論文の内容の要旨

論文題目 **Endothelin receptor type-A expression defines a distinct subdomain within the heart field and contributes to chamber myocardium formation**

和訳 **（エンドセリンA型受容体発現解析による心臓予定領域内特定細胞集団の同定と心形成におけるエンドセリンシグナルの役割の解明）**

指導教員 栗原裕基教授

東京大学大学院医学系研究科

平成19年4月進学

医学博士課程

分子細胞生物学専攻

氏名　淺井　理恵子

The avian and mammalian heart originates from the two embryonic regions, the crescent-forming first heart field and the second heart field located in the pharyngeal mesoderm. It remains largely unknown when and how these subdivisions of the heart field divide into regions with different fates.

The endothelin-1 (*Edn1*)/endothelin type-A receptor (*EdnrA*) signaling is now implicated in craniofacial and cardiovascular development. To identify target cells of the *Edn1/EdnrA* signaling in heart development, we knocked-in *lacZ/EGFP* marker genes into the mouse *EdnrA* locus. In developing heart, *lacZ/EGFP* was expressed in cardiac neural crest-derived structures in the outflow tract and pharyngeal arteries. In addition, *lacZ/EGFP* expression was also found in the inflow tract at primitive heart tube through

looping/ballooning stages. This expression overlapped partially with expression of first heart field marker, *Nkx2.5* and *Mlc2a*, in the ventral side from early heat developing stage, indicating the first heart field origin of *lacZ/EGFP*-expressing cells. Toward chamber formation, distribution of *lacZ* expression was extended along the left ventrolateral side of the atrium to the left ventricle in a characteristic pattern. This apparent upward movement was confirmed fluorescent dye labeling into the inflow region and transplantation experiment in which excised *EGFP* positive inflow tissues were placed into the same region of wild-type embryos.

Furthermore, the *Ednra-lacZ/EGFP*-expressing subpopulation is characterized by the presence of *Tbx5*-expressing cells. *Ednra*-null embryonic hearts often demonstrate hypoplasia of the ventricular wall, low mitotic activity and decreased *Tbx5*-expression with reciprocal expansion of *Tbx2* expression. Conversely, endothelin-1 stimulates ERK phosphorylation and *Tbx5* expression in the early embryonic heart. These results indicate that early *Ednra* expression defines a subdomain of the first heart field contributing to chamber formation in which *Edn1/Ednra* signaling is involved.

Here, I identify in the mouse a subpopulation of the first (crescent-forming) field marked by *Ednra* gene expression, which contributes to chamber myocardium through a unique type of cell behavior. The present finding provides an insight into how subpopulations within the crescent-forming (first) heart field contribute to the coordination of heart morphogenesis through spatiotemporally defined cell movements. These findings may

contribute to the understanding of coordinating cell behavior in cardiac morphogenesis.