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

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Elucidation of the Transcriptional Regulation of Runx2 and Development of the Drugs for Osteoporosis and Osteoarthritis

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Research Project Number : 26221310 Researcher Number : 00252677
Research Area : Morphological basic dentistry
Keyword : transcriptional regulation, development and differentiation, drug discovery, cell and tissue, gene

【Purpose and Background of the Research】

We have clarified that Runx2 is an essential transcription factor for skeletal development, that Runx2 is essential for osteoblast differentiation and chondrocyte maturation, and that Runx2 is a responsible molecule for osteoarthritis (Fig. 1).

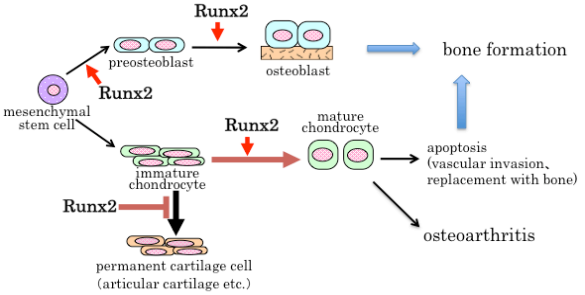

Fig. 1 The functions of Runx2

Therefore, Runx2 exerts positive effects on bone but negative effects on cartilage. The elucidation of the transcriptional regulation of Runx2 in osteoblasts and chondrocytes makes a great advance in the understanding of the molecular mechanism of skeletal development and maintenance. Further, it makes possible to regulate Runx2 in osteoblasts and chondrocytes separately, which allows us to develop the drugs for osteoporosis and osteoarthritis. In this study, we elucidate the transcriptional regulation of Runx2, and develop the drugs for osteoporosis and osteoarthritis based on the molecular mechanisms of the transcriptional regulation.

【Research Methods】

We generate reporter mice driven by genome DNA of Runx2 locus and identify the enhancers for Runx2 expression in osteoblasts and chondrocytes. Next, the molecular mechanisms of the activation of the enhancers are elucidated. The chemical compounds, which enhance Runx2 expression in osteoblast precursors, are candidates of the drugs for osteoporosis, and the chemical compounds, which inhibit Runx2 expression in chondrocytes, are candidates of the drugs for osteoarthritis (Fig. 2). Therefore, we identify the chemical compounds, which enhance osteoblast-specific enhancer or inhibit chondrocyte-specific enhancer, through high throughput screening, and examine the effects using animal models.

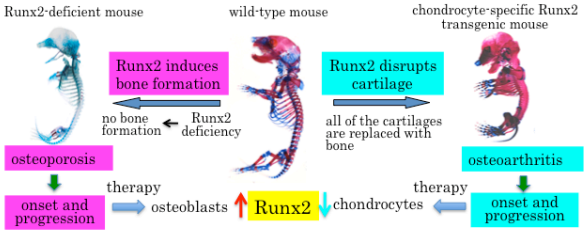

Fig. 2 The development of the drugs for osteoporosis and osteoarthritis by regulating Runx2 expression

【Expected Research Achievements and Scientific Significance】

As Runx2 plays a central role in skeletal development, the elucidation of the transcriptional regulation of Runx2 makes a great advance in the understanding of skeletal development. This study also contributes to the treatment of osteoporosis and osteoarthritis by developing the drugs.

【Publications Relevant to the Project】

・Kawane T, Komori H, (10 authors), and Komori T. Dlx5 and Mef2 Regulate a Novel Runx2 Enhancer for Osteoblast-Specific Expression. J Bone Miner Res. 2014 Apr 1. doi: 10.1002/jbmr.2240. [Epub ahead of print]
・Komori T. Signaling networks in RUNX2-dependent bone development. J Cell Biochem. 112 (3): 750-755, 2011.

【Term of Project】 FY2014-2018

【Budget Allocation】 150,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.de.nagasaki-u.ac.jp/dokuji/kaibou-2/index.html