JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 9, 2022

EDITORIAL COMMENT

A Nervous Touch on Heart Repair*

Marco Mongillo, MD, PhD[a,b]

While continuous advances in care and management of acute myocardial infarct have consistently improved short-term survival rates in the last decades, such achievements mirrored the increased burden of postischemic consequences, including increased arrhythmic vulnerability, ventricular remodeling, and development of heart failure. Thorough understanding of the mechanisms of myocardial repair is therefore an unmet need critical to develop therapeutics safeguarding cardiac function after ischemic damage.

It is widely recognized that ischemic death of myocardial cells triggers inflammation, which involves innate and acquired immunity in a complex series of cross interactions between heart-intrinsic and infiltrating cell types and signaling molecules. The inflammatory response, and its fine regulation throughout the different phases following ischemic injury are critical factors reflecting on tissue repair. In the first few days after ischemia, the cellular composition of the damaged myocardial microenvironment is hallmarked by neutrophils, activated monocytes, and inflammatory—"M1" polarized—macrophages, which clear the tissue from dead cells and debris. Subsequently, release of suppressor cytokines and phagocytosis of necrotic cell components trigger polarization of macrophages toward a reparative "M2" phenotype, which contributes to tissue protection and scar formation. At this point, the tissue context, includes dendritic cells and regulatory T lymphocytes (Tregs), which are centrally implicated in the negative regulation of inflammation and promote macrophage M2 polarization.

Prolonged activation and failure to suppress the inflammatory responses after myocardial infarction have been associated with adverse consequences, including excessive matrix degradation and cardiac rupture, as well as qualitative changes in the scar constituents and expansion of the damaged area.[1]

While the mechanisms promoting transition of macrophages from the classically activated M1 inflammatory to the alternatively activated M2 phenotype have not been thoroughly identified, a large number of studies has coherently shown that suppression of inflammation by M2 macrophages is advantageous for postischemic heart repair. Thus, therapeutic strategies targeted to modulate macrophage polarization hold a clinically relevant promise to prevent adverse remodeling after myocardial infarction.

A frequently under-rated consequence of myocardial ischemia is the inevitable injury of neuronal processes, mostly represented by noradrenaline-releasing sympathetic neurons, which densely innervate every heart region. Though it has long been appreciated that cardiac neurons underlie neurocardiac regulation, as exemplified by the acute activation of heart inotropy and chronotropy during the fight-or-flight reaction, a series of noncanonical effects of neuronal inputs on both myocyte and nonmyocyte myocardial cell types has recently been described. Beyond cardiomyocyte contractility, sympathetic neurons were shown to influence cardiac electrophysiology and regulate cell size and cell division in postnatal heart development. Furthermore, noradrenaline affects fibroblast activation and modulates the differentiation and activity of inflammatory cells, including dendritic cells, and directly stimulates Tregs, via β2 adrenoceptors.[1]

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the [a]Department of Biomedical Sciences, University of Padova, Padova, Italy; and the [b]Molecular Cardiology, Veneto Institute of Molecular Medicine, Padova, Italy.

The author attests he is in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2022.06.007

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 9, 2022
SEPTEMBER 2022:931–933

Remarkably, acute and chronic neurocardiac modulation of cardiac cells takes place through interaction sites at the contact between neuronal varicosities and target cells,[2] and as such, neurons regulate myocardial cells with strict spatial discrimination. It follows that local degeneration of cardiac neurons, as occurring on myocardial ischemia caused by coronary artery occlusion, by causing unbalanced sympathetic inputs between cells localized in the infarcted or the noninfarcted heart regions, generates local heterogeneity in electrophysiology favoring arrhythmias.[3]

In this issue of *JACC: Basic to Translational Science*, Sepe et al[4] build on these concepts and on a series of previous discoveries and assess the hypothesis that sympathetic reinnervation after ischemic damage would alter the inflammatory cells repertoire present in the scarred area and promote favorable remodeling of the postischemic myocardium.

First, the investigators use novel small molecule compounds, (HJ-01 and HJ-02) previously shown to promote axon outgrowth in vitro, to treat mice subjected to ischemia reperfusion injury, successfully rescuing the normal innervation density of the infarcted area. Consistent with previous discoveries of the group,[5] reinnervated hearts were less susceptible to catecholamine-induced arrhythmias. HJ-01 also associated to a remarkable effect on infarct size, measured 15 days after ischemia reperfusion induction, which was significantly lower in in drug- versus vehicle-treated hearts. Finally, in reinnervated hearts, cardiac contractile function was maintained to levels almost indistinguishable from those of sham-operated mice.

The investigators therefore use sequential immunohistochemical cell phenotyping to analyze the immune cell subsets present in the infarcted myocardial area in situ[6] and compared drug-treated, denervated versus vehicle-treated reinnervated hearts. By using a large number of markers (23 in the study) on a single slide, Sepe et al[4] showed that the cell repertoire of reinnervated hearts was characterized by fewer M1-inflammatory, and more abundant M2-reparative macrophages, and a higher fraction of negative regulators of inflammation including dendritic cells and Tregs. Thus, growth and re-establishment of sympathetic nerves during the evolution of inflammatory response to myocardial ischemia-reperfusion injury seems to promote suppression of inflammation and favor transition toward the tissue repair phase. Although the investigators did not specifically investigate the link between sympathetic neurons and inflammatory cells regulation, previous findings of the same group surmise that a dendritic cells/Treg/macrophage axis, initiated via neuronal-dependent stimulation of dendritic cells β2-adrenergic receptors, and resulting in macrophage polarization toward a M2-reparative phenotype, is likely.[5]

Results of the study by Sepe et al[4] are in line with the previous evidence that suppression of the robust inflammatory responses, characterizing the early postischemic phases, is beneficial for heart tissue repair;[1] the concept has further been extended, showing that rescue of cardiac innervation may be exploited to promote transition from the inflammatory to the reparative phases following ischemic tissue damage. Such approach offers several advantages: first, restoring sympathetic nerves acts on 2 fronts of the adverse electrophysiologic consequences of myocardial denervation, by protecting hearts from arrhythmias, on the one hand, and by improving postischemic tissue remodeling and function, on the other; second, "indirect" modulation of inflammation through sympathetic neurons allows better control of the intensity of anti-inflammatory effects, which are limited to the degree neurons may suppress immune responses. Third, even if administered systemically, the HJ drugs promoting nerve restoration are only effective on the myocardial area denervated as a result of the ischemic insult, and thus therapy is "targeted" to the same regions where inflammatory responses mostly take place, and tissue repair is needed. The mechanism of action of HJ-01, ablating the inhibitory effect of chondroitin sulfate proteoglycans on neuronal growth within the infarct,[5] is conditional, because it affects neuron growth only when growth is inhibited. This property adds a further level of safety, because potentially excessive neuronal outgrowth is not expected, as demonstrated by the similar neuronal density among the injured and uninjured peri-infarct myocardium of treated mice and the sham-operated mouse hearts.

It may be foreseen that favorable postischemic remodeling in reinnervated hearts would mitigate long-term consequences, including development of heart failure, and only further studies along this route will provide the definitive answers.

Further work in fundamental immunology is certainly needed to identify mechanisms whereby neurons control immune cell balance in the damaged myocardium.

Nevertheless, the approach described by Sepe et al[4] has a clear translational value and adds important progress in the pursuit of strategies to specifically target inflammation in the injured heart.

ACKNOWLEDGMENT The author wishes to thank Dr Tania Zaglia, for critically reading the work and unremittently sharing views and opinions on the role of cardiac innervation in the vast realm of heart pathology.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Mongillo has received institutional grants from the University of Padova.

ADDRESS FOR CORRESPONDENCE: Dr Marco Mongillo, Department of Biomedical Sciences, University of Padova, Via Ugo Bassi, 58/b, 35131 Padova, Italy. E-mail: marco.mongillo@unipd.it.

REFERENCES

1. Huang S, Frangogiannis NG. Anti-inflammatory therapies in myocardial infarction: failures, hopes and challenges. *Br J Pharmacol*. 2018;175(9):1377–1400.

2. Pianca N, Di Bona A, Lazzeri E, et al. Cardiac sympathetic innervation network shapes the myocardium by locally controlling cardiomyocyte size through the cellular proteolytic machinery. *J Physiol*. 2019;597(14):3639–3656.

3. Rubart M, Zipes DP. Mechanisms of sudden cardiac death. *J Clin Invest*. 2005;115(9):2305–2315.

4. Sepe JJ, Gardner RT, Blake MR, et al. Therapeutics that promote sympathetic reinnervation modulate the inflammatory response after myocardial infarction. *J Am Coll Cardiol Basic Trans Science*. 2022;7(9):915–930.

5. Gardner RT, Wang L, Lang BT, et al. Targeting protein tyrosine phosphatase σ after myocardial infarction restores cardiac sympathetic innervation and prevents arrhythmias. *Nat Commun*. 2015;6:6235.

6. Tsujikawa T, Kumar S, Borkar RN, et al. Quantitative multiplex immunohistochemistry reveals myeloid-inflamed tumor-immune complexity associated with poor prognosis. *Cell Rep*. 2017;19(1):203–217.

KEY WORDS inflammation, macrophages, multiplex immunohistochemistry, myocardial infarction, sympathetic nervous system