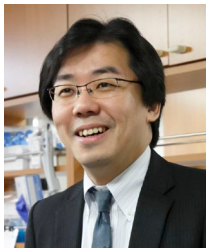
【Grant-in-Aid for Scientific Research (S)】

Broad Section I



Title of Project： Identification and control of pathogenic osteoclasts

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Research Project Number：19H05657 Researcher Number：10324758
Keyword：medicine and welfare, immunology

【Purpose and Background of the Research】

Osteoclasts play a key role in maintaining skeletal homeostasis by supporting steady-state bone remodelling in the bone marrow (BM). However, in contrast to this physiological role, osteoclasts are also involved in pathological arthritic bone erosion in patients with rheumatoid arthritis (RA), which occurs where the hypertrophied synovium (called “pannus”) invades the outer surface of the articular bone. Extensive studies have been performed to identify the osteoclast precursor (OP) population in BM. Nevertheless, precise analysis of OPs in inflammatory conditions has not yet been performed, especially in “inflamed synovium”, the actual site of bone erosion in arthritis, mainly due to technical difficulties associated with approaching and isolating tiny synovial tissues. Thus, whether the two osteoclast populations in the BM and synovial tissue settings have a similar pathway of differentiation and arise from similar precursor states remains unknown (Figure 1). The objectives of the current study are, (1) to identify the osteoclast precursor (OP) population in the inflamed synovium and elucidate the molecular mechanisms responsible for regulating this population, and (2) to elucidate the functional characteristics of osteoclasts in the pannus-bone interface compared with conventional osteoclasts in BM.

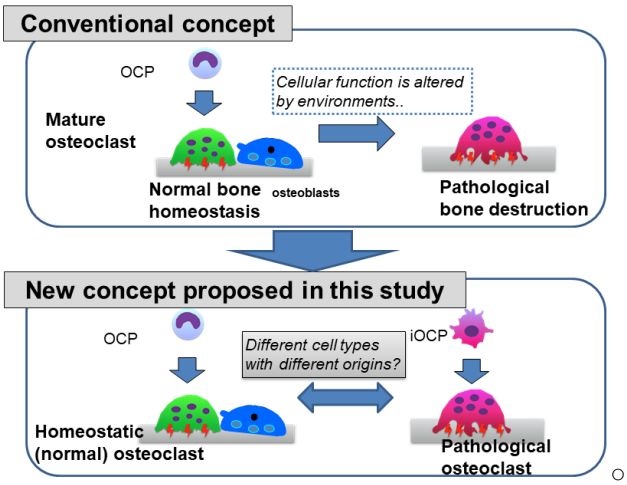

Figure 1. Conventional and novel concepts on osteoclasts in inflammatory conditions. Are they just different in terms of their activation status, or they are essentially different cell types from respectively distinct precursors?

【Research Methods】

Using the original protocol to isolate the inflamed synovium, we identify the OP population in the synovium and then characterize the molecular mechanisms as well as the predicted critical regulator for differentiation of these cell types, by using exhaustive expression analyses, such as RNA sequencing. For analyzing their origins, cellular tracing and intravital imaging with photo-convertible fluorophore will be conducted. Furthermore, by targeting the molecule(s) which we identify specifically expressed in inflammatory OP fractions, we plan to develop novel therapeutics against inflammatory bone destructions. We also further analyze the possible involvement of this novel line of osteoclasts in another pathological conditions such as bone-metastatic tumors. For such analyses, direct visualization of osteoclasts will clarify the differences and characteristics, which may lead to the development of optimized treatment for bone diseases.

【Expected Research Achievements and Scientific Significance】

This work, with its identification and characterization of a novel OPs specifically involved in arthritic bone destruction, and with elucidation of the functional differences between osteoclasts in the BM and pannus-bone interface, will lead to pathogenic-osteoclast specific treatment in patients with rheumatoid arthritis (RA).

【Publications Relevant to the Project】

Furuya, et al., Direct cell-cell contact between mature osteoblasts and osteoclasts dynamically controls their functions in vivo. Nat. Commun., 9: 300, 2018.
Matsuura et al. In vivo visualization of different modes of action of biologic DMARDs inhibiting osteoclastic bone resorption. Ann. Rheum. Dis., 77 :1219-1225, 2018.

【Term of Project】 FY2019-2023

【Budget Allocation】 153,700 Thousand Yen

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