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Permanent Link:	http://hdl.handle.net/1805/5495
Date:	2014
Committee Chair:	Ingram, David A., Jr.
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Degree:	Ph.D.
Degree Year:	2014
Department:	Department of Biochemistry & Molecular Biology
Grantor:	Indiana University
Keywords:	Cardiac development ; Sympathetic innervation ; Shp2 ; pERK ; Bradycardia
LC Subjects:	Heart -- Innervation -- Research -- Analysis ; Heart -- Diseases ; Autonomic nervous system -- Physiology ; Heart -- Growth ; Sympathetic nervous system ; Protein-tyrosine phosphatase ; Heart conduction system ; Heart -- Diseases -- Treatment ; Protein kinases ; Developmental neurobiology -- Research ; Heart rate monitoring ; Neural crest -- Research ; Cell differentiation -- Molecular aspects ; Bradycardia -- Etiology ; Mice -- Diseases -- Molecular aspects

Abstract:

Autonomic innervation of the heart begins in utero and continues during the neonatal phase of life. A balance between the sympathetic and parasympathetic arms of the autonomic nervous system is required to regulate heart rate as well as the force of each contraction. Our lab studies the development of sympathetic innervation of the early postnatal heart in a conditional knockout (cKO) of Src homology protein tyrosine phosphatase 2 (Shp2). Shp2 is a ubiquitously expressed non-receptor phosphatase involved in a variety of cellular functions including survival, proliferation, and differentiation. We targeted Shp2 in post-migratory neural crest (NC) lineages using our novel Periostin-Cre. This resulted in a fully penetrant mouse model of diminished cardiac sympathetic innervation and concomitant bradycardia that progressively worsen. Shp2 is thought to mediate its basic cellular functions through a plethora of signaling cascades including extracellular signal-regulated kinases (ERK) 1 and 2. We hypothesize that abrogation of downstream ERK1/2 signaling in NC lineages is primarily responsible for the failed sympathetic innervation phenotype observed in our mouse model. Shp2 cKOs are indistinguishable from control littermates at birth and exhibit no gross structural cardiac anomalies; however, in vivo electrocardiogram (ECG) characterization revealed sinus bradycardia that develops as the Shp2 cKO ages. Significantly, 100% of Shp2 cKOs die within 3 weeks after birth. Characterization of the expression pattern of the sympathetic nerve marker tyrosine hydroxylase (TH) revealed a loss of functional sympathetic ganglionic neurons and reduction of cardiac sympathetic axon density in Shp2 cKOs. Shp2 cKOs exhibit lineage-specific suppression of activated pERK1/2 signaling, but not of other downstream targets of Shp2 such as pAKT (phosphorylated-Protein kinase B). Interestingly, restoration of pERK signaling via lineage-specific expression of constitutively active MEK1 (Mitogen-activated protein kinase kinase1) rescued TH-positive cardiac innervation as well as heart rate. These data suggest that the diminished sympathetic cardiac innervation and the resulting ECG abnormalities are a result of decreased pERK signaling in post-migratory NC lineages.

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