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Regulation of Chondrogenesis

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Editorial

Mesenchymal Stem Cells (MSCs) represent one of the most promising stem cells for regenerative medicine. As the most widely used stem cells for clinical trial, MSCs are able to differentiate into cartilage, bone and fat. Chondrogenesis is the process in which multipotent MSCs differentiate into chondrocytes to form cartilage, which involves recruitment, migration and condensation of mesenchymal stem cells, chondrocytes differentiation and deposition of cartilaginous Extra Cellular Matrix (ECM), resulting in the formation of cartilage and bone [1]. Chondrogenesis is delicately regulated by various signaling pathways in a temporal-spatial manner. Although MSCs have been studied for over 50 years, some gains in the understanding of the molecular basis underlying cartilage differentiation have been made, relatively limiting genetic factors involved in chondrogenesis have been identified, and gene network of chondrogenesis remains poorly understood. It is well known that Sox9 is master regulator of chondrogenesis [2,3]. Sox9 is highly expressed in mesenchymal stem cells, the proliferating and pre-hypertrophic chondrocytes but declines in the hypertrophic chondrocytes, suggesting that Sox9 plays a critical role in initiating and promoting early chondrocytes but repressing later maturation of chondrocytes [4,5]. Mutations in human Sox9 cause campomelic dysplasia, which displays abnormalities in cartilage formation [2,3]. Sox9 exerts its effects on chondrogenesis by directing the expression of chondrocytes-specific genes such as COL2A1, COL9A1, COL11A1 and Agc1 [6-9]. Expression or transcriptional activity of Sox9 is delicately regulated by upstream factors to regulate chondrogenesis. Overexpression of ZNF145 improves chondrogenesis whereas knockdown of ZNF145 slows down chondrogenesis, ZNF145 overexpression up-regulates Sox9 but Sox9 overexpression does not up-regulate ZNF145, indicating ZNF145 regulates chondrogenesis as an upstream factor of Sox9 [10]. However, how ZNF145 regulates Sox9 is still not fully understood. Knock down of Estrogen-Related Receptor alpha (ESRRα) decreases chondrogenic genes, including Sox9. It was shown that ESRRα directly binds to Sox9 to regulate its expression and cartilage development [11]. As a Nuclear Factor kappa B (NF-kB) member, RelA is co-localized with Sox9 in the limb cartilage. RelA is shown to induce chondrogenesis by binding to human Sox9 promoter [12]. Long non-coding RNA (lncRNAs) and microRNAs are also involved in regulation of chondrogenesis. lncRNAs, LOC102723505 (ROCR) is expressed with chondrogenic genes, its depletion reduces cartilage-specific gene expression including Sox9, leading to incomplete matrix component production. Overexpression of Sox9 rescues impaired chondrogenesis by ROCR depletion, suggesting ROCR is an upstream factors of Sox9 [13]. The expression or transcriptional activity of Sox9 is also regulated by cofactors to regulate chondrogenesis. L-Sox5 and Sox6 have been shown to be essential transcriptional partners of Sox9 to enhance Sox9 activation of chondrocytes-specific genes during chondrogenesis. Sox5 and Sox6 double knockout mice display severe cartilage defects [14]. Sox5 and Sox6 are undetected in Sox9 conditional-deficient mice, indicating Sox5 and Sox6 are downstream factors of Sox9 [15]. PGC-1α directly interacts with Sox9 to promote Sox9 dependent transcriptional activity as a transcriptional co activator of Sox9 [16]. Znf219 acts as a transcriptional partner of Sox9 to enhance the transcriptional activity of Sox9 on the Col2a1 gene promoter [17]. Wwp2 interacts physically with Sox9 to regulate Sox9 transcriptional activity via its nuclear translocation [18]. P54nrb is co-localized with Sox9 protein in nuclear para-speckle bodies, which physically interacted with Sox9 to enhance Sox9 dependent transcriptional activation of the Col2a1 promoter [19]. Jun and Sox9 co-bound and co-activated a Col10a1 enhancer to promote hypertrophic gene expression [20]. Besides chondrocyte specific genes, Sox9 also regulates other chondrocytes related genes. It is shown that CTGF/CCN2 stimulates chondrocytes proliferation and maturation. The loss of Sox9 leads to the decrease in CTGF expression. Further study demonstrates that SOX9 binds to -70/-64 region of the Ctgf promoter, suggesting Ctgf is the direct target gene of SOX9 in chondrocytes [21]. MiR-140 is a cartilage specific microRNA that regulates cartilage development and homeostasis. Sox9 promotes miR-140 expression by binding to its promoter region [5]. With the development of state-of-the-art techniques and more efforts put in the field, more genes regulating chondrogenesis

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have been identified. However, little is known about gene network of chondrogenesis. Chondrocytes are embedded in cartilage matrix, which make it hard to obtain enough cells for the use. ChIP-Seq is a powerful method to identify genome wide DNA binding sites for transcription factors and other proteins. However, ChIP-seq is not well established in the field of chondrogenesis due to limited chondrocytes. To move forward, it is necessary to establish platforms requiring fewer cells in the field of chondrogenesis. In addition, identification of more regulators involved in chondrogenesis will further our understanding toward regulation of chondrogenesis. Understanding of gene network of chondrogenesis will help us develop more effective therapies for cartilage regeneration and treatment of cartilage diseases.

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