# TRANSGENIC USE OF SMAD7 TO SUPPRESS TGFβ SIGNALING DURING MOUSE DEVELOPMENT



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## Abstract:

Neural crest cells (NCC) are a multipotent population of cells that form at the dorsal region of neural tube, migrate and contribute to a vast array of embryonic structures, including the majority of the head, the septum of the cardiac outflow tract (OFT), smooth muscle subpopulations, sympathetic nervous system and many other organs. Anomalous NCC morphogenesis is responsible for a wide variety of congenital defects. Importantly, several individual members of the TGFβ superfamily have been shown to play essential roles in various aspects of normal NCC development. However, it remains unclear what role Smad7, a negative regulator of TGFβ superfamily signaling, plays during development and moreover what the spatiotemporal effects are of combined suppression of TGFβ superfamily signaling during NCC formation and colonization of the developing embryo. Using a cre/loxP three-component triple transgenic system, expression of Smad7 was induced via doxycycline in the majority of pre- and post-migratory NCC lineages (via Wnt1-Cre mice). Further,

expression of Smad7 was induced via doxycycline in a subset of post-migratory NCC lineages (via Periostin-Cre mice, after the NCC had reached their target organs and undergone differentiation). Induction of Smad7 within NCC significantly suppressed TGFβ superfamily signaling, as revealed via diminished phosphorylation levels of both Smad1/5/8 and Smad2/3 in vivo. This resulted in subsequent loss of NCC-derived craniofacial, pharyngeal and cardiac OFT cushion tissues. ROSA26r NCC lineage mapping demonstrated that cardiac NCC emigration and initial migration were unaffected, but subsequent colonization of the OFT was significantly reduced. At the cellular level, increased cell death was observed, but cell proliferation and NCC-derived smooth muscle differentiation were unaltered. Molecular analysis demonstrated that Smad7 induction resulted in selective increased phospho-p38 levels, which in turn resulted in the observed initiation of apoptosis in trigenic mutant embryos. Taken together, these data demonstrate that tightly regulated TGFβ superfamily signaling is essential for normal craniofacial and cardiac NCC colonization and cell survival in vivo.

**Description:**

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