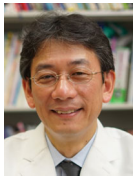
【Grant-in-Aid for Scientific Research (S)】

Establishment of an integrated locomotive science including spatiotemporal dynamics of bone-articular cells



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Purpose and Background of the Research

●Outline of the Research

The locomotor system consists of various somatic cells, fibroblasts, immune cells such as macrophages, T cells, and innate lymphoid cells. They maintain bone and joint homeostasis by interacting with each other. We have elucidated the roles of immune cells in regulating the maintenance of the locomotor system and the development of joint diseases by single-cell RNA sequencing. We have also found the heterogeneity of the cells, ranging from undifferentiated progenitor cells to mature somatic cells, that closely communicate with immune cells. We clarified that locomotive tissue has a gradual continuum of cells, including undifferentiated progenitors and mature cells interacting with immune cells. In this project, we develop our previous findings and investigate how the locomotor system's development, maintenance, repair, and degeneration under mechanical stress are regulated by progenitors and immune cells using single-cell analysis techniques, spatial analysis, and the methods of the latest multi-omics analysis (Figure 1). By investigating the dynamics of the locomotor system in the development and degeneration at the single-cell resolution, we will promote Integrated Locomotive Science (ILS) to a higher level, leading to the development of disease control by uncovering the biological mechanism.

Figure 1. Scheme of the research

①Development of the locomotor system
- Mouse embryos
- Human surgical specimens
- Stem cell-derived bone tissue models

→ Focus on tissue boundaries

②Maintenance of the locomotor system
- Human surgical specimens
- Mice and rats (treadmill/tail suspension model)

③Repair and degeneration of the locomoter system
- Human surgical specimens (osteoarthritis/rheumatoid arthritis/fracture/trauma)
- Mice and rats (trauma model / disease model / menopause model / aging)

Elucidation of the mechanism of Mechanosensing/mechanoresponse and identification of responsible cells

④Resolution of pain

Mice and rats (CatWalk/von Frey)

Evaluation of inflammatory and neuropathic pain and analysis of dorsal root ganglia

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A) Histrogical analysis of structure
- Tissue Staining
- Immunostaining
- X-ray/μCT
- LMD

B) Bulk analyses
- qPCR
- Bulk RNA Sequencing
- ATAC Sequence
- ChIP Sequence

C) Single cell analyses
- Single cell RNA sequencing
- Single cell ATAC sequencing
- CyTOF
- Spatial analyses

D) Integrative analysis of GWAS
- GWAS analysis
- eQTL analysis
- Partitioning heritability analysis

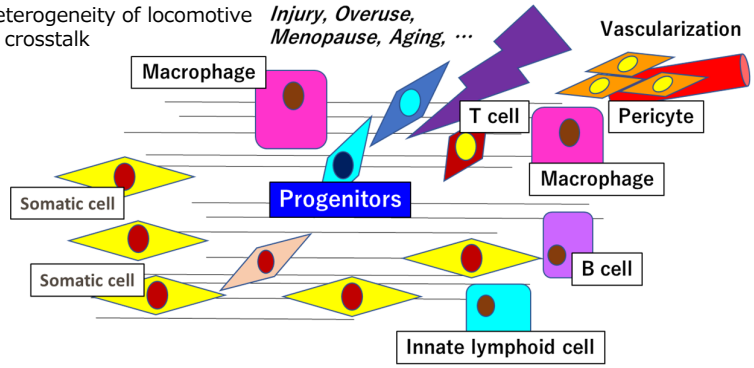
Crosstalk and interaction of tissues and cells in the locomotor system

➡ Development of disease-modifying drugs

Background and Purpose of Research

The locomotor system is a complex of various tissues unable to lubricate motion, including bone, cartilage, muscle, tendon, ligament, and synovium (Figure 2). Although the locomotor organs possess the biological functions of locomotion over a long period, they are also known to frequently show dysfunction due to overuse, injury from trauma, postmenopausal changes, degeneration due to aging, and inflammation. It is well known that the locomotor organs such as bone, cartilage, and muscle develop during growth, and these changes also occur in pathological conditions. This evidence is elucidated by a cohort study (BMJ Open 2:e001520,2012) showing that the pathologies of systemic diseases such as osteoporosis, osteoarthritis, and sarcopenia interrelate with bone, cartilage, and muscle changes. However, such a relation cannot be explained by the aging phenomenon alone, suggesting a cooperative mechanism that regulates the dynamics of tissues. Besides, the regulatory mechanism of the locomotor organs, has yet to be elucidated.

Figure 2. Heterogeneity of locomotive cell and the crosstalk



This study aims to elucidate how the locomotive tissues and the cells are regulated and how the different tissues work together to integrate the locomotor system. The project will use the latest molecular and cell biological techniques, including single-cell analysis and mechanobiology, and the latest advances in expression data and genomic and epigenomic approaches. The individual research integrates bioinformatics technologies with expression data and genomic/epigenomic data. We use biological systems, such as cultured cells, experimental animal models, and human clinical samples. All of these methods are necessary to understand the whole system of the locomotor. The research team, composed of experts in the respective fields, cooperates to achieve the project's goal to establish and refine ILS to the next level.

Expected Research Achievements

This project will uncover the role of somatic cells, progenitors, immune cells, and tissue-resident cells in the bone, cartilage, synovium, tendons, and ligaments. The research aims to understand the pathology of diseases and the development, maintenance, repair, and degeneration of the locomotor system. We clarify how the locomotor system changes in conditions with mechanical loading, aging, and menopause. Integrating with GWAS data, we extract the genomic regions involved in locomotive diseases, identify the tissues, cell types, and subsets affected by disease-sensitive polymorphisms/genes, and establish novel disease-modifying tools for preventing and treating diseases.

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