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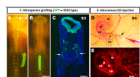
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Acknowledgements

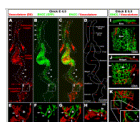
Appendix A. Supporting information

References

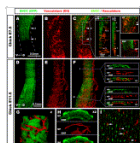
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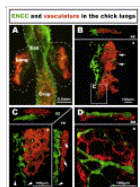
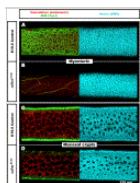
Video 1



Video 2



Video 3



Developmental Biology

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Vascularisation is not necessary for gut colonisation by enteric neural crest cells ☆

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Highlights

- The gut vasculature is thought to direct migrating enteric neural crest cells (ENCC).
- We visualised ENCC and the vasculature in the developing gastrointestinal tract.
- Enteric and vascular networks initially had little correlation.
- ENCC colonised the gut when vascular development was impaired in vivo or in vitro.
- Blood vessels are thus not necessary to guide migrating ENCC during ENS formation.

Abstract

The vasculature and nervous system share striking similarities in their networked, tree-like architecture and in the way they are super-imposed in mature organs. It has previously been suggested that the intestinal microvasculature network directs the migration of enteric neural crest cells (ENCC) along the gut to promote the formation of the enteric nervous system (ENS). To investigate the inter-relationship of migrating ENCC, ENS formation and gut vascular development we combined fate-mapping of ENCC with immunolabelling and intravascular dye injection to visualise nascent blood vessel networks. We found that the enteric and vascular networks initially had very distinct patterns of development. In the foregut, ENCC migrated through areas devoid of established vascular networks. In vessel-rich areas, such as the midgut and hindgut, the distribution of migrating ENCC did not support the idea that these cells followed a pre-established vascular network. Moreover, when gut vascular development was impaired, either genetically in *Vegfa*^{120/120} or *Tie2-Cre;Nrp1*^{fl/fl} mice or using an in vitro *Wnt1-Cre;Rosa26*^{Yfp/+} mouse model of ENS development, ENCC still colonised the entire length of the gut, including the terminal hindgut. These results demonstrate that blood vessel networks are not necessary to guide migrating ENCC during ENS development. Conversely, in *miRet*⁵¹ mice, which lack ENS in the hindgut, the vascular network in this region appeared to be normal suggesting that in early development both networks form independently of each other.

Keywords

Enteric nervous system; Vascular system; Neural crest cells; Blood vessels; Migration

Introduction

During vertebrate development, organs and tissues must connect to the blood vascular system to receive fluids, nutrients and oxygen, and to the nervous system to receive and send sensory, autonomic or functional information. Consequently, both mature networks share obvious similarities at the anatomical level, and they also use similar cellular and molecular mechanisms to orchestrate their parallel developmental programs (Bates et al., 2003, Eichmann et al., 2005, Eichmann and Thomas, 2013 and Tam and Watts, 2010). Recent evidence suggests that the two networks also influence each other's development through direct molecular interactions. For example, neuronal progenitors and neurons secrete the vascular growth factor VEGF to stimulate or pattern their vascular supply (Haigh et al., 2003,