Cbfβ/Runx1 complex is important for the articular cartilage integrity.

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Abstract

Osteoarthritis (OA), a leading age-related disease in society, still lacks a clear molecular mechanism. Here, we explored in vivo role of core binding factor β (Cbfβ) in OA by generating articular cartilagespecific Cbfβ-deleted mice (Cbfβâ– ³ac/â– ³ac) using Gdf5 promoter-driven Cre mice. OA was induced through destabilization of the medial meniscus (DMM) surgery in 12-week-old male mice. At 8 weeks after surgery, OA phenotypes were more accelerated in Cbfβâ– ³ ac/â– ³ ac mice than wild type (WT) mice with increased expression of Mmp13 and decreased expression of Type II collagen. Interestingly, the expression of Cbfβ was reduced during aging as determined by immunohistochemisty. Furthermore at 5 months of age Cbfβâ– ³ac/â– ³ac mice, but not in WT, exhibited OA naturally without developmental defects in joint and skeletal tissue formation.

Keywords: Osteoarthritis, DMM.

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Introduction

To explore the molecular mechanism of the protective role of Cbfβ in OA, we measured the expression of chondrocyte markers, Runx transcription factors, and Cbfβ in articular cartilage. Expression of chondrocyte markers such as type II collagen, Aggrecan, and Cbfβ was attenuated in chondrocytes derived from Cbfβâ– ³ac/â– ³ac OA mice compared to WT mice. Among Runx family, Runx1, but not Runx2 and Runx3, was highly expressed in particular chondrocytes. Expression of Runx1 was gradually decreased during OA progression in WT mice. Importantly, Runx1 expression was further diminished in Cbfβâ□³ac/â□³ac OA mice. Cbfβ formed a complex with Runx1 and protected Runx1 from proteosomal degradation in primary articular chondrocytes as well as in ATDC5 cells. Consistently, forced expression of Cbfβ in Cbfβ-deficient primary articular chondrocytes restored the chondrocyte markers and Runx1 expression. Collectively, these results demonstrate that Cbfβ is required for Runx1 stability as a partner protein in articular cartilage and that the formation of the Cbfβ-Runx1 complex plays an essential role for maintenance of articular cartilage integrity. Runt-related transcription factor-1 (Runx1), also known as core-binding factor 2 or acute myeloid leukaemia (AML1), is a crucial component of hematopoiesis and blood cancers. 1 The RUNX1 gene is one of the most frequently altered genes in acute leukaemia in humans. *1*

Conventional Runx1 deletion in newborn mice results in a loss of hematopoietic capability, and individuals are unable to survive the early embryonic stage. Myeloid malignancies such as myelodysplastic syndrome, myeloproliferative neoplasm-like illness, and acute myeloid leukaemia are caused by conditional knockout (CKO) of Runx1 in the hematopoietic lineage in adult mice (AML). Runx1 has been linked to a variety of organ development processes and disease occurrences outside of the haematological system as a master regulatory transcription factor. When it comes to skeletal development, Runx1 is involved in the lineage determination of progenitor cells in the periosteum, calvarial sutures, and perichondrium, and hence plays a role in early skeletogenesis. Luo et al. discovered that Runx1 controlled osteogenic differentiation of bone marrow stem cells (BMSCs) in vitro by blocking adipogenesis via the Wnt/-catenin pathway. Overexpression of Runx1 caused BMSCs to undergo chondrogenic differentiation, according to Wang et al. Due to mineralization impairment generated by CKO of Runx1 in paired-related homeobox transcription factor-1 (Prrx1)- and Col2a1-Cre mice, Kimura et al. discovered that Runx1 was a key regulatory factor in sternal morphogenesis in vivo.

Runx1 was previously shown to increase chondrocyte-to-osteoblast lineage commitment2 and to be a need for mouse osteoblast development and ultimate bone formation. Although Runx1's significance in skeletal development has been steadily revealed, its role in cartilage illnesses such as osteoarthritis (OA) is still unknown. Cbf-alpha (Cbf) and Cbf-beta (Cbf) are two core-binding factors that make up Runx1. Cbf is encoded by the runt-related transcription factors (Runxs) Runx1, 2 and 3. Cbf is encoded by a single gene. Although they are highly conserved in the runt domain and bind to the consensus DNA sequence through the dimerization of Cbf, members of the Runx family exhibit diverse spatial-temporal and tissue-specific expression patterns as well as distinct and nonredundant biological activities.

Runx1 is well defined and is crucial in hematopoiesis and haematological malignancies like AML (hence, Runx1 is also known as AML1), but its complex implications in multiple signalling pathways and physiological mechanisms dictates its potent role as a master-regulator transcription factor. 17 Runx2 is best known for playing an important part in osteoblast differentiation.

One of the most common joint disorders, OA, is a primary cause of disability and is quickly becoming a global economic burden. Despite its growing importance, no licenced medicines can stop OA from progressing, and due to its numerous etiologies, no consensus on the pathological mechanism of OA has been found. In this study, we looked at Runx1's key involvement in OA and its possible therapeutic benefit in a mouse model of the disease genetics perspective. To further examine the effect of Runx1 knockout at the late stage of OA, we analyzed pathological changes in growth plate cartilage in the femur at 24 weeks after ACLT surgery.

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