A Temporo-Spatial Regulation of Sema3c Is Essential for Interaction of Progenitor Cells during Cardiac Outflow Tract Development

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The two cardiac progenitor cell lineages, cardiac neural crest cells (cNCCs) and the second heart field (SHF), play key roles in the development of the cardiac outflow tract (OFT). Both cardiac progenitor cells interact with each other and contribute to OFT formation cooperatively. The neurovascular guiding molecule, semaphorin 3c (Sema3c), is thought to serve as a key attractant for the migration of cNCCs. A previous study reported that *Tbx1* null mice showed a significant reduction in Sema3c expression in the OFT region [1]. However, the regulatory effect of *Tbx1* on Sema3c was unclear. Here, we show that Sema3c plays key roles in cNCCs-SHF interactions through the regulation by *Tbx1* and other molecules during OFT development [2].

By generating reporter transgenic mice harboring *Sema3c* enhancer fragments and lacZ transgene, we found that *Foxc1/c2* directly regulated Sema3c expression in the OFT via direct binding to the Fox-site on the 5' flanking sequence of *Sema3c* where *Tbx1* synergistically enhanced the *Foxc1/c2* function. In comparison, *Tbx1* in the SHF inhibited ectopic Sema3c expression in cNCCs within the pharyngeal arch region via Fgf8-ERK signaling. Consistently, the ectopic expression of Sema3c in the cNCCs of *Tbx1* hypomorphic mouse embryos caused abnormal migration and/or aggregation, and the overexpression of Sema3c in cultured cNCCs inhibited their migration, resulting in their aggregation. These results suggest that *Tbx1*-Fgf8-ERK signaling negatively regulates Sema3c expression in cNCCs for the proper guidance of their migration from the dorsal pharyngeal region to the OFT.

In conclusion, a proper temporo-spatial expression of Sema3c, which is tightly regulated positively by *Foxc1/c2* and negatively by the *Tbx1*-Fgf8 cascade, is essential for the correct navigation of cNCCs towards the OFT (Fig. 58.1). This report is the first evidence of a detailed signal transduction mechanism for the interaction between cNCCs and SHF progenitor cells through Sema3c, providing a new molecular basis for a potential therapeutic strategy for congenital heart diseases involving OFT defects.

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Fig. 58.1 Temporo-spatial regulation of Sema3c by Foxc1/c2 and Tbx1-Fgf8 cascade from the second heart field for proper navigation of cardiac neural crest cells towards the developing outflow tract

References

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