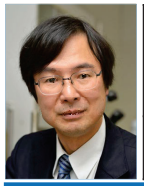
【Grant-in-Aid for Scientific Research (S)】

Integrative understanding of cardiac and mediastinal diseases based on the common developmental origins



Principal Investigator	The University of Tokyo, Graduate School of Medicine, Professor KURIHARA Hiroki Researcher Number:20221947
Project Information	Project Number : 22H04991 Project Period (FY) : 2022-2026 Keywords : Cardiogenesis, Mediastinum, Neural crest, Macrophage

Purpose and Background of the Research

●Outline of the Research

The mediastinum is a space between the left and right lungs, which contains many thoracic organs such as the heart, great vessels, thymus, trachea, and esophagus. During embryonic development, various cell populations migrate into this region and interact with each other, resulting in dynamic changes of their phenotypes. Thus, this region can be called a 'melting pot' of cell types. In this study, we aim to clarify cell origins and lineages common to the heart and other mediastinal organs focusing on neural crest cells, pharyngeal mesoderm (second heart field) and macrophages. We also investigate the dynamics and roles of their interactions as a common basis for organogenesis. Furthermore, we will elucidate how these cell lineages and their interactions are involved in the pathogenesis and pathophysiology of congenital heart disease, tissue calcification, tissue repair after myocardial infarction, and mediastinal tumors. In this way, we will build a new framework for an integrated understanding of heart diseases and mediastinal diseases, which have been considered separately in clinical practice, and will establish 'clinical embryology' that aims at the clarification of pathogenesis and pathophysiology based on developmental biology.

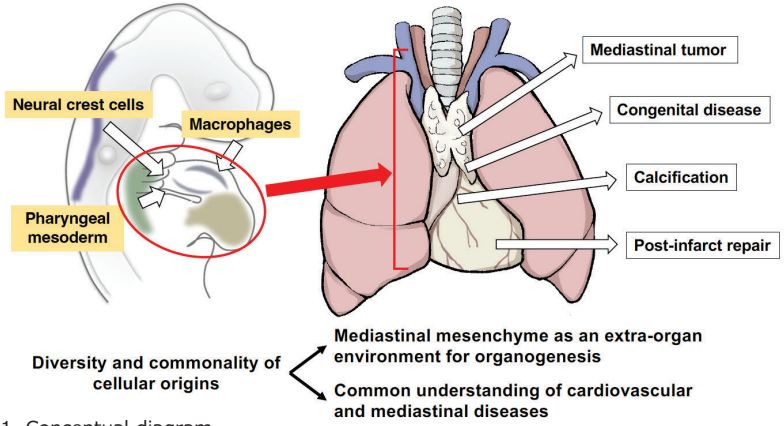


Figure 1. Conceptual diagram

●Background of the Research

Different tissues and organs in the mediastinum share many developmental origins. However, Clinical medicine considers heart diseases and mediastinal diseases as different categories. Even for 22q11.2 syndrome (Di George syndrome) involving the heart, great vessels and thymus etc., few integrative studies have done with the mediastinum as a common place for organogenesis.

The PI and colleagues have investigated on endothelin and neural crest cells, which has founded a basis for studies on mediastinal development.

These findings are expected to provide a clue to cross-disciplinary understanding of various diseases based on a common extra-organ environment in the mediastinum during organogenesis, leading us to the concept of this study.

● Purpose of the Research

This study addresses the following three questions:

(1) What are commonalities and differences in the differentiation and interactions of multiple cell lineages between heart development and mediastinal formation?
(2) What factors mediate and control these inter-lineage interactions?
(3) To what extent can we understand the pathophysiology of heart and mediastinal diseases through inter-lineage interactions during development?

We focus on neural crest cells, pharyngeal mesoderm and macrophages to investigate the fates and dynamics of multiple cell lineages in a common extra-organ environment. Furthermore, we analyze mediating signals and gene regulatory networks in each cell lineage. Based on these findings and further studies using clinical specimens and disease model animals, we will pave the way for understanding heart and mediastinal diseases and developing new therapeutic strategies.

Expected Research Achievements

● Diversity and commonality of cellular origins

We isolate neural crest cells, pharyngeal mesodermal cells, and macrophages from mouse mediastinal regions to identify subsets within each cell lineage by single-cell analysis. Mutual relationships between subsets are estimated by spatial transcriptome and immunostaining, which will be verified by avian chimeric experiments.

● Inter-lineage interactions

We estimate inter-subset signalling and gene regulatory networks by multiome analysis, which will be verified by avian chimeric experiments and in-vitro 3-D reconstruction culture systems.

● Understanding pathophysiology

(1) Congenital diseases: We perform single-cell analysis on endothelin-deficient mouse embryos showing a phenotype similar to 22q11.2 deletion syndrome to reveal underlying mechanisms, especially focusing on the extra-organ environment in the mediastinal mesenchyme. If a cell lineage subset directly related to the disease is estimated, lineage-specific knockout mice will be generated for verification.

(2) Calcification: We extract gene regulatory networks specific for neural crest cells or common to skeletogenic cells from single-cell data to analyze their changes in a pathological model that causes calcification. In addition, we will create a pathological model in lineage-labeled mice to identify novel genes involved in calcification. Their involvement in pathogenesis will be verified by creating genetically modified mice.

(3) Tissue repair after myocardial infarction: We create mouse myocardial infarction model to analyze changes in the phenotype of each cell lineage during tissue remodeling after myocardial injury and compare them with subsets during heart development to clarify commonalities and differences in gene regulatory networks.

(4) Mediastinal tumors: We perform single-cell analysis on human mediastinal tumors to identify the cell origin and degree of differentiation in reference to developmental lineages. If a candidate driver mutation is identified, we will try to establish model mice by introducing a cell lineage-specific gene mutation.

【Goals after 5 years】

- Analyses on multilineage interactions will prove the significance of the mediastinal mesenchyme as an extra-organ environment for organogenesis.
- A common developmental basis will facilitate understanding the pathophysiology of heart and mediastinal diseases, paving a way for the development of new therapies.

Homepage Address, etc.	http://bio.m.u-tokyo.ac.jp/home-j.html https://researchmap.jp/read0123008