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The Nervous Heart: Role of Sympathetic Re-innervation in Cardiac Regeneration

Venkata Naga Srikanth Garikipati[1], **Suresh Verma**[1], and **Raj Kishore**[1,2,*]

[1]Center for Translational Medicine, Temple University School of Medicine, Philadelphia, PA, 19140

[2]Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA 19140

The regenerative capability of the heart is clinically relevant, as is the inability of adult heart to replace the lost cardiomyocytes post cardiac injury contributes to the ongoing encumbrance of heart failure [1]. However, compared to adult mammals, lower organisms can regenerate their hearts after an injury including frogs, newts and zebrafish. [2–7]. Remarkably, neonatal mice can also regenerate their hearts for up to 7 days after their birth [8, 9]. In this perspective, a thorough understanding of the regulatory mechanisms in the neonatal hearts will help to unravel the obstacles in reactivating the hidden regenerative capability of adult hearts.

Several conserved mechanisms for cardiac regeneration have been put forward, such as cardiomyocyte proliferation [8, 9], epicardial cell activation [10, 11], monocyte/macrophages and angiogenesis [12]. Further understanding on other potential factors that trigger the adult mammalian cardiac regeneration is of a key scientific and therapeutic importance. Along these lines, the study by White and colleagues in this issue of *Circulation Research*, provides a new avenue on the role of sympathetic nerves for neonatal cardiac regeneration[24].

For more than a century now, it has been reported that, nerves make a crucial contribution to regeneration in various tissues in vertebrates and invertebrates [13]. The seminal work by Todd way back in 1820s, first showed the inhibitory effects of denervation on hind limb regeneration in newts and further experiments on denervation of larval urodele limbs showed that limb regeneration is a nerve dependent process (reviewed in)[14]. Another report suggested that denervation impairs regeneration of amputated zebrafish fins [15]. It has also been shown that, ocular denervation negatively regulates corneal stem/progenitor cells number and function in a mouse model of ocular denervation [16]. A recent report demonstrated that ablation of parasympathetic branch of the autonomic system by surgical vagotomy inhibits cardiac regeneration [17]. However the role of sympathetic nerves has not been studied and is the focus of the new report in *Circulation Research*.

[*]**Correspondence to:** Raj Kishore, PhD, FAHA, Center for Translational Medicine, Temple University School of Medicine, MERB-953, 3500 N Broad Street, Philadelphia, PA 19140, Phone: 215-707-2523, Fax: 215-707-9890, raj.kishore@temple.edu.

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The heart is extensively innervated via the autonomic nervous system comprising sympathetic and parasympathetic nerves. Sympathetic innervation density is tightly regulated in the heart and densely seen in the sub-epicardium and central conduction system [18]. Intriguingly cardiac innervation density is affected in cardiac pathologies, such as after myocardial infarction (MI) or heart failure, [19] in which the cardiac nerves undergo Wallerian degeneration [20] and denervated myocardium leads to the generation of post-infarct arrhythmias [21]. Given the clinical significance of sympathetic denervation in cardiac pathologies[21–23], addressing the activation of the sympathetic re-innervation might be a novel therapeutic target for adult mammalian cardiac regeneration.

In this issue of *Circulation Research*, White and colleagues [24] rigorously addressed the important role of sympathetic re-innervation in neonatal cardiac regeneration. They generated a Wnt1-Cre: tdTomato transgenic mice that allowed labeling of the neural crest cell lineages and peripheral autonomic nerves and for visualization by epifluorescence stereomicroscopy. Specific immunofluorescence was used to identify sympathetic nerves by staining for tyrosine hydroxylase (TH), and choline acetyltransferase (ChAT). Co-localization of TH+ with only Wnt1-Cre+ fibers suggested the localization of sympathetic nerves in the sub-epicardium region. However, future studies should also focus on delineation of the role of the parasympathetic branch of autonomic nervous system in this process, since other studies support the concept that both the sympathetic and parasympathetic branches function together to maintain normal function of the cardiovascular system[25]. An interesting aspect of the new study is that, after apical resection of the ventricle, 14 days post-injury, an area of heavy dendrite hyper-innervation at the injury border was seen and varicose fibers emerging from the border into the site of active regeneration, associated with a complete regeneration by day 21, as reported earlier [26]. By day 21 post-injury, the apex completely regenerated and was re-innervated with fibers throughout the four chambers of the heart. Thus using this transgenic model, White and colleagues [24] provide important new insights into the role of sympathetic nerves in neonatal cardiac regeneration.

To further strengthen their findings, White and colleagues [24] ablated sympathetic nerves using a chemical inhibitor, 6-Hydroxydopamine hydrobromide (6-OHDA)[27], which resulted in robust denervation of sub-epicardial nerves in the neonate heart and eventually, denervation mediated myocardial injury and fibrosis. 6-OHDA completely inhibited neonatal cardiac regeneration, emphasizing the significance of sympathetic nerves in in this process.

Of note, a recent study suggested that vagotomy, mainly affecting parasympathetic nerves, impairs myocyte proliferation and cardiac regeneration in the neonatal heart. Interestingly this study demonstrated that the hypoinnveration effect on cardiac regeneration was partially rescued by nerve growth factor (NGF) proteins [17]. Results from these studies strongly support the role of both, sympathetic and parasympathetic nerves in neonatal cardiac regeneration. New studies will be required to understand the interaction of different branches of autonomic nervous system on cardiac regeneration.

In this transgenic Wnt1-Cre: tdTomato model it would be interesting to see if the observed reinnervation follows the neurotrophic hypothesis postulated by Singer et al, that nerves secrete neurotrophic factors and might participate in tissue regeneration post injury [20, 28]. Thus activating, cardiomyocyte proliferation or cardiac progenitor cells or vasculature thereby ultimately leading to cardiac regeneration, remains to be understood.

In summary, the current report by White and colleagues[24] provides important new information to the active field of cardiac regeneration by identifying a role of sympathetic nerves in neonatal mammalian heart regeneration. However, molecular mechanisms of the sympathetic nerve mediated regulation of cardiac regeneration were not defined. Further work will be required to determine if/how sympathetic innervation influences cardiac regeneration in the adult heart.

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