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Review article

Growth of the mandible and biological characteristics of the mandibular condylar cartilage



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Received 11 May 2013; received in revised form 26 July 2013; accepted 30 July 2013

KEYWORDS

Mandible;
Growth;
Maxillofacial morphology;
Condylar cartilage;
Extracellular matrix;
Collagen

Summary Mandibular condylar cartilage is the center of greatest growth in the craniofacial complex, and is associated with maxillofacial skeleton morphogenesis and temporomandibular joint function. The condylar process grows in a wide range of directions from anterosuperior to posterior, resulting in highly diverse mandibular growth and morphology. Condylar growth direction is closely related to mandibular displacement direction and vertical jaw deviations (i.e., high or low angle). Condylar cartilage, which is ontogenetically designated secondary cartilage, differs from other primary cartilage (e.g., articular cartilage and growth plate of a long bone cranial base cartilage, nasal septal cartilage) in the following ways. (1) Condylar cartilage is a heterogeneous tissue containing fibroblasts, osteochondral progenitor cells, and chondrocytes. (2) Type I collagen, which is derived from progenitor cells, and cartilage-characteristic type II collagen are colocalized in the cartilaginous cell layer. Colocalization of both collagen types may be an adaptation to the complex biomechanical environments of condylar cartilage. (3) Peripheral condylar cartilage contains chondroid bone, a specialized calcified tissue with morphological properties intermediate between those of bone and cartilage. This hybrid tissue may play an important role in regulating different rates of bone formation in intramembranous and endochondral ossification, allowing for highly diverse growth directions and condylar and maxillofacial morphology.

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1. Introduction

Growth of the craniofacial skeleton largely influences occlusal relationships, jaw relationships, and orofacial functions [1–8]. In the growth of the craniofacial skeleton, cartilaginous tissues, including those of the sphenoccipital synchondrosis in the cranial base, the nasal septal cartilage in the nasomaxillary complex, and the condylar cartilage in the mandible, play important roles as major growth sites for the respective anatomical components [8–10]. Among these, the condylar cartilage acts as the center of greatest growth in the craniofacial complex [3,11] and is associated with morphogenesis of the craniofacial skeleton and temporomandibular joint function [1–8,12–14].

Condylar cartilage, which is designated as secondary cartilage [15–18], differs from other primary cartilage in histological organization; modes of proliferation, differentiation and calcification; and response to environmental factors (e.g., biomechanical stress, hormones and growth factors) [15]. The condylar cartilage is a unique and interesting tissue among cartilaginous tissues in the human body. The present article reviews the relationship between maxillofacial morphology and mandible growth behavior from a clinical viewpoint, as well as biological characteristics of the condylar cartilage, with particular focus on the extracellular matrix (ECM).

2. Relationship between maxillofacial skeletal morphology and occlusion

To diagnose maxillofacial skeletal morphology, two-dimensional analysis is performed using a lateral cephalogram [19,20]. Based on the anteroposterior jaw relationship, three types of skeletal relationship may be defined: (1) a normal relationship between the maxilla and mandible (Class I); (2) distal position of the mandible relative to the maxilla due to a protruded maxilla and/or retruded mandible (Class II); and (3) mesial position of the mandible relative to the maxilla due to a retruded maxilla and/or protruded mandible (Class III) (Fig. 1). In contrast, based on the vertical jaw relationship, three types of jaw relationship may be defined: (1) medium angle (normal face, mesiofacial pattern), (2) low angle (short face, brachyfacial pattern, skeletal deep bite and hypodivergent type), and (3) high angle (long face, dolichofacial pattern, skeletal open bite and hyperdivergent type) [19–26]. In patients with low angles, small anterior facial heights and mandibular plane angles (angle between the mandibular plane and the FH plane, and angle between the mandibular

plane to the cranial base) and large mandibular ramus lengths and shallow antegonial notches can be observed; the opposite features are present in patients with high angles [19–26].

These vertical deviations are closely associated with anterior overbite; patients with low angles tend to have deep bites and those with high angles tend to have open bites [19–26]. In addition, vertical deviations largely influence not only overbite, but also anteroposterior occlusal relationships [27]. The following observations were made after comparing the occlusal conditions of two patients with almost the same anteroposterior jaw relationship, but opposite vertical jaw deviations. The patient with a low angle had an anterior deep bite, and Class I canine and molar relationships, whereas the patient with a high angle showed a small overbite, and Class III canine and molar relationships (Fig. 2). The question arises as to why the vertical jaw deviations influence anteroposterior occlusal relationships, as in these patients. The vertical jaw relationships are closely associated with the occlusal plane angles (angle between the occlusal plane and the FH

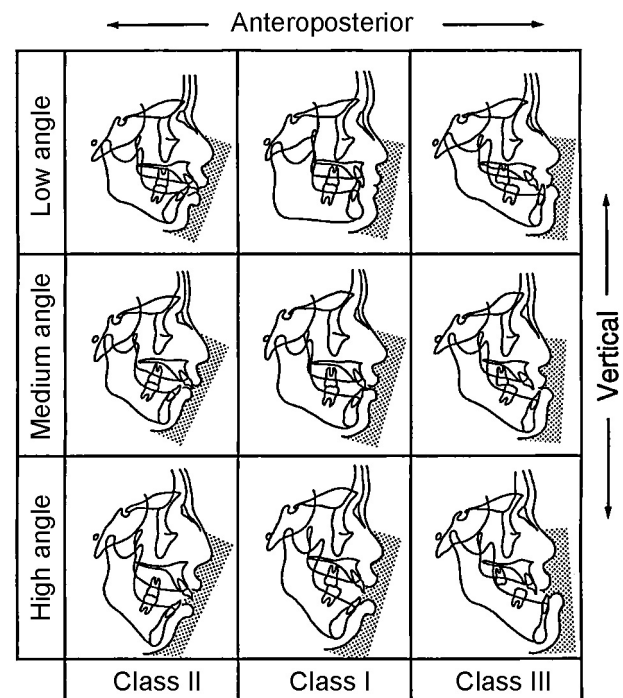


Figure 1 Nine types of maxillofacial skeletal morphology. Reproduced with permission from Sugawara and Kawamura [20], with vertical deviation names changed from those in the original.

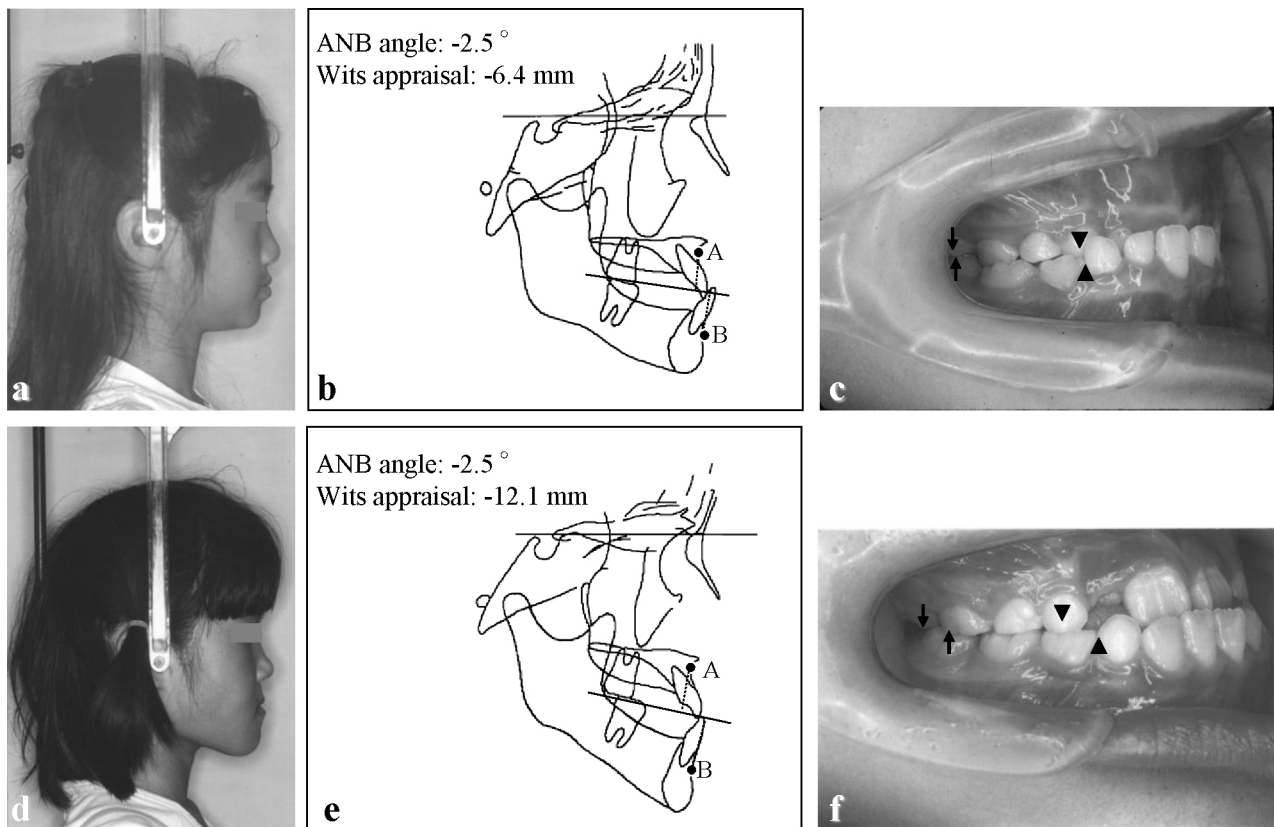


Figure 2 Facial and oral photographs and cephalometric tracing of two patients with similar anteroposterior jaw relationships, as shown by ANB angles, but opposite vertical jaw deviations. (a–c) A patient with a low angle and skeletal Class III relationship. (d–f) A patient with a high angle and skeletal Class III relationship. Note that the Class III dental relationship is more severe in the patient with a high angle.

plane, and angle between the occlusal plane to the cranial base); patients with low angles tend to have small occlusal plane angles and the opposite is true of those with high angles [21,22]. According to mathematical model analysis, steepening of the occlusal plane results in the posteriorization of the maxillary dentition relative to the mandibular dentition, i.e., a shift from a Class II to Class III [27]. Thus, the low angle patients with flatter occlusal planes tend to have Class II occlusions, and the high angle patients with steeper occlusal planes tend to have Class III occlusions.

3. Relationships between growth pattern of the mandible and maxillofacial skeletal morphology

Growth of the mandibular condyle contributes not only to increased mandible size, but also to antero-inferior displacement (transposition) of the mandible [1–8]. Using longitudinal cephalometric studies with tantalum implants, Bjork and coworkers [2–4] provided variable information about individual variation in the growth pattern of the mandible. Whereas the length of a long bone increases in a rectilinear direction along its long axis, the condylar process grows in a wide range of directions from anterosuperior to posterior (Fig. 3). This divergent growth allows for highly diverse growth and morphology of the mandible. Condylar growth

direction is closely related to the displacement (transposition) direction of the mandible and vertical jaw deviations [2–4]. In individuals with low angles, mandibular growth is characterized by anterosuperior growth of the condyle, absorption of the inferior gonial border, and anterior displacement of the mandible [2–4] (Figs. 3 and 4a). In contrast, individuals with high angles show posterosuperior growth of the condyle, apposition at the inferior gonial border, and inferoposterior displacement of the mandible [2–4] (Figs. 3 and 4b).

4. Role of the condylar cartilage in mandibular growth

In a long bone, two spatially separated cartilages (i.e., articular cartilage and growth plate) exist during the growth stage [28,29]. The articular cartilage functions as a shock absorber against mechanical loading and the growth plate functions as a growth site. In contrast, only a single cartilage, the mandibular condylar cartilage, exists in the mandible throughout life, and plays roles in articulating function and growth. Therefore, the condylar cartilage is an “all-in-one type tissue” [28,29]. The disturbance of condylar growth greatly influences maxillofacial morphology and occlusal relationships [12–14]. When the bilateral condyles are affected, the mandible rotates in the posteroinferior

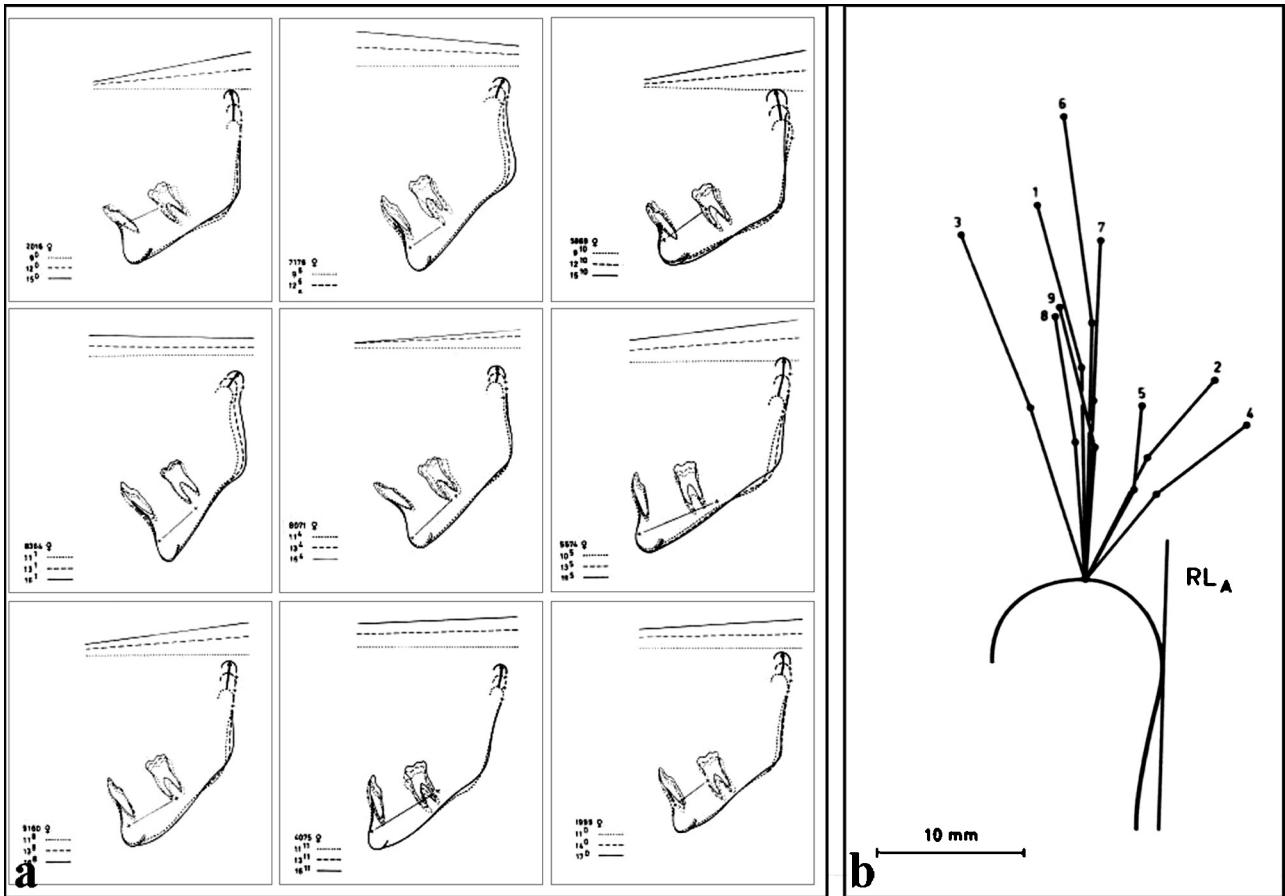


Figure 3 Mandibular growth in nine girls over a 6-year period. (a) Individual superimposition of the mandible on an implant line. Arrows indicate condylar growth direction. (b) Condylar growth directions in nine girls in relation to the ramus line (RL_A) at the initial stage. The condyles grow in a wide range of directions. Reproduced with permission from Bjork and Skieller [3].

(clockwise) direction, resulting in an anterior open bite [12–14]. When a unilateral condyle is affected, displacement of the mandible to the affected side, facial asymmetry, and a lateral cross bite are elicited [12].

For example, let us examine the case of a patient with juvenile rheumatoid arthritis (JRA) and subsequent condylar growth disturbance [30]. The patient suffered JRA at the age

of 16 months and was completely cured by the age of 5.25 years [30]. At initial examination (at the age of 8.25 years), she showed excessive overjet, anterior open bite, a skeletal Class II relationship with a retruded mandible, and flattening of the right and left mandibular condyles (Fig. 5a and b). After examining the growth behavior of the mandible in detail by cephalometric superimposition, we observed that

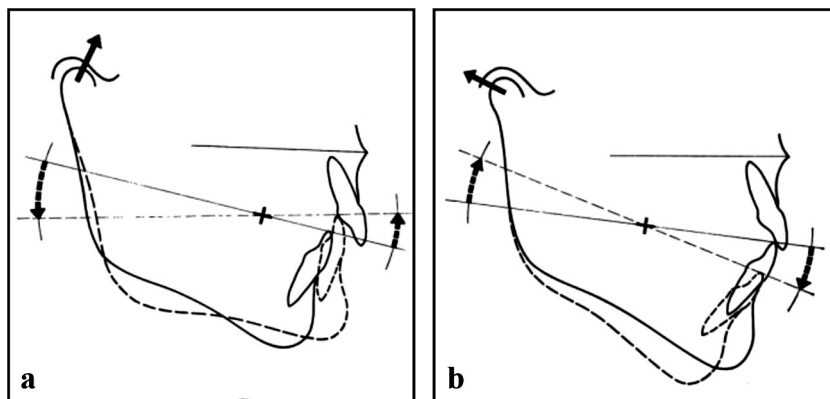


Figure 4 Comparison of mandibular growth in individuals with low and high angles. Reproduced with permission from Bjork and Skieller [3].

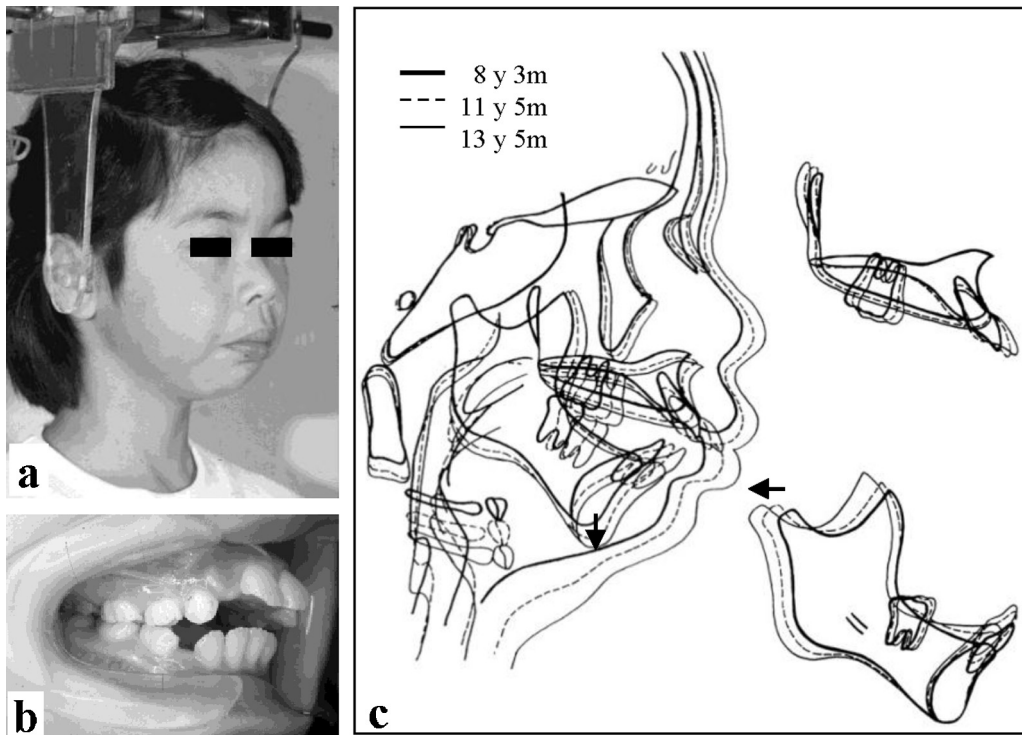


Figure 5 A patient with juvenile rheumatoid arthritis. (a) Facial photograph at the age of 8.25 years. (b) Oral photograph. (c) Cephalometric superimposition from 8 to 13 years. Reproduced with permission from Yoshimura et al. [30].

the posterior margin of the ramus, gonial angle, and anterior alveolar ridge, in which intramembranous ossification occurs, showed prominent bone apposition (Fig. 5c). In contrast, the condyle did not grow in the superior direction, but in an almost posterior direction. When the condylar cartilage is

destroyed, as in this case, endochondral ossification, which provides the condyle with growth ability to resist against compressive forces exerted on it [11,17,26], is disturbed. As a result, the condyle cannot grow in the superior direction, and compensatory posterior growth due to intramembranous

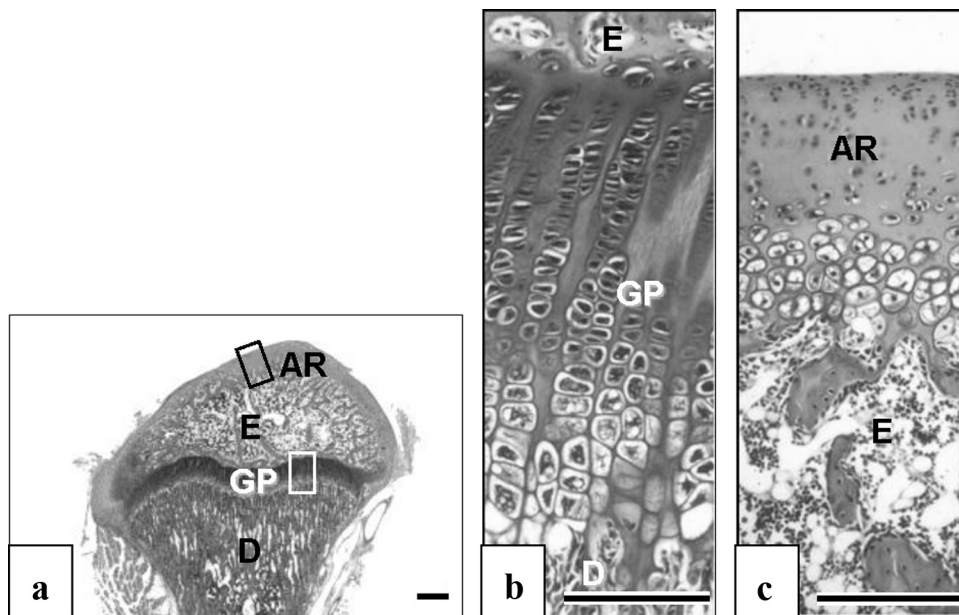


Figure 6 The growth plate and articular cartilage of the tibia in a growing rat. (a) Hematoxylin and eosin staining. (b) High-magnification image of the growth plate in the area corresponding to the boxed area shown in (a). (c) High-magnification image of the articular cartilage in the area corresponding to the boxed area shown in (a). AR, articular cartilage; GP, growth plate; E, epiphysis; D, diaphysis. Scale bar = 100 μ m.

ossification at the posterior condylar margin becomes predominant, which is one characteristic of the high-angle type [2,26]. These results suggest that the balance between intramembranous and endochondral ossification in the condyle may be a factor determining divergent condylar growth direction.

5. Histological organization of mandibular condylar cartilage

5.1. Classification of condylar cartilage cell layers

Primary cartilage, such as articular cartilage and growth plates in a long bone, synchondroses in the cranial base, and nasal septal cartilage, consists of a chondrocyte population (Fig. 6). In contrast, condylar cartilage (i.e., secondary cartilage) is a heterogeneous tissue containing cells at various stages of chondrogenic maturation [31–41] (Fig. 7). Classifications and terminology related to condylar cartilage cell layers differ among investigators (Table 1). Cell layer classification depends on animal species and growth stage, histological method, and molecular markers used in a given study. In this paper, a classification comprising four cell layers is used to explain the characteristics of each cell layer because four cell layers can be easily distinguished from each other based on type I and II collagen localization.

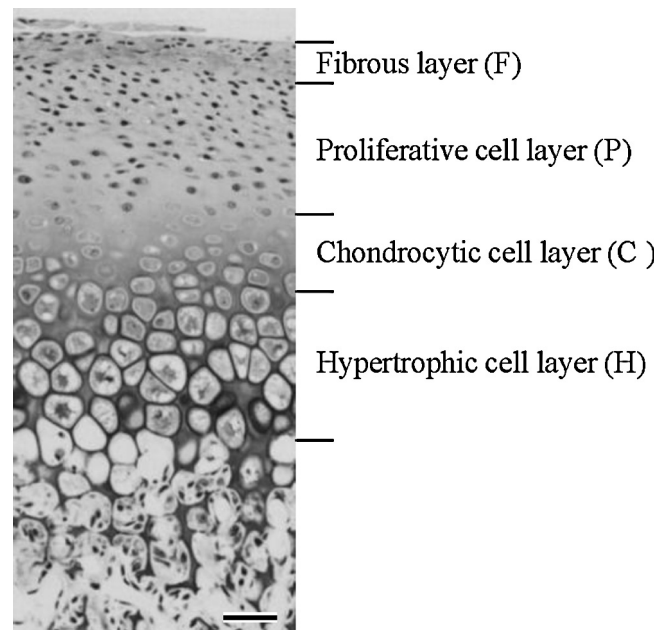


Figure 7 Mandibular condylar cartilage cell layers in a growing rat (hematoxylin and eosin staining). F, fibrous layer; P, proliferative cell layer; C, chondrocytic cell layer; H, hypertrophic cell layer. Scale bar = 50 μ m.

Table 1 Overview of terminology of the cell layers of the mandibular condylar cartilage.

Authors	Non-cartilaginous (perichondrial)			Cartilaginous		
	Layer 1	Layer 2	Layer 3	Layer 4	Layer 5	Layer 6
Greenspan et al. [31]	Articular	Proliferating			Hypertrophic (premineralizing)	Hypertrophic (mineralizing)
Folke and Stallard [44]	Fibrous	Embryonic	Intermediate		Vesicular	Erosion
Carlson et al. [33]	Articular	Prechondroblastic (proliferative)			Chondroblastic (maturation)	Chondroblastic (hypertrophy)
Morita [39]	Fibrous	Proliferative cell			Mature cell	Hypertrophic cell
Terashima [40]	Fibrous	Subfibrous cell	Osteochondro progenitor	Chondroblastic ^a	Chondrocytic	Hypertrophic cell
Copray et al. [29]	Articular	Proliferative			Transitional	Hypertrophic
Silbermann et al. [36]	Articular	Progenitor cell			Chondroblastic	Hypertrophic
Luder et al. [38]	Articular	Polymorphic cell	Flattened cell		Upper hypertrophic cell	Lower hypertrophic cell
Kantomaa et al. [50]	Articular cell	Polymorphic cell	Flattened cell		Upper hypertrophic cell	Lower hypertrophic cell
Strauss et al. [48]	Perichondral cell	Progenitor			Mature chondroblasts	Hypertrophic chondrocytes
Petrovic [35]	Fibrous capsule	Skeletoblasts and prechondroblasts			Functional chondroblasts	Hypertrophic chondroblasts
Shibukawa et al. [58]	Fibroblastic	Polymorphic			Flattened chondrocytes	Hypertrophic chondrocytes
This paper	Fibrous	Proliferative cell			Chondrocytic	Hypertrophic cell

^a It is unknown whether this layer contains chondrocytes or cells at a stage prior to chondrocytes.

5.2. Fibrous layer

The most superficial layer of the condylar cartilage consists of dense fibrous connective tissue with scattered cells, and its periphery is continuous with the outer layer of the periosteum (Fig. 7). The cells are flat and surrounded by dense collagen bundles [38–40]. This layer is not related to deeper chondrogenic differentiation, but functions as a protective covering for the underlying cartilaginous tissue [38]. Recently, Ohno et al. [42] revealed that superficial zone protein, also known as proteoglycan-4 and lubricin, is restricted to the superficial part of the condylar cartilage and functions as a joint boundary lubricant.

5.3. Proliferative cell layer

Based on cellular morphology, this layer is further divided into two sublayers: the upper sublayer (i.e., polymorphic cell layer), where irregular polygonal cells with large round nuclei are densely packed; and the lower sublayer (i.e., flattened cell layer), where flattened cells are oriented with their long axes parallel to the articular surface [38] (Fig. 7). The cells in the upper sublayer have poorly developed cytoplasmic organelles, extend thin cell processes to the adjacent cells, and form gap junctions [38]. Autoradiographic studies using ^3H -thymidine and ^3H -proline have indicated that proliferative activities are limited almost exclusively to cells in the polymorphic cell layer and the upper part of the lower flattened cell layer, and that collagen synthesis activity was low in the proliferative cell layer [32,38,43–47].

One unique characteristic of the condylar cartilage is that the cells in the proliferative layer have multilineage potential and can differentiate into osteoblasts or chondrocytes (osteochondral progenitors), and more differentiated cells committed to becoming chondrocytes (chondroprogenitors) or fat progenitor cells [32–41]. Their differentiation pathway is regulated by biomechanical force. Under physiological conditions, progenitor cells differentiate into chondrocytes. Under non-functional conditions, however, such as in vitro

organ culture and in vivo immobilization experiments, or under excessive tensile loading, progenitor cells undergoing chondrogenic differentiation are replaced by intramembranous bone, along with a phenotypic switch from type II to type I collagen [17,36,37,41,48–52]. In addition, a considerable amount of information has recently become available regarding local regulatory factors of osteochondrogenic differentiation, including growth factors and signaling molecules, such as bone morphogenetic proteins (BMPs) [53,54], transforming growth factor- β [55], interleukin 1 [56], Indian hedgehog [57,58], and parathyroid hormone-related protein [58–60], and transcription factors such as SOX9, RUNX2, and Osterix [61,62].

5.4. Chondrocytic cell layer

The chondrocytic cell layer contains chondrocytes at various stages of maturation. Cellular morphology changes from flattened to spherical with progressive depth (Fig. 7). The ECM in this layer has an increased area and shows hematoxylin-philic staining and metachromatic staining with toluidine blue, indicating active deposition of cartilage-characteristic matrices [63]. Synthetic activity of collagens, proteoglycans, and sulfated glycosaminoglycans peak in this cell layer [38,46,61,62,64].

5.5. Hypertrophic cell layer

Hypertrophy, the terminal differentiation stage of the chondrogenic lineage, is required for the replacement of cartilage with bone (endochondral ossification) (Fig. 7). With advancing hypertrophy, chondrocytes increase in volume, initiate calcification of the surrounding matrix, and are invaded by the bone marrow vasculature accompanied by chondroclastic and osteogenic precursor cells [65,66]. The calcified cartilaginous matrix is degraded by differentiated chondroclasts, and newly secreted bone matrix is then deposited onto the cartilage remnants [65]. In the hypertrophic cell layer, although synthetic activity of matrix synthesis is decreased,

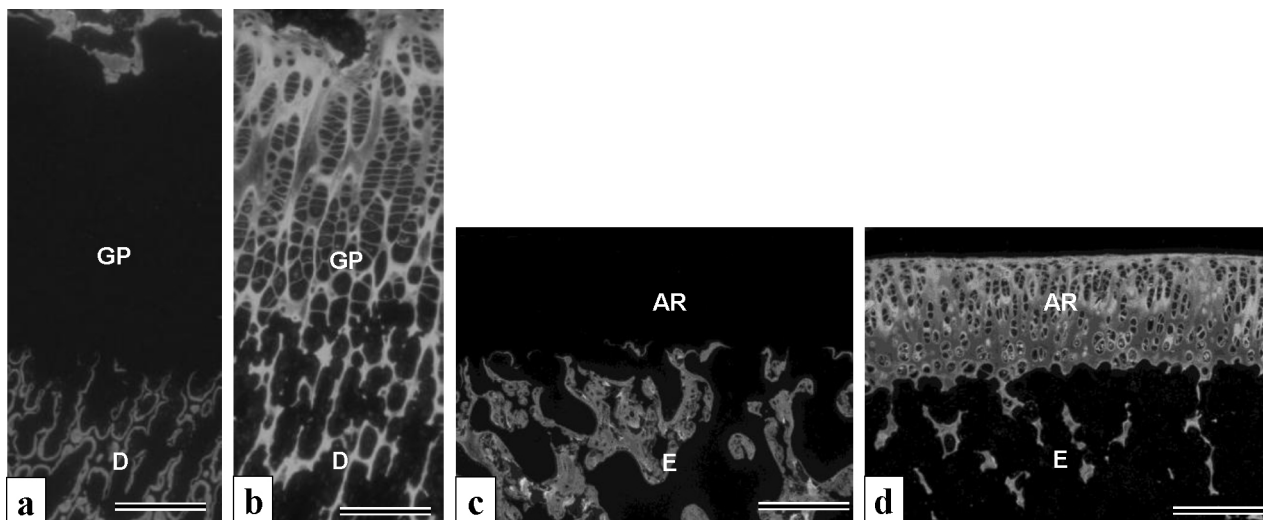


Figure 8 Immunohistochemical localization of types I and II collagen in the growth plate (a, b) and articular cartilage (c, d) of a growing rat. (a, c) Localization of type I collagen. b, d Localization of type II collagen. GP, growth plate; D, diaphysis; AR, articular cartilage; E, epiphysis. Scale bar = 100 μm .

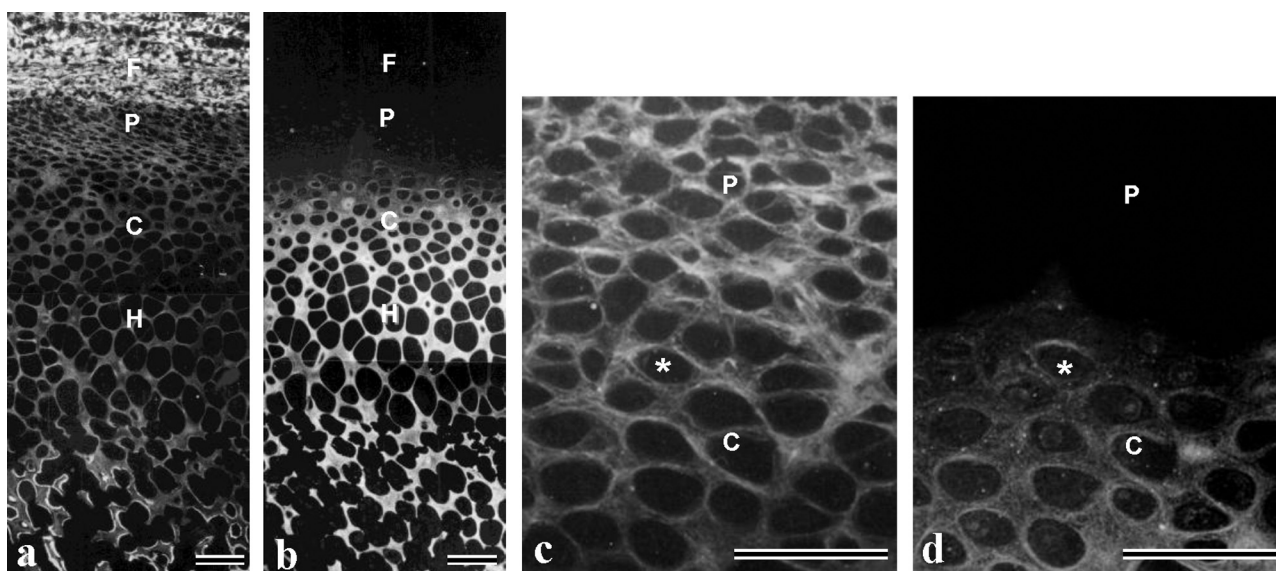


Figure 9 Immunohistochemical localization of types I and II collagen in the mandibular condylar cartilage of a growing rat. (a) Type I collagen is present throughout the cell layers. (b) Type II collagen is restricted to the chondrocytic and hypertrophic cell layers. (c) Magnified view of immunolocalization of type I collagen in the proliferative and chondrocytic cell layers. (d) Magnified view of immunolocalization of type II collagen in the proliferative and chondrocytic cell layers. F, fibrous layer; P, proliferative cell layer; C, chondrocytic cell layer; H, hypertrophic cell layer. *, The same cell in adjacent serial sections. Types I and II collagen are present in the extracellular matrix. Scale bar = 50 μm .

phenotypic transition from type II to type X collagen occurs [37,41,58,62,64,67–69]. The hypertrophied chondrocytes are generally believed to undergo apoptosis, but some researchers have suggested that some survive and transform into osteogenic cells [70–72].

Growth in length of the mandibular condyle results from the following three phenomena: proliferation of progenitor cells, production of cartilaginous matrix, and enlargement (hypertrophy) of chondrocytes. Among these, chondrocyte hypertrophy contributes most to condylar growth [66].

6. Types I and II collagen in condylar cartilage

ECM molecules can be classified into four major groups (i.e., collagens, elastins, structured glycoproteins, and proteoglycans) that provide structural support to tissues and biological cellular activities [73]. Among these ECM components, types I and II collagen are well-established molecular markers used to detect chondrogenic differentiation [74,75]. In the growth plate, type I collagen is completely absent from all cartilaginous cell layers and is present only in the bone matrix around calcified cartilage remnants [76] (Fig. 8a), which is in accordance with the findings of biochemical [77] and in situ hybridization [78] studies. The ECM of a growth plate consists mainly of type II collagen and the hyaluronan-binding proteoglycan aggrecan, with the remainder comprised of minor ECM collagens, such as types IX and X collagen [79] (Fig. 8b). Distribution of types I and II collagen is almost the same in articular cartilage (Fig. 8c and d). In contrast, type I collagen staining is present throughout condylar cartilage cell layers [36,37,68,80–83] (Fig. 9a and c). Staining intensity decreases and is limited to cell peripheries with progressive

depth within this layer. Staining for type II collagen is restricted to the chondrocytic and hypertrophic cell layers [36–38,41,68,80–83] (Fig. 9b and d). This complex collagen localization is thought to be associated with complex tissue organization, cell population, and cell differentiation processes.

Colocalization of types I and II collagen is also observed in fibrous cartilage [84] and intervertebral discs [85]. ECM composition and organization in skeletal and connective tissues reflect the biomechanical forces exerted on them. For example, type I collagen, which is abundant in bone, skin,

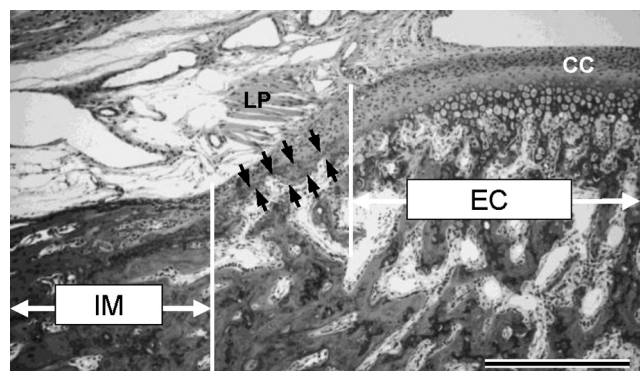


Figure 10 The anterior region of the mandibular condylar cartilage in a growing rat. The thickness of the condylar cartilage decreases anteriorly, and it is replaced by the periosteum at the condylar neck. Chondroid bone (arrows) is located between the condylar cartilage and condylar neck. CC, condylar cartilage; IM, intramembranous ossification region of the condylar neck; EC, endochondral ossification region of the condyle; LP, lateral pterygoid muscle. Scale bar = 500 μm .

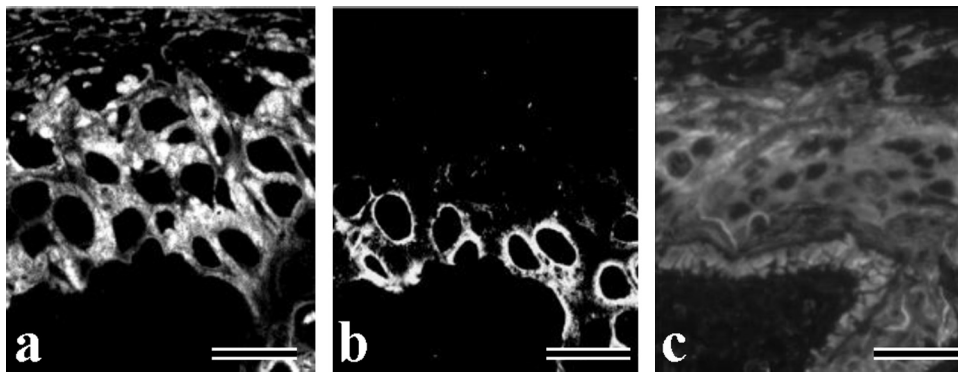


Figure 11 Chondroid bone of the condylar neck in a growing rat. (a) Localization of type I collagen. (b) Localization of type II collagen. (c) Localization of osteocalcin. Types I and II collagen and osteocalcin are present in the extracellular matrix of the chondroid bone. Scale bar = 25 μ m.

and periodontal ligament, forms thick rope-like fibers and provides tissues with resistance against tensile forces [86]. On the other hand, cartilage-characteristic type II collagen forms a three-dimensional meshwork in which proteoglycans with hydrophilic glycosaminoglycans are entrapped and provides compressive strength to cartilaginous tissue [87]. Condylar cartilage is located in a region that is subjected to complex compressive and tensile forces [88,89]; therefore, colocalization of both types of collagen in the condylar cartilage is assumed to be an adaptation to biomechanical demands. Understanding the characteristics of ECM components in the condylar cartilage may aid in better understanding the complex biomechanical environment of this cartilage.

7. Bone formation in the condyle: Presence of a third bone formation process

Two processes are involved in bone formation: endochondral and intramembranous. Because progenitor cells in the perichondrium and periosteum overlying the condyle can differentiate into chondrocytes or osteoblasts, five bone formation-related cell populations are present in the condyle: progenitor cells, chondrocytes, hypertrophied chondrocytes, osteoblasts, and osteocytes. Detailed observation of the peripheral condylar cartilage reveals the presence of peculiar cells that differ morphologically from chondrocytes, osteocytes, and progenitor cells (Fig. 10). These cells have a chondrocyte-like appearance, but are surrounded by eosinophilic matrix like osteocytes. This tissue is referred to as chondroid bone [16,65,90–98].

Chondroid bone is a specialized calcified tissue with morphological properties intermediate between those of bone and cartilage [16]. Electron microscopic observation of chondroid bone shows that its cell processes and junctions are similar to those of chondrocytes [90]. This tissue is found in craniofacial regions, including the mandibular symphysis [90,91], alveolar bone [92,93], glenoid fossa [94], mandibular condylar cartilage [65,95–97], and upper pharyngeal jaws of the teleost [98]. In addition, chondroid bone can be observed in ectopic bone formation induced by BMPs [53].

Immunohistochemical studies showed an intense matrix reaction for type I collagen and weak or faint pericellular reaction for type II collagen in chondroid bone [53,69,91,96,97] (Fig. 11a and b). These staining patterns differ markedly from those in intramembranous and endochondral ossification. Colocalization of both types of collagen is also observed in the condylar cartilage, but the staining pattern differs from that in chondroid bone [97]. In addition, a bone-specific glycoprotein, osteocalcin, and hypertrophic chondrocyte-specific type X collagen are present in chondroid bone ECM [69] (Fig. 11c). Two possible explanations concerning the identity of chondroid bone may be offered, although the reason for the presence of bone- and cartilage-characteristic matrices remains unclear: (1) progenitor cells differentiate into specialized cells that acquire properties intermediate between those of osteocytes and chondrocytes and secrete bone- and cartilage-characteristic matrices simultaneously [16]; or (2) chondrocytes dedifferentiate into osteogenic cells [92,95].

Chondroid bone is localized in regions that seem to require accelerated growth [92]. Chondroid bone is located at the boundary between the periosteum of the condylar neck, which undergoes slow bone formation (intramembranous ossification), and the condylar cartilage, which undergoes endochondral ossification at a faster rate [35]. Therefore, chondroid bone may play an important role in regulating different rates of bone formation in two different calcification processes [69,92]. The transitional nature of chondroid bone may also allow for highly diverse condylar growth and maxillofacial morphology.

Funding

This work was supported in part by grants-in-aid (nos. 02857309, 03857291, 07557282, 07557283, 08672356, and 25293421) for scientific research from the Ministry of Education, Science, Culture, and Sports of Japan.

Conflict of interest

None to declare.

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