Endothelin Receptor Type A-Expressing Cell Population in the Inflow Tract Contributes to Chamber Formation

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The avian and mammalian heart mainly originates from two distinct embryonic regions: an early differentiating first heart field and a dorsomedially located second heart field. It remains largely unknown when and how these subpopulations of the heart field are established as regions with different fates.

Endothelin-1 (Edn-1) acts on cardiac neural crest cells through endothelin receptor type A (Ednra) and is involved in the normal formation of pharyngeal artery-derived great vessels and ventricular septum [1]. Previously, we identified a distinct cell population defined by the expression of *Ednra* in the mouse inflow region [2]. These cells are derived from a part of the first heart field, and largely confined to the inflow region at E8.25.

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From the expression patterns of β-gal in the *Ednra-lacZ* knock-in mice, we thought a possibility that this *Ednra*-positive cell population might move into cardiac chambers from the inflow region. By dye injection and transplantation experiments, we showed that the *Ednra*-positive cell population moved toward not only the left and right atria but also the left ventricle.

Then, to perform lineage analysis, we have generated an *Ednra-CreERT2* mouse line (unpublished). We activated Cre recombinase by tamoxifen at E7.25 and E8.25 and analyzed the distribution of β-gal-labeled cells in the $Ednra^{CreERT2/+}$;*R26R* embryo hearts. As a result, the β-gal-labeled cells were found to contribute to the left ventricle and both atria.

To facilitate this lineage analysis, we established a mouse-chick chimera model. When we transplanted the inflow region of the $Ednra^{CreERT2/+}$;*R26R* mouse embryos (tamoxifen i.p. at E7.25) to orthotopically into chick embryos, β-gal-positive cells were detected in the right atrium and left ventricles 7 days after transplantation.

From these results, we conclude that the *Ednra*-positive cell lineage in the early inflow tract certainly contribute to chamber myocardial formation.

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