidone treatment improved LV ejection fraction, lowered incidence of inducible VT, and preserved CV by reducing total LV fibrosis and infarct size [84].

Therefore, directly inhibiting fibroblast/Mfb activity reduces total fibrosis, improves structural remodeling, and reduces propensity to arrhythmias by preventing fibrosis-induced slowing of conduction. Importantly, Mfbs are also a source of pro-inflammatory cytokines [45], therefore, suppression of Mfb activation may also be anti-arrhythmic by inhibiting cytokine production. Considering Mfb-myocyte coupling, however, treatments that increase Mfb numbers [82,83] may be pro-arrhythmic by increasing electrotonic loading on myocytes. Thus, the pro- or anti-arrhythmic effects of Mfb inhibition require further study.

The activity of several MMPs, including MMP-1, -2, -3, -7, -8, -9, -13, and -14 is upregulated following MI [85]. ECM fragments produced by MMPs are bioactive and act to promote fibrosis, ECM turnover, and LV remodeling. Indeed, several mouse models of MMP over-expression have shown adverse LV remodeling and increased mortality [86,87]. As such, modulation of MMPs, or their inhibitors—mainly TIMPs 1 and 2—is a possible avenue for post-MI therapy [88] and may reduce arrhythmogenesis by limiting interstitial fibrosis. Furthermore, MMPs degrade connexins [52], thus MMP inhibition may improve cell-cell coupling and conduction. As a note of caution, MMPs are widespread and expressed in most tissues and broad-spectrum MMP inhibitors have been unsuccessful in clinical trials due to musculoskeletal toxicity. Thus, therapeutics with affinities for specific MMPs may prove more beneficial [88]. For more discussion on MMP roles in post-MI remodeling, see Lindsey *et al*. in this issue [**JMCC9601**].

5. Conclusions

We have briefly reviewed the inflammatory and reparative/proliferative phases of post-MI healing and the mechanisms by which overactivity of either phase may contribute to malignant ventricular arrhythmias. Pharmacological therapies that target the post-MI electrophysiological substrate (i.e., ion channel blockers) have been largely unsuccessful in treating ventricular arrhythmias. Thus, by shifting the focus upstream of electrophysiological remodeling (i.e., to the inflammatory and fibrotic mechanisms that ultimately potentiate arrhythmia), novel anti-arrhythmic targets may be uncovered. An improved understanding of these mechanisms in arrhythmogenesis in the post-MI heart will provide more individualized treatment options for patients with MI.

Acknowledgments

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Highlights

- Post-MI healing is divided into 3 phases: inflammatory, reparative, and maturation
- Timely progression through each phase is required for optimal healing
- Over-activity of either the inflammatory or reparative phase may lead to arrhythmia
- Targeting inflammation or fibrotic repair may lead to new anti-arrhythmics

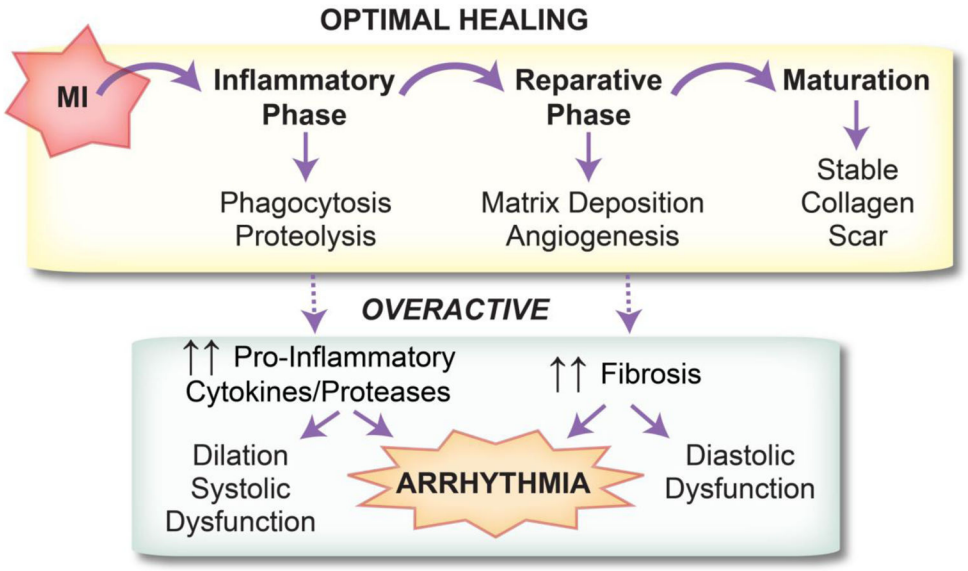

Figure 1.

Optimal post-MI healing is comprised of three phases: inflammatory, reparative/proliferative, and maturation. Timely progression and resolution of each phase is required for proper healing. An overactive inflammatory or reparative phase can lead to ventricular arrhythmia.

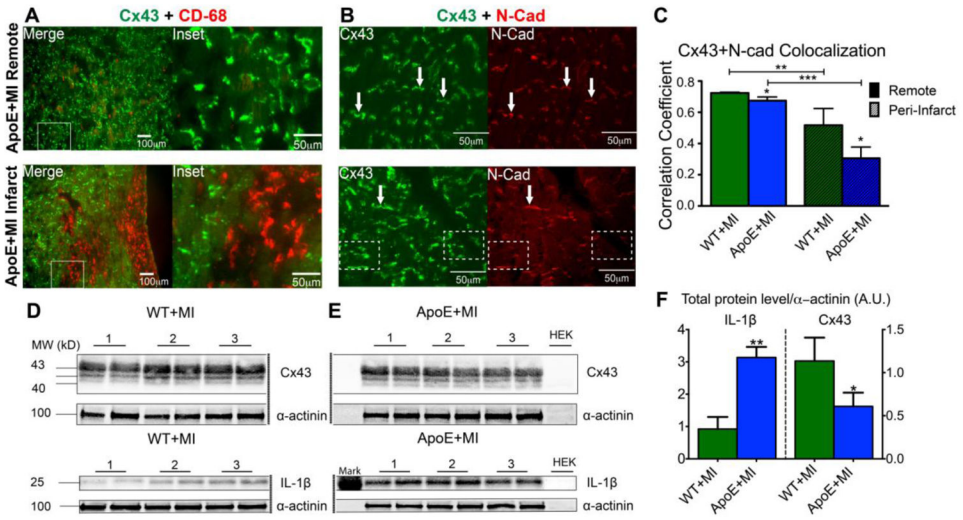

Figure 2.

Inflammation and Cx43. **A)** Immunofluorescence images of Cx43 (green) and CD-68 (red, macrophage marker) show abundant macrophage infiltration in the infarct region of an ApoE+MI heart (bottom). Myocytes adjacent to macrophages show internalization of Cx43 (Inset). **B) Top:** Cx43 (green) normally co-localizes with N-cadherin (N-Cad, red), a marker of the intercalated disc. Arrows indicate examples of obvious co-localization of Cx43 and N-Cad. **Bottom:** In the infarct region of an ApoE+MI heart, Cx43 expression is observed without corresponding N-Cad staining, indicating Cx43 internalization or lateralization to areas outside of the intercalated disc. Arrows indicate obvious examples of co-localization. Dashed boxes indicate examples of internalization (Cx43 without corresponding N-Cad). **C)** Quantification of Cx43 and N-Cad co-localization, demonstrating increased Cx43 internalization/lateralization in the infarct compared to remote regions, and in ApoE+MI compared to WT+MI hearts. **D–F)** ApoE+MI hearts have a ~3-fold increase in IL-1β expression and a corresponding ~2-fold decrease in Cx43 expression. Reprinted with permission from [47].

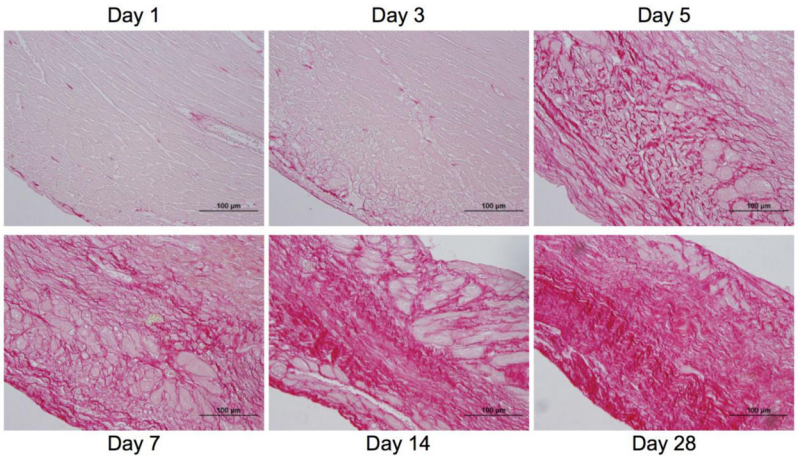

Figure 3.

The temporal progression of collagen deposition through 28 days post-MI. Sections were stained with 1% picosirius red, which stains collagen red. Reprinted with permission from [85].

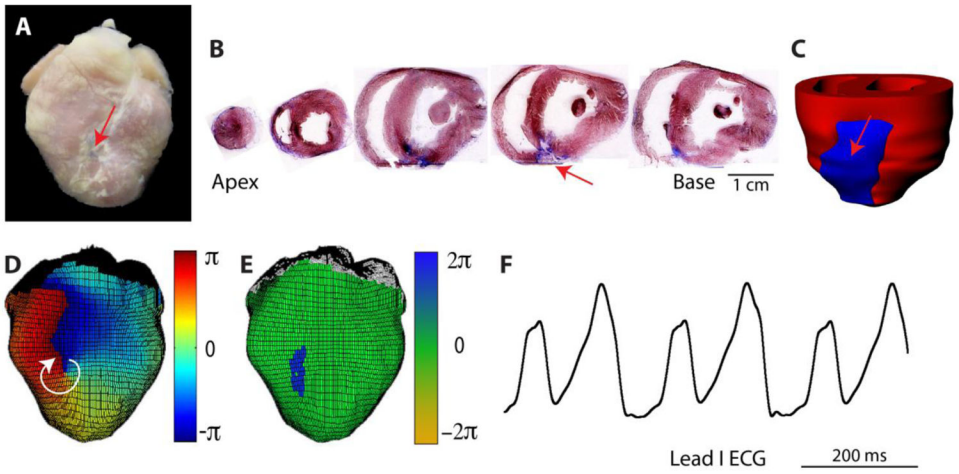

Figure 4.

Sustained VT anchored to compact scar. **A)** Photograph of post-MI rabbit heart. Arrow indicates infarct. **B)** Masson trichrome staining of short-axis slices. Blue indicates fibrosis. **C)** 3D histological reconstruction showing entire infarct region in blue. **D)** Phase map of stable reentrant VT rotating clockwise, anchored to compact scar. **E)** Location of phase singularities (center of reentry) corresponds to infarct location. **F)** Lead I ECG during VT. Reprinted with permission from [57].

Table 1

A selection of references demonstrating the impact of inflammatory cytokines and proteases on ionic currents, intracellular Ca^{2+} handling, and gap junction coupling. Arrows indicate an increase (↑), decrease (↓), or no change (↔) in given parameter.

TNF-α		**Ref.**	**Sample Type***
I_{CaL}	Current ↔	[22,23,36]	Ventricular myocytes from TNF-α overexpressing mice [22]; neonatal ventricular myocytes [36]
I_{to}	Current ↓ Kv4.2, Kv4.3 protein ↓ *KCND2*, *KCNIP2* mRNA ↓	[22–24] [22,23] [24,89]	Ventricular myocytes from TNF-α overexpressing mice [22,89]
I_{Ks}	Current ↓ during PKA activation	[90]	
I_{Kr}	Current ↓ hERG protein ↔	[25] [25]	Cardiomyocytes or HERG(+) HEK293 cells
$I_{K,slow1}$, $I_{K,slow2}$	Current ↓ Kv1.5 protein ↓	[22] [22]	Ventricular myocytes from TNF-α overexpressing mice
I_{K1}	*KCNJ12* mRNA ↓	[89]	Whole hearts from TNF-α overexpressing mice
Systolic $[Ca^{2+}]_i$	↓	[21,27]	Whole hearts from TNF-α overexpressing mice [21]
Diastolic $[Ca^{2+}]_i$	↑	[21]	Whole hearts from TNF-α overexpressing mice
$[Ca^{2+}]_{SR}$	↓	[27]	
Spontaneous SR Ca^{2+} release	↑ synergistically with IL-1β co-application	[29]	
SERCA	Slowed Ca^{2+} reuptake Gene ↓	[28] [28]	HL-1 cells
PLB	Gene ↔	[42]	Neonatal ventricular myocytes
Cx43	Total protein ↔ but lateralization/ internalization ↓ activity of promoter region of Cx43 gene	[30] [31]	Whole hearts from TNF-α overexpressing mice [30]; whole hearts following hepatic ischemia or LPS [31]
IL-1β			
I_{CaL}	Current ↓ Current ↑ Suppressed response to β-AR stimulation *CACNA1C* gene ↓	[34–36] [37] [38] [41]	Neonatal ventricular myocytes [36,41]
Systolic $[Ca^{2+}]_i$	↓ ↓ further with TNF-α co-administration ↔ to β-AR stimulation	[39] [29] [42]	Neonatal ventricular myocytes [39,42]
$[Ca^{2+}]_{SR}$	↓ synergistically with TNF-α co-application	[29]	
Spontaneous SR Ca^{2+} release	↑ synergistically with TNF-α co-application	[29]	
RyR	Gene ↓	[41]	Neonatal ventricular myocytes
SERCA	Protein ↓ Gene ↓	[39] [39,41–43]	Neonatal ventricular myocytes
PLB	Protein ↓ Gene ↓	[39,42] [39,42]	Neonatal ventricular myocytes
Cx43	↓ conductance (dye spread assay) Protein ↓	[45,46] [45,46]	MDCK cells and neonatal ventricular myocytes [45,46]
IL-6			
I_{CaL}	Current ↑	[48]	

TNF-α		**Ref.**	**Sample Type***
Systolic $[Ca^{2+}]_i$	↑	[48]	
SERCA	Slowed Ca^{2+} reuptake Gene ↓	[28] [28,49]	HL-1 cells [28]; neonatal ventricular myocytes [49]
PLB	↓ phosphorylation	[50]	
MMPs			
Cx43	Directly cleaved by MMP-7 Protein ↓ by MMP-2 Hypoxia-induced ↓ dependent on MMP-9 MMP-9 activation associated with slow conduction and Cx43 degradation, but MMP-9 found not to cleave Cx43	[52] [55] [53] [54]	Whole hearts from MMP-7-deficient mice with MI [52]; retinal endothelial cells [55]; H9c2 cardiomyocytes [53]; whole hearts from M9PROM mice with myocardial injury [54]

*Unless otherwise indicated, studies were performed in isolated adult ventricular myocytes treated with the cytokine/protease indicated.