Seminars in Cell & Developmental Biology 62 (2017) 34–49

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Transcriptional control of chondrocyte specification and differentiation

Chia-Feng Liu[a,*], William E. Samsa[b], Guang Zhou[b,c,d], Véronique Lefebvre[a,*]

[a] Department of Cellular and Molecular Medicine, Cleveland Clinic Lerner Research Institute, Cleveland, OH, 44195, USA
[b] Department of Orthopaedics, Case Western Reserve University, Cleveland, OH, USA
[c] Department of Genetics and Genome Sciences, Case Western Reserve University, Cleveland, OH, USA
[d] Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH, USA

ARTICLE INFO

Article history:
Received 14 October 2016
Accepted 18 October 2016
Available online 19 October 2016

Keywords:
Cartilage
Cell lineage
Differentiation
Master regulator
Specification
Transcription

ABSTRACT

A milestone in the evolutionary emergence of vertebrates was the invention of cartilage, a tissue that has key roles in modeling, protecting and complementing the bony skeleton. Cartilage is elaborated and maintained by chondrocytes. These cells derive from multipotent skeletal progenitors and they perform highly specialized functions as they proceed through sequential lineage commitment and differentiation steps. They form cartilage primordia, the primary skeleton of the embryo. They then transform these primordia either into cartilage growth plates, temporary drivers of skeletal elongation and endochondral ossification, or into permanent tissues, namely articular cartilage. Chondrocyte fate decisions and differentiated activities are controlled by numerous extrinsic and intrinsic cues, and they are implemented at the gene expression level by transcription factors. The latter are the focus of this review. Meritorious efforts from many research groups have led over the last two decades to the identification of dozens of key chondrogenic transcription factors. These regulators belong to all types of transcription factor families. Some have master roles at one or several differentiation steps. They include SOX9 and RUNX2/3. Others decisively assist or antagonize the activities of these masters. They include TWIST1, SOX5/6, and MEF2C/D. Many more have tissue-patterning roles and regulate cell survival, proliferation and the pace of cell differentiation. They include, but are not limited to, homeodomain-containing proteins and growth factor signaling mediators. We here review current knowledge of all these factors, one superclass, class, and family at a time. We then compile all knowledge into transcriptional networks. We also identify remaining gaps in knowledge and directions for future research to fill these gaps and thereby provide novel insights into cartilage disease mechanisms and treatment options.

Contents

Abbreviations: AC, articular cartilage; ACC, articular chondrocyte; CC, columnar chondrocyte; EC, early chondrocyte; EO, endochondral ossification; GP, growth plate; GPC, growth plate chondrocyte; HC, hypertrophic chondrocyte; JP, joint progenitor cells; OB, osteoblast; OCP, osteochondroprogenitor; PC, prechondrocyte; PHC, prehypertrophic chondrocyte; SSC, skeletal progenitor/stem cell; TC, terminal chondrocyte; TF, transcription factor.

* Corresponding authors.
E-mail addresses: liuc2@ccf.org (C.-F. Liu), lefebvv@ccf.org (V. Lefebvre).

http://dx.doi.org/10.1016/j.semcdb.2016.10.004
1084-9521/

1. Introduction

Chondrogenesis is a critical process in the development and healthy maintenance of the vertebrate skeleton [1]. It consists in generating chondrocytes and in directing these cells through successive steps of commitment and differentiation in order to build, renew or remodel cartilage tissues in a tightly controlled spatial and temporal manner. Deciphering the cellular and molecular mechanisms that drive and regulate chondrogenesis is a prerequisite to decoding the causes of the various types of cartilage diseases that affect humans and to developing highly needed treatments for these diseases. Among these diseases, chondrodysplasias are fairly rare, but exist in hundreds of forms [2]. They vary from mild malformations of discrete skeletal elements to generalized skeletal malformations that can be lethal in the perinatal period or result in dwarfism. Osteoarthritis, in contrast, is a highly prevalent, adult-onset disease, primarily characterized by progressive, irreversible degeneration of articular cartilage [3].

Chondrocytes arise in development from multipotent skeletogenic progenitor/stem cells (SSCs), which themselves derive from embryonic cranial neural crest and from paraxial and lateral plate mesoderm. SSCs give rise to two main types of chondrocytes. They become growth plate chondrocytes (GPCs) by proceeding through an intermediate, bipotent osteochondroprogenitor (OCPs) stage (with osteoblast [OB] and chondrocyte potential), and become articular chondrocytes (ACCs) via a multipotent joint progenitor (JP) stage (with chondrocyte, synovial and other joint cell type potential). Once committed to either fate, prechondrocytes (PCs) coalesce into precartilaginous condensations. They next differentiate into early chondrocytes (ECs) and build cartilage primordia by proliferating and producing copious amounts of cartilage extracellular matrix (namely expressing the genes for collagen type II [*COL2A1*] and aggrecan [*ACAN*]). GPCs then follow multiple steps of maturation. They first continue to dynamically proliferate and produce cartilage matrix while aligning themselves in longitudinal columns. These activities allow fast and linear growth of skeletal elements and provide an orderly arranged extracellular matrix template upon which trabecular bone will later be deposited. The so-called columnar chondrocytes (CCs) undergo cell cycle arrest as they transition to prehypertrophy. While still expressing early cartilage matrix genes at maximal levels, prehypertrophic chondrocytes (PHCs) also express stage-specific markers (e.g., *IHH,* Indian hedgehog gene) and initiate expression of hypertrophic markers (e.g., *COL10A1,* collagen type 10 gene). They have a central regulatory role in skeleton development. They emit signals, namely IHH and non-canonical WNTs (including WNT5A), that stimulate CC proliferation and alignment, respectively. IHH also regulates the pace of GPC maturation and induces cortical bone formation in adjacent perichondrium. Next, hypertrophic chondrocytes (HCs) massively expand their cytoplasmic volume and fully switch to a new genetic program. They are as important as CCs to elongate skeletal elements. In addition, they contribute to endochondral ossification (EO) by modifying the cartilage matrix and emitting such signals as the vascular endothelial growth factor VEGFA. At the end of the GPC journey, terminal chondrocytes (TCs) express an osteoblast-like phenotype, remodeling and mineralizing the cartilage matrix (e.g., expressing the genes for the bone sialoprotein [*IBSP*] and matrix metalloproteinase 13 [*MMP13*]). They eventually die or fully adopt the OB fate in nascent endochondral bone. Compared to the highly dynamic and transient GPC program, the ACC pathway appears as a conservative one. ACCs proliferate and productively assemble extracellular matrix as they develop their tissue. Once articular cartilage (AC) acquires its adult size, ACCs hardly ever proliferate and they limit their activity to turning over a subset of extracellular matrix components, including aggrecan, but not collagens. Their tissue features layers that are reminiscent of growth plate (GP) zones in terms of differential extracellular matrix composition and cell morphology, but it remains unclear how ACCs form these layers. One school of thought is that the tissue grows in an appositional manner, chondrocytes differentiating from JPs located near the tissue surface and arresting at progressively more mature stages as they reach the subchondral bone [1]. Another view is that JPs are initially distributed uniformly across the tissue and that ACCs directly acquire spatial specialization as they differentiate [4]. It is also unclear when and how distinctions are made between the ACC and GPC programs. As indicated earlier, SSCs appear to adopt either fate as they develop into OCPs or JPs, even though articular and growth plate ECs share many phenotypic features. ACCs are distinguished from GPCs notably by not proceeding to prehypertrophy. As a result, they are unable to