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Review Article

Epigenetic regulation of chondrocyte differentiation

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Summary Chondrocytes play an essential role in endochondral bone development, which is requisite for mammalian skeletal development. During endochondral bone development, chondrocytes undergo well-organized stages of sequential differentiation, including proliferation and hypertrophy, a process harmoniously modulated by various transcription factors. Epigenetics, including DNA methylation and histone modification, has recently emerged as an essential regulatory system for gene expression, not only in physiological conditions, but also in human disease. During chondrocyte differentiation, transcriptional co-regulators, which form transcriptional protein complexes with specific transcription factors, are predominantly involved in this epigenetic process and cooperatively regulate chondrocyte gene expression. Importantly, several studies indicate that epigenetic regulators correlate with cartilage-related diseases, such as osteoarthritis, and are noted as a potential therapeutic target. Here, current studies of epigenetic regulation of chondrocyte differentiation are reviewed and novel aspects for the molecular mechanisms involved in chondrogenesis are introduced.

Contents

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1. Introduction

Epigenetics has recently emerged as an essential regulatory system for gene expression, not only in physiological conditions, but also in human disease. The word 'epigenetic' is defined as heritable changes in gene expression without changes in the DNA coding sequences [1]. Epigenetics is a developing area of research in many biological studies and has now become a potential therapeutic target for many human diseases, including cancer. One of the major epigenetic regulation processes is DNA methylation, into which a considerable number of studies have been made [2,3]. However, recent progress in the field of epigenetic research has revealed that various regulatory systems, including histone modification and dynamic chromatin structure, are involved in epigenetic regulation. In this article, the mechanism of chondrocyte differentiation is first introduced and then recent findings about epigenetic regulation of chondrocyte differentiation are reviewed, focusing on DNA methylation and histone modification. It is well established that miRNAs regulate diverse biological processes both post-transcriptionally and epigenetically. However, little is known about the direct association between miRNA and epigenetic programs in mammalian cells. Therefore, the role of miRNA in cartilage homeostasis and chondrocyte differentiation, through post-transcriptional regulation as a part of miRNA function, is also introduced.

2. Mechanism of chondrocyte differentiation

The majority of bones, including craniofacial bones, are formed by a unique biological event called endochondral bone formation [4,5]. Endochondral bone formation starts with mesenchymal cell condensation followed by differentiation into chondrocytes, which then form cartilage by producing an abundant extracellular matrix comprising, *Col2a1* (collagen type II, alpha 1) and *Acan* (aggrecan). From here, the chondrocytes undertake sequential steps of differentiation into proliferating, hypertrophic and terminal chondrocytes (Fig. 1) [4,5]. This process generates the chondrocyte differentiation layer of the growth plate. Finally, the chondrocytes die by apoptosis and are replaced by bone formation following blood vessel invasion. At each differentiation step, chondrocytes produce stage-specific marker genes. These include *Col2a1* and *Acan* in proliferating chondrocytes, *Ihh* (Indian hedgehog) and *Pth1r* (parathyroid hormone 1 receptor) in pre-hypertrophic chondrocytes, and *Col10a1* (collagen, type X, alpha 1) and *Mmp13* (matrix metalloproteinase 13) in hypertrophic chondrocytes (Fig. 1).

These well-organized chondrocyte differentiation processes are harmoniously regulated by several transcription factors in a temporal-spatial manner (Fig. 1). At the beginning of chondrocyte differentiation, *Sox9* (SRY-box containing gene 9) and its cofactors, *Sox5* (SRY-box containing gene 5) and *Sox6* (SRY-box containing gene 6), play essential roles in *Col2a1* gene expression [6,7] and chondrocyte-specific Sox9-deficient mice show severe defects in skeletal development [8]. In humans, mutation of the *SOX9* gene causes campomelic dysplasia, characterized by severe chondrodysplasia and autosomal sex reversal [9,10]. Moreover, disruption of the cis-regulatory element of *SOX9*, which leads to decreased *SOX9* transcription, causes Pierre Robin Sequence characterized by cleft palate [11]. During the process of chondrocyte hypertrophy, expression of *Mef2C* (myocyte-specific enhancer factor 2C), Forkhead box (FoxA) proteins, and Runx (runt-related transcription factor) family

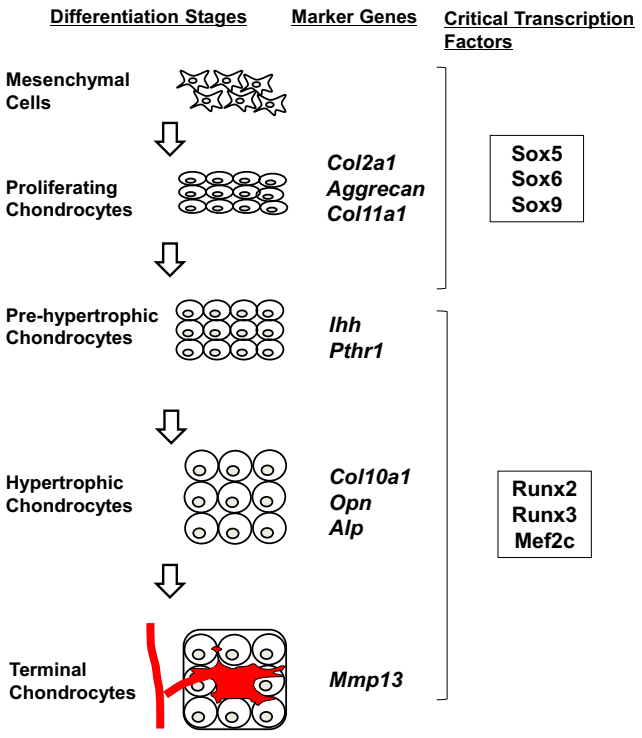

Figure 1 Schematic of chondrocyte differentiation steps during endochondral bone formation. Endochondral bone formation starts with mesenchymal condensation followed by the sequential differentiation steps as indicated in the figure. Morphological features, specific marker genes, and essential transcription factors for each differentiation step are shown.