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

Broad Section I

Title of Project : Elucidation of the mechanism in the regulation of chondrocyte-specific Runx2 enhancer and development of the drug for osteoarthritis

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Keyword : chondrocyte, osteoarthritis, enhancer, Runx2

【Purpose and Background of the Research】

We are pursuing to elucidate the mechanism of the formation and maintenance of bone and cartilage focusing on Runx2. We clarified that Runx2 is an essential transcription factor for osteoblast differentiation and chondrocyte maturation, and is responsible for osteoarthritis (Fig. 1, 2). Therefore, Runx2 positively works in adult bone by increasing bone formation and negatively works in articular cartilage by destructing it. 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 mechanism of the activation of chondrocyte-specific enhancers and develop the drugs for osteoarthritis using the enhancers.

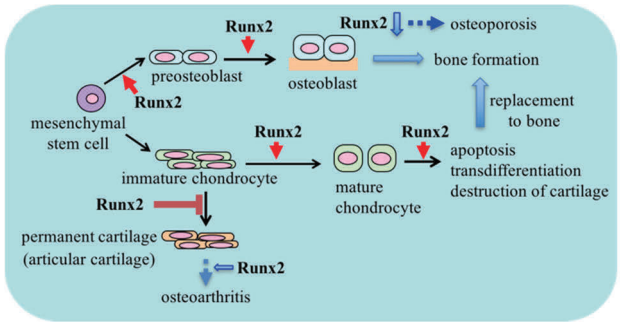

Fig. 1 The functions of Runx2

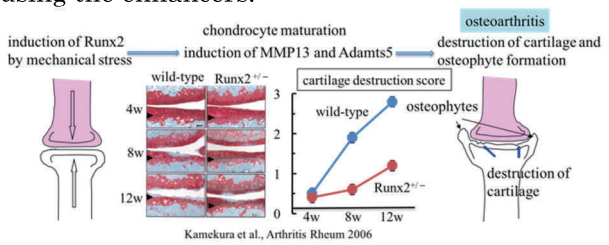

Fig. 2 The development of osteoarthritis by Runx2

【Research Methods】

We clarify the transcription factors and cofactors, which activate chondrocyte-specific Runx2 enhancers, the structure of the enhanceosome, and the interaction of enhancers and promoters. By high throughput screening, we identify the chemical compounds, which inhibit the activity of chondrocyte-specific enhancers and suppress Runx2 expression only in chondrocytes. We evaluate the effect of the selected chemical compounds using osteoarthritis mouse models, identify the molecules interacting with them, and elucidate the mechanisms of action of the selected compounds. From these data, we determine the candidates for the drug for osteoarthritis.

【Expected Research Achievements and Scientific Significance】

More than 25 million people suffer osteoarthritis of knee joints in Japan. Osteoarthritis is caused by the destruction of articular cartilage through the repetitive mechanical stress and its accumulation. It causes disability of walking due to the severe pain. The prosthetic replacement arthroplasty is the only therapy. This is a unique study to develop the drugs for osteoarthritis by using chondrocyte-specific Runx2 enhancers. From this study, we will have the drugs to inhibit the development and progress of osteoarthritis.

【Publications Relevant to the Project】

Komori T: Runx2, an inducer of osteoblast and chondrocyte differentiation. Histochem Cell Biol. 149(4):313-323, 2018.
Kawane T, et. al.: Dlx5 and Mef2 regulate a novel Runx2 enhancer for osteoblast-specific expression. J Bone Miner Res. 29(9):1960-1969, 2014.

【Term of Project】 FY2018-2022

【Budget Allocation】 148,800 Thousand Yen

【Homepage Address and Other Contact Information】

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