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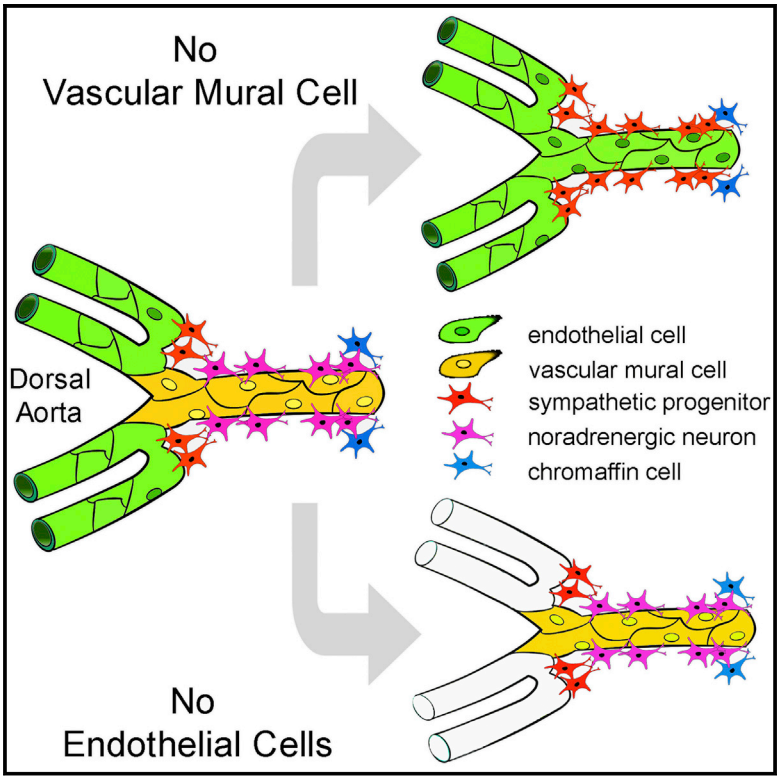
Vascular Mural Cells Promote Noradrenergic Differentiation of Embryonic Sympathetic Neurons

Graphical Abstract



Highlights

- SN precursors close to the DA acquire NA markers (TH and DβH)
- NA differentiation requires vascular remodeling and VMC recruitment
- Inhibition of PDGFR signaling prevents VMC recruitment and NA differentiation
- VMC are sufficient to direct SN development in absence of endothelial cells

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In Brief

Fortuna et al. show that neurovascular interactions between the aorta and sympathetic precursors are mediated by PDGFR-driven mural cell recruitment that promotes noradrenergic differentiation.

Fortuna et al., 2015, Cell Reports *11*, 1786–1796
June 23, 2015
http://dx.doi.org/10.1016/j.celrep.2015.05.028

CellPress

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Vascular Mural Cells Promote Noradrenergic Differentiation of Embryonic Sympathetic Neurons

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http://dx.doi.org/10.1016/j.celrep.2015.05.028

SUMMARY

The sympathetic nervous system controls smooth muscle tone and heart rate in the cardiovascular system. Postganglionic sympathetic neurons (SNs) develop in close proximity to the dorsal aorta (DA) and innervate visceral smooth muscle targets. Here, we use the zebrafish embryo to ask whether the DA is required for SN development. We show that noradrenergic (NA) differentiation of SN precursors temporally coincides with vascular mural cell (VMC) recruitment to the DA and vascular maturation. Blocking vascular maturation inhibits VMC recruitment and blocks NA differentiation of SN precursors. Inhibition of platelet-derived growth factor receptor (PDGFR) signaling prevents VMC differentiation and also blocks NA differentiation of SN precursors. NA differentiation is normal in *cloche* mutants that are devoid of endothelial cells but have VMCs. Thus, PDGFR-mediated mural cell recruitment mediates neurovascular interactions between the aorta and sympathetic precursors and promotes their noradrenergic differentiation.

INTRODUCTION

The sympathetic nervous system (SNS) controls involuntary body functions such as circulation, respiration, body temperature, sweating, digestion, and metabolism (Kuntz, 1948). SNS activation elevates blood pressure by increasing heart rate and peripheral vascular resistance. Cardiovascular responses to sympathetic activation are mediated by postganglionic sympathetic neurons (hereafter abbreviated SNs) that innervate visceral, vascular, and cardiac smooth muscle throughout the body. Dysfunction of the SNS leads to pathologies including congestive heart failure and hypertension, which affect millions of people worldwide. Understanding how SNs develop may offer new approaches to combat these diseases.

SNs are derived from the trunk neural crest (NC), a highly migratory multipotent cell population in developing vertebrate embryos (Le Douarin et al., 1981). NC cells delaminate from the dorsal neural tube (NT) and migrate along specific pathways to generate SNs and various additional cell types, including sensory neurons of dorsal root ganglia, ganglion satellite cells, Schwann cells of peripheral nerves, and melanocytes (Le Douarin and Kalcheim, 1999). NC cells forming the sympathetic ganglia migrate ventrally toward the main embryonic artery, the dorsal aorta (DA), where they differentiate and acquire a noradrenergic (NA) phenotype (Bronner-Fraser, 1986; Nitzan et al., 2013; Stern et al., 1991).

Here, we ask if the DA instructs early SN development in zebrafish embryos. SN development is conserved between vertebrate species and involves a series of differentiation steps and gene regulators that transform NC progenitors into mature SNs (An et al., 2002; Apostolova and Dechant, 2009; Guo et al., 1999; Rohrer, 2011; Stewart et al., 2010). Sequential expression of a number of transcription factors, starting with Mash1 (Zash-1 in zebrafish) (Allende and Weinberg, 1994) and Phox2b, followed by Insm1, Hand2, Phox2a, and Gata2, direct SN progenitor survival and proliferation, NA differentiation, and maintenance of differentiated properties (Howard et al., 2000; Rohrer, 2011; Tsarovina et al., 2004; Wildner et al., 2008). Tracking of zebrafish and avian NC cells showed that restriction to a neural fate already occurs before migration from the NT (McKinney et al., 2013, Raible and Eisen, 1996; Shtukmaster et al., 2013). However, misrouting of sympathetic NC progenitors does not result in ectopic NA neurons, indicating that migrating NC cells are not yet determined toward the SN lineage (Krispin et al., 2010, Stern et al., 1991). NA differentiation of sympathetic progenitors starts once they have reached the vicinity of the DA. Here, they acquire postmitotic and NA markers, including the expression of dopamine-beta hydroxylase (DβH) and tyrosine hydroxylase (TH), the enzyme catalyzing the rate-limiting step in catecholamine biosynthesis, followed by catecholamine storage (Flatmark, 2000; Saito et al., 2012).

SN progenitor migration and differentiation are controlled by three cytokine families, bone morphogenetic proteins (BMPs), the chemokine stromal-cell-derived factor-1 (SDF1, also called