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CRANIOFACIAL SKELETON (WE ROBERTS, SECTION EDITOR)

Part I: Development and Physiology of the Temporomandibular Joint

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Abstract

Purpose of Review Investigate the developmental physiology of the temporomandibular joint (TMJ), a unique articulation between the cranium and the mandible.

Recent Findings Principal regulatory factors for TMJ and disc development are Indian hedgehog (IHH) and bone morphogenetic protein (BMP-2). The mechanism is closely associated with ear morphogenesis. Secondary condylar cartilage emerges as a subperiosteal blastema on the medial surface of the posterior mandible. The condylar articular surface is immunoreactive for tenascin-C, so it is a modified fibrous periosteum with an underlying proliferative zone (cambrium layer) that differentiates into fibrocartilage. The latter cushions high loads and subsequently produces endochondral bone. The TMJ is a heavily loaded joint with three cushioning layers of fibrocartilage in the disc, as well as in subarticular zones in the fossa and mandibular condyle.

Summary The periosteal articular surface produces fibrocartilage to resist heavy loads, and has unique healing and adaptive properties for maintaining life support functions under adverse environmental conditions.

Keywords TMJ · Indian hedgehog · BMP-2 · Healing blastema · Tenascin-C · Fibrocartilage · Periosteum · Morphogenesis · Pharyngeal arch

Introduction

The temporomandibular joint (TMJ) is a synovial joint comprised of the mandibular condyle and glenoid fossa of the temporal bone. An intermediate articular disc of fibrocartilage divides the joint cavity into upper and lower compartments. The surrounding connective tissue capsule is attached to muscles and tendons (Fig. 1).

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The capsule is lined by a synovium that secretes lubricating synovial fluid. The articular disc is attached to the capsule and positioned between the mandibular condyle and the glenoid fossa. The TMJs are very mobile bilateral articulations of the mandible, a bone that is highly evolved for accommodating a variety of respiratory, speech, and omnivore masticatory functions. It can be argued that the mandible has a stronger influence on the human gene pool than any other bone in the body because it is essential for three important elements of survival and propagation: mastication, communication, and routine mating success. Anomalies and trauma to the mandible and TMJ may interfere with life support functions. They often manifest as a facial esthetic deficit with craniomandibular disorder (CMD) symptoms including ear pain and tinnitus [2].

The evolutionary origin of the mammalian TMJ is intimately connected with that of the middle ear bones [3]. Mammals have three middle ear bones, the malleus, incus, and stapes. Reptiles and birds have only one middle ear bone that is homologous to the mammalian stapes. Based on anatomical comparisons, Reichert (1837) [4] proposed that the additional two mammalian middle ear bones were homologous to the quadrate of the non-mammalian jaw joint and Gaupp (1912) [5] extended this idea by describing the development of a primary jaw joint between the malleus and the incus, and a secondary jaw joint, unique to mammals, between

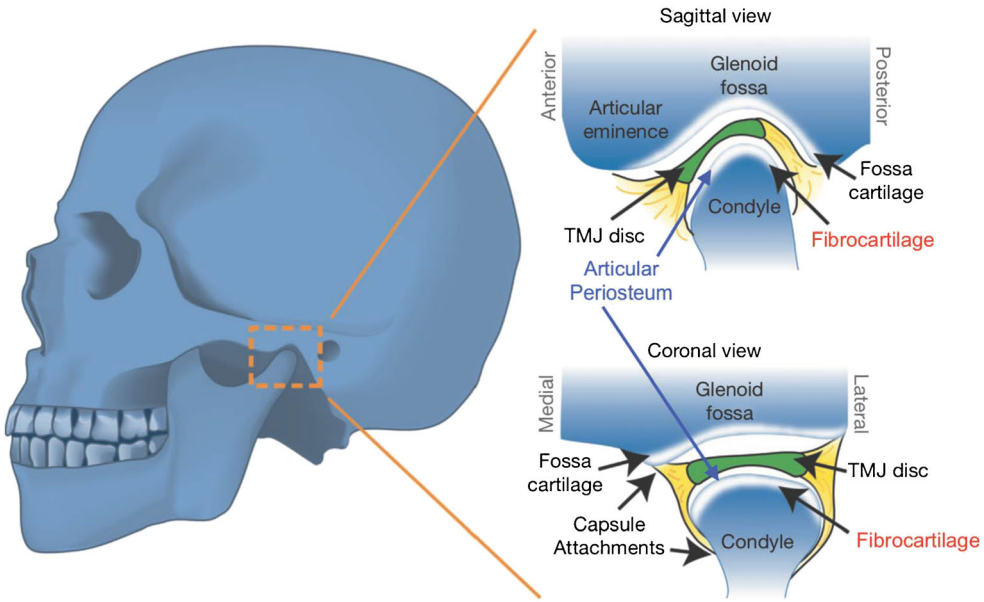

Fig. 1 The TMJ is shown in the sagittal and coronal (frontal) view. As described in the text, synovial surfaces of both the fossa and the condyle are fibrous periosteum. There are three layers of cushioning fibrocartilage, in the disc and the subarticular areas of the fossa mandibular condyle. Adapted from Willard, Zhang, and Athanasiou (2011) [1]

the squamosal and dentary bones [3]. Evidence from the fossil record, and from cellular and molecular developmental biology studies, have further supported this interpretation of the evolution of the TMJ [3].

The first part of this comprehensive review focuses on the basic cell and molecular biology relative to the structure and development of the TMJ. This is a highly adaptable joint resulting from a complex interaction of genetic and environmental factors that are unique to this articulation. In the follow-up review (Part II), cone-beam computed tomography (CBCT) imaging [6] is used to assess TMJ clinical problems such as fracture repair, condylar regeneration, joint degeneration, post-traumatic healing, and the long-term adaptability to a changing environment.

Cellular and Biochemical Composition of the Mature Condylar Cartilage, Disc, and Fossa

The cellular and biochemical composition of the components for the mature TMJ is a subject that has been reviewed by Willard et al. [1] with a focus on engineering biomimetic components for failed joints.

Condyle and Fossa Mature condylar cartilage of the mandible consists of four zones: (1) articular surface of fibrous tissue facing the disc expressing collagen I, (2) proliferative cells in the prechondroblastic zone expressing collagen I, (3) a chondroblastic zone expressing collagen II, the proteoglycans aggrecan, decorin, chondroitin sulfate PG, and keratin sulfate PG, and (4) a hypertrophic zone adjacent to bone expressing collagen X. The fibrous cell layers are described in the literature as a fibrocartilage articular surface [1, 7]. However, there is an alternative view that is a principal element of this review. Developmental and histologic evidence suggests the TMJ articular surface is actually a modified periosteum with an underlying layer of fibrocartilage (Fig. 2), a load-related connective tissue that is also associated with muscle attachments. The articular surface of the mandibular condyle is the fibrous layer of the periosteum, and the underlying proliferative zone is the cambium layer (Fig. 3). Although two proliferative populations were originally proposed [8], the cell kinetic data is consistent with the proliferative zone of the periosteal cambium layer, supplying cells for both the fibrous layer of the periosteum and the underlying fibrocartilage. Similar to the TMJ disc, the condylar fibrocartilage is a load-bearing cushion that helps protect the underlying bone of the supporting condylar metaphysis. Fibrocartilage has no inherent growth potential, and is derived from the proliferating cambium layer of the overlying periosteum (Fig. 3). In effect, there are three cushioning masses of fibrocartilage in the TMJ, one is the disc and the others are the subarticular regions of the fossa and the mandibular condyle (Fig. 1). The fibrocartilage cushioning of the mandibular condyle is associated with a six-fold decrease in the remodeling rate of trabecular bone in the mandibular condyle compared to the vertebrae [9].

Articular Disc The articular disc is a biconcave fibrocartilage attached to the capsule and condyle that distributes loads, similar to the menisci of the knee joint. The fibrocartilage is a mixture of 30% chondrocytes, lacking a hyaline pericellular matrix, and 70% fibroblasts [10]. The main extracellular matrix (ECM) component of the disc is collagen I, with small amounts of collagen II and trace amounts of type III as well as non-fibrillar collagens (VI, IX, XII) [11]. Collagen fibers are arranged in a ring on the periphery of the disc and run mediolaterally in the center of the disc. The fibers in the

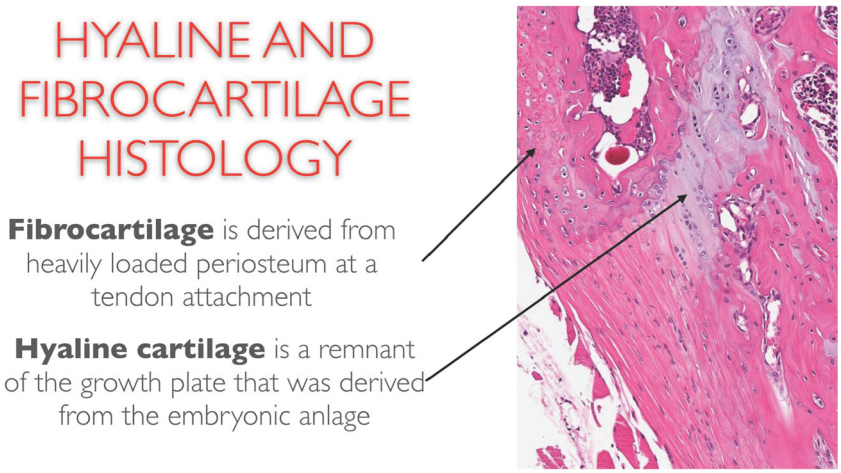

Fig. 2 Adjacent areas of hyaline and fibrocartilage are shown near a muscle attachment of a young growing rat. Section courtesy of Carol Bain, Research Tissue Processing Specialist, Indiana University, Simon Cancer Center, Indianapolis, IN

intermediate zone run in an anteroposterior direction [10]. These alignments are important for the tensile strength of the various regions of the tissue. The primary glycosaminoglycans of the disc are chondroitin sulfate and dermatan sulfate as part of the corresponding proteoglycans [12].

Fibrocartilage Fibrocartilage is a specialized, load-bearing tissue that is found in few locations in the body: the TMJ disc, mandibular condyle, pubic symphysis, intervertebral discs, joint menisci, and the tendon-bone interface. Fibrocartilage has a distinct appearance from hyaline cartilage (Fig. 2). The latter is a remnant of the original cartilage anlage, but fibrocartilage is secondary tissue derived from perivascular osteogenic cells near a heavily loaded muscle attachment. Despite morphology that is similar to hyaline cartilage, condylar secondary cartilage (CSC) is actually a type of fibrocartilage [7]. Mature fibrocartilage has a denser ECM of fibrous connective tissue (Figs. 2 and 3). CSC is distinct from

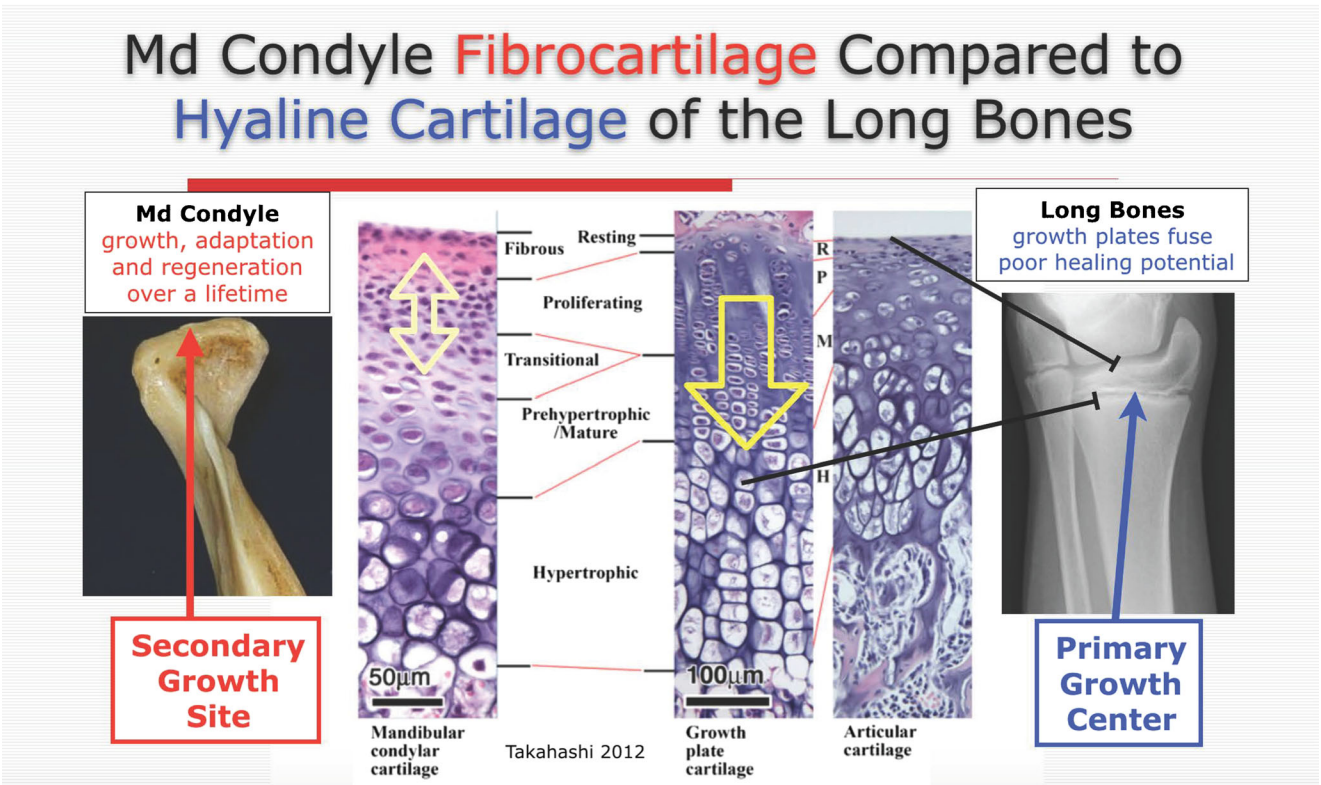

Fig. 3 The articular surface of the rat mandibular condyle is periosteum overlying a zone of fibrocartilage. This configuration is a secondary growth site capable of bilateral growth (double-ended yellow arrow) and post-traumatic healing over a lifetime. In contrast, the hyaline cartilage on the articular surface of long bones has poor healing potential and interstitial growth of cartilage (large yellow arrow) as a primary growth center ceases when the growth plate fuses. See text for details. Histology adapted from Takahashi (2014)

primary cartilage, where Type II collagen predominates, because of the presence of Type I collagen throughout the cartilaginous cell layers [13]. Type I collagen is a defining character for fibrocartilage, and its relative prevalence suggests a history of loading [14]. Utreja et al. [15••] experimentally loaded the TMJ and demonstrated that the induction of Type I collagen distinguishes the articular surface of the mandibular condyle from the underlying fibrocartilage. A series of inductive reactions is associated with mechanical loading of mandibular condyles. Dkk3 expression in the superficial proliferative zone interacts with the Wnt signaling pathway to induce differentiation [16, 17]. Type I collagen is expressed as fibrocartilage is formed [15••]. Conversely, Outani et al. [18] view fibrocartilage as a type of scar tissue, with respect to the wound healing of long bone articulations, so suppression of Type I collagen is introduced to produce a more hyaline-type cartilage from dermal tissue. These data indicate that fibrocartilage is a variable tissue containing Type I collagen that is directly proportionate to the history of loading.

Takahashi [19] reviewed the literature and provided histologic evidence that the articular surface of the mandibular condyle is the periosteum (Fig. 3). The articular surface of the temporal fossa is traditionally thought to be fibrocartilage, but there is a dearth of studies on its exact cellular and biochemical composition. Histologic demonstration of the periosteal articular layer of the mandibular condyle requires careful fixation, embedding, and sectioning technique. The periosteal articular surface is labile and subject to autolysis. Careful studies are needed to determine if the articular surface of the fossa is similar to the head of the condyle. Perfusion fixation and sectioning of the intact joint may be necessary. Koyama et al. [20] produced frontal sections of the intact mouse TMJ to study lubricin deficiency. The wild-type controls show similar layers of periosteum-like tissue with underlying fibrocartilage on the condylar and fossa surfaces. However, the fibrous and proliferating layers of the periosteum on the articular surfaces were not clearly defined as shown by Takahashi [19] (Fig. 3), which may reflect some articular surface autolysis during tissue processing. Overall, available evidence is consistent with similar articular surfaces in the fossa and on the condyle: periosteal, fibrocartilage, and bone layers.

Development of the Mammalian TMJ

The embryonic origin of the TMJ involves neural crest mesenchyme migrating ventrally to form the first (mandibular) pharyngeal arch. The initial life support function of the mandible is to control the tongue position to maintain a patent pharyngeal airway, which will be discussed in a clinical context in Part II. Evolution of the vertebrate jaw can be interpreted as a change in the program that specifies the development of neural crest cells. Development of the TMJ is similar among mammalian species, but contrasts with the development of other synovial joints, such as the knee, which appears first as an interzone within a single cartilage condensation. The edges of the interzone mesenchyme form the articular surfaces of the adjoining bones that make up the joint, while the rest of the interzone cells undergo apoptosis [21]. By contrast, the TMJ develops from three separate mesenchymal condensations representing the glenoid fossa of the temporal bone, the condylar process of the mandibular ramus, and the articular disc. This more complex process is consistent with the TMJ being a secondary joint with a periosteal articular surface that has regenerative potential, as will be discussed in Part II of this review.

The standard features of mammalian development are illustrated in the developmental anatomy of the human TMJ [22]. Neural crest mesenchyme migrates during the fourth week of embryonic development to form the first branchial (mandibular) arches surrounding the prospective stomodeal region. The dorsal half of the arch gives rise to the maxillary process and the ventral half to the mandibular process. Within the mandibular process, Meckel's cartilage develops from the 8th to 16th weeks. Meckel's cartilage extends dorsally out of the mandibular process as the tympanic process. The end of the tympanic process thickens into the primordium of the malleus, which articulates with the primordial incus developing from a separate mesenchymal condensation. The malleus later separates from Meckel's cartilage, and ossifies when in contact on the lateral surface with the tympanic membrane of the ear, thereby forming a synovial joint medially with the incus. Within the mandibular process, intramembranous bone formation replaces Meckel's cartilage. During this time, a blastema forming the condylar secondary cartilage (CSC) develops beneath the periosteum from the ramal surface of the developing mandibular body. Figure 4a, b illustrates the development of the mandibular condyle. The secondary cartilage blastema that forms the ramus and condyle arises at around 6 weeks in utero, from the medial surface of the intramembranous bone of the primordial mandibular body (Fig. 4a). Note that the blastema originates in the subperiosteal space from osteogenic perivascular cells, so the secondary cartilage is covered with periosteum (blue outline) throughout its development. At about 20 weeks, the carrot-shaped condyle is formed (arrow in Fig. 4b) via secondary cartilage that is mineralized to form the endochondral bone that composes a substantial portion of the subcondylar ramus (Fig. 4c). The periosteal articular surface of the mandibular condyle is composed of the fibrous and cambium layers of the periosteum with an underlying cushion of fibrocartilage (Fig. 3) [19]. Note that the buds for the deciduous molars are formed at the same time as the condyle (Fig. 4b).

"Perichondrium" of the mandibular condyle is immunoreactive for tenascin-C and not versican [23••] indicating it is actually periosteum (Fig. 4a, b) rather than perichondium. The proximal end of the CSC (covered by periosteum) grows dorsally

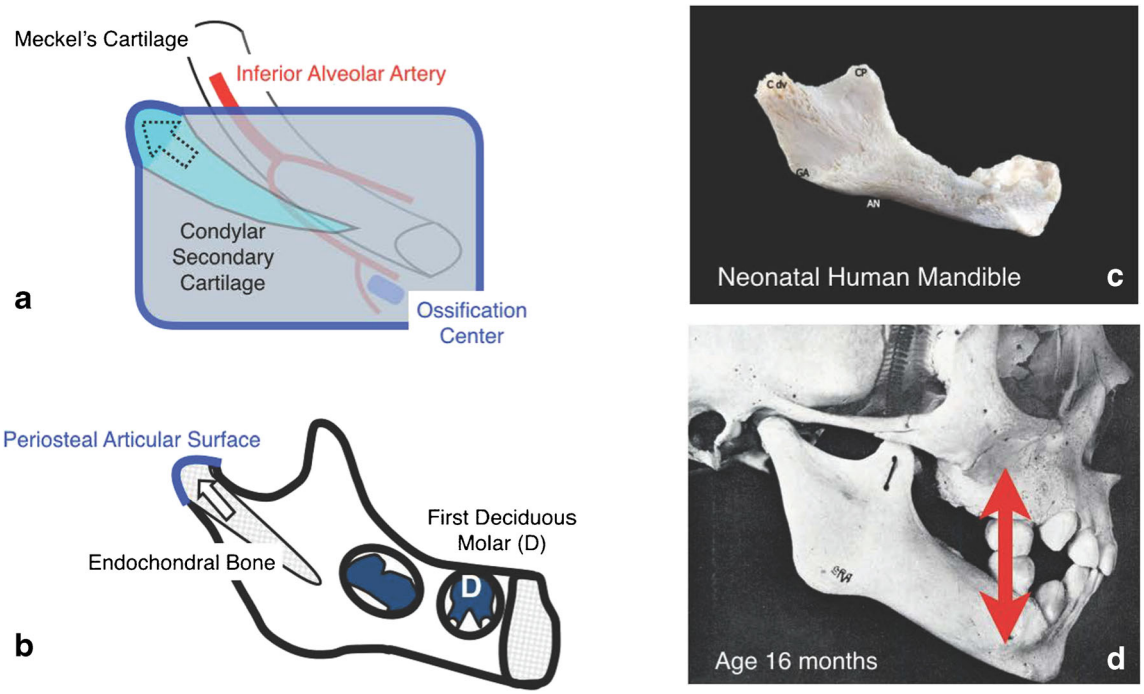

Fig. 4 Biomechanics of mandibular development is illustrated for the right side: **a** At 6–8 weeks in utero, bone formation begins at the ossification center and grows into a plate of bone (gray) surrounded by a periosteum (blue line). The condylar secondary cartilage emerges as a subperiosteal blastema from the lingual surface. **b** From 8–20 weeks, the condyle grows in a superior and inferior direction. The condyle has a periosteal articular surface (blue line) with an underlying fibrocartilage layer that forms endochondral bone. The first deciduous molar (**d**) is forming at the same time. **c** Neonatal human mandible shows the following skeletal landmarks: osseous portion of the condylar process (Cdr), gonial angle (GA), antegonial notch (AN), and corinoid process (CP). **d** At ~16 months of age, the first deciduous molars (Ds) occlude bilaterally, resulting in heavy loads (red double-headed arrow) being equally distributed to the mandible and the cranium

toward the glenoid fossa of the temporal bone thereby forming the mandibular ramus, from which will arise the coronoid and condylar processes. The active growth component of the condylar process is a secondary cartilage derived from the medial periosteal cells expressing tenascin-C of the mandibular ramus that will undergo endochondral ossification [24, 25].

The human TMJ develops in three stages between the 7th and 20th week [22]. The first phase is the approximation of the condylar process to the developing concavity of the glenoid fossa at the base of the temporal bone (7th–8th week). The second phase (9th–11th week) encompasses the coordinated development of the condyle and fossa, the articular disc, joint capsule, and joint cavities. Endochondral ossification of the condylar process begins in the 17th week, and after the 20th week the secondary cartilage is almost entirely ossified. The articular disc and joint capsule develop between the articular fossa and the condylar process. The disc forms in a biconcave shape and separates the joint cavity into two spaces, an upper space between the disc and the glenoid fossa, and a lower space between the disc and the condyle. By the 20th week, the articular disc has differentiated into periosteal articular surface with underlying fibrocartilage (Fig. 3).

The histological development of the TMJ has been studied in mice between embryonic day 13.5 and postnatal day 180 with stains that show general cellular and ECM features (H&E) and cartilage and bone (Safranin O-Fast Green, Azon red/Analin blue) (Liang et al. 2016) [25]. These stains, along with BrdU incorporation studies, showed that the cells of the condyle and fossa undergo rapid proliferation. The condylar cartilage begins endochondral ossification prior to the fossa, at E13.5. The traditional interpretation is the end of the condyle forms a cartilaginous growth region (carrot) consisting of four zones: the distal fibrous cell layer, a proliferative chondroprogenitor cell layer, a zone of flattened, mature chondrocytes, and a zone of hypertrophic chondrocytes [1, 25, 26]. The elongation of the condyle toward the fossa is due to appositional growth at its apex in which cells of the progenitor cell layer undergo chondrogenesis to become part of the condylar cartilaginous tissue. The disc appears at E16.5 contiguous to the condyle, and separates from the condyle to form the lower joint cavity, while mesenchymal cells between the disc and glenoid fossa undergo apoptosis to form the upper joint cavity. The glenoid fossa undergoes intramembranous ossification.

Hinton [7] reviewed the genes regulating the morphogenesis and growth of the TMJ. Collagens I, II, III, and the proteoglycan aggrecan are expressed during development of the fossa, condyle and disc [1, 27–29]. Collagen I, along with collagen III, is expressed in the fibrous and proliferative zones of the condyle. Collagen II, with some collagen X, is the primary collagen of the mature cartilage and hypertrophic

zone. Immunocytochemistry revealed that collagens I, II, and aggrecan are expressed weakly in the condylar cartilage at E14.5, and strongly by E17.5. Zymographic studies show the ECM of this cartilage is remodeled during its development by the action of MMP 9 and MMP 13, which degrade collagen II and aggrecan. Versican is expressed prominently in the anterior and posterior peripheral attachments of the disc in 8-week postnatal rats [30]. In situ hybridization for transcripts of *Sox-9*, *Runx2*, and *Osterix* showed that these transcripts are expressed in the developing TMJ as condylar cartilage is formed and replaced by bone [25, 31]. *Sox9* is expressed primarily in the proliferative zone of the secondary condylar cartilage, which is distinct from the proliferative zone of the articular periosteum as shown in Fig. 3.

Runx2-negative mice do not form bone but do form primary mandibular cartilage. Secondary cartilages of the mandible, however, are lacking, though a small condylar condensation forms (Shibata et al. 2004) [32]. Inactivation of *Sox9* in cranial neural crest cells results in a lack of condylar cartilage, though intramembranous mandibular bone develops due to the continued expression of *Runx2* [7]. Explants of *Runx2*-negative condylar condensations can be induced to undergo chondrogenic differentiation by BMP2, suggesting that secretory products of osteoblasts are required for secondary cartilage formation [33]. Displacement of the developing condyle arrests development of the fossa, indicating that the latter is dependent on the normal positioning of the developing condyle, whether the reverse is true is unknown. Mice lacking the *Sprouty 1* and *2* genes fail to form the fossa. These genes encode intracellular inhibitors of RTK signaling pathways, which include those initiated by Fgfs. The temporal and pterygoid muscles are much larger than normal in these mice, suggesting a mechanical impediment to the formation of the fossa.

IHH and BMP-2 are important signaling pathways regulating the development of the TMJ condyle. In the growth plates of long bones, IHH and PTHrP constitute a feedback loop that controls the rate at which chondroprogenitor cells undergo hypertrophy (Vortkamp et al. 1996; Vortkamp et al. 1998) [34, 35]. IHH is expressed by pre-hypertrophic chondrocytes and maintains proliferation of chondroprogenitor cells. Furthermore, it diffuses centripetally and distally to perichondrial cells, inducing them through Gli2 to express PTHrP that diffuses proximally into the chondroprogenitor zone, thereby slowing the differentiation of *Sox9*+ cells into chondrocytes to become hypertrophied chondrocytes. Maintaining a normal proliferation rate also requires BMP-2 in parallel with IHH signaling, and BMP-2 also modulates the expression of Ihh [36].

Ihh plays a similar role in condylar growth and also in disc formation. Ihh and its downstream transcriptional effector Gli2 are expressed strongly in condylar cartilage by E15.5, while the expression of Gli2 and PTHrP indicates that the range of action for IHH reaches the polymorphic chondroprogenitor layer as well as the zone of disc condensation [37••, 38]. Cavitation was accompanied by secretion of the anti-adhesive lubricant molecule lubricin. In IHH-negative mutant mice, condyle growth is subnormal due to low *Sox9*+ cell proliferation in the chondroprogenitor zone, restricting the supply of cells for appositional growth. In addition, the articular disc and joint cavities do not develop, indicating that these features are dependent on IHH expression in the condyle [37••, 38].

Purcell et al. [37••] performed laser capture dissection at E.16.5 on mouse glenoid fossa tissue and condylar tissue, which included the developing disc, and subjected the extracted RNA to microarray analysis. In addition to IHH, they reported signaling that involved a number of other highly upregulated genes. The Fgf receptors 1 and 2 were expressed in the periosteum and perichondrium, respectively, of both fossa and condyle. Fgfr3 was expressed in the immature chondrocytes of the condyle. Wnt6 was enriched in the condylar perichondrium, and Zfp445 prevailed in the chondroprogenitor cells, disc, and glenoid fossa. Zfp445 encodes a zinc finger protein of unknown function, and its role in TMJ formation is thus unclear. The IHH pathway downstream effector genes, *Smo*, *Ptc1*, and *Gli 1–3*, were co-expressed in the condylar cartilage. *Gli2* showed the strongest expression in both the condyle and disc. *Gdf5*, *6*, and *7*, characteristic of limb joints, were not expressed in the TMJ. Comparison of gene expression in the development of other joints with the developing TMJ revealed that there were some similarities between the hip joint and TMJ, but in general the TMJ has a molecular expression pattern distinct from other synovial joints.

The role of BMPs (2 and 7) in appendicular joint development is well known. The receptor for BMP family ligands, BMPR1A, is expressed in the interzone, perichondrium, periarticular cartilage, and hypertrophic chondrocytes of the growth plate in developing joint regions of the appendicular skeleton. BMP2 and 7 are expressed in the TMJ condyle [37••]. Gu et al. [39••] carried out a detailed study of BMPR1A expression in mouse TMJ development. BMPR1A is expressed in the developing condyle, glenoid fossa, and interzone mesenchymal cells between the two. Transgenic inactivation of the BMPR1A gene in cranial neural crest cells resulted in a phenotype much like that of Ihh-negative mice: hypoplastic condyle, failure to form a functional fibrocartilage layer on the articular surface of the condyle and glenoid fossa, and failure of cavitation. Ihh expression is downregulated, indicating that BMPR1A is a positive regulator of IHH. Transgenic overexpression of BMPR1A led to the degeneration of the developing TMJ. These results led Gu et al. [39••] to propose a model in which BMPR1A-mediated signaling interacts with Ihh signaling to control disc separation, synovial membrane formation, and cavitation (Fig. 5).

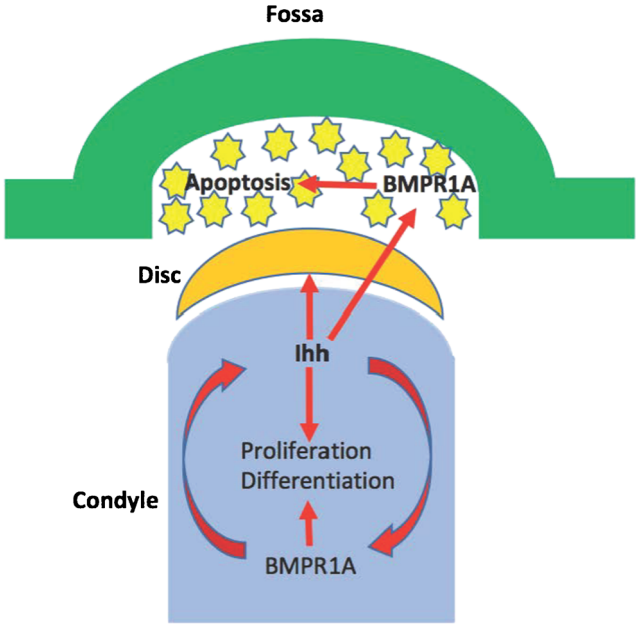

Fig. 5 BMP and Ihh signaling are the primary regulators of TMJ development. BMPs signal through BMPR1A. Ihh upregulates BMPR1A in the condylar process and interzone between the disc and glenoid fossa, allowing the positive regulation of IHH by BMPs, as well as the apoptosis of interzone cells to form the upper synovial cavity. Adapted from Gu et al. 2014.39

Origin of the Disc

A major unanswered question about TMJ development is the origin of the articular disc. There is some inconsistency in published descriptions of disc formation. According to Frommer [40], the disc develops from a separate mesenchymal condensation between the condyle and fossa and differentiates into fibrocartilage as also described by Shibukawa et al. [38] However, the histological studies of Liang et al. [25] suggest that the disc develops in contiguity with the fibrous layer of the condyle, and thus might actually be derived by the separation of cells from the fibrous surface of the condyle. Their studies indicate that the upper cavity of the TMJ is formed by apoptosis of loose mesenchymal cells between the disc and the fossa by E15.5, whereas the lower joint cavity is formed by E17.5, when the layers of disc cells appear fully separated from the condyle. There is no signature marker for early disc cells, so it is currently impossible to say whether the disc is formed from mesenchyme, continuous with the tip of the condyle, or if the disc arises as a separate mesenchymal condensation very close to the tip of the condyle blastema.

Ihh is expressed in condensing mesenchymal cells of the condyle prior to disc formation [37••, 41]. In the absence of either *Ihh* [42] or *Gli2* [37••] expression in the condyle, the disc fails to form, suggesting that condylar Ihh signaling acts early and directly to induce formation of the disc condensation. Alternatively, other as yet unidentified signals from the condyle condensation might be involved in this induction, with the disc condensation expressing Ihh independently from the condyle. *Gli2* continues to be expressed within the disc after it has initiated differentiation, suggesting that Ihh might be required to maintain the disc. To investigate this possibility, Purcell et al. [37••] conditionally removed *Smo*, which is activated by Ihh signaling, from mice after disc cells initiated chondrogenesis. The mutant TMJ formed a complete disc that did not separate from the condyle, so the lower joint space did not form. This suggests that Ihh signaling is required not only to initiate disc formation, but also for normal differentiation to produce a lower joint cavitation.

Conclusions

The TMJ is the most highly conserved joint in the body because it is essential for three important elements of survival and propagation: mastication, communication, and mating success. The TMJ may be the most heavily loaded joint in the body, so there are three cushioning layers of fibrocartilage: subarticular fossa, disc, and subarticular condyle. The articular surface of the condyle is composed of modified periosteum, which is divided into a fibrous layer (synovial surface) and an underlying proliferative layer (cambium periosteum). Mechanically induced differentiation of cells in the cambium layer produces an underlying layer of fibrocartilage that is subsequently mineralized to form bone. The gene expression pattern during TMJ development is distinct from other synovial joints, and is closely associated with ear development, which may relate to manifestation of TMJ dysfunction in the ears. The principal regulatory factors in TMJ development are IHH and BMP. Developmental origin of the disc is unknown, but disc formation and differentiation requires IHH signaling.

Compliance with Ethical Standards

Conflict of Interest David Stocum and Eugene Roberts declare no conflict of interest. Dr. Roberts is the section editor for this section of the journal, but the paper was reviewed by an outside reviewer to avoid conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Willard VP, Zhang L, Athanasiou KA. Tissue engineering of the temporomandibular joint. Elsevier 2011.

2. Nokar S, Sadighpour L, Shirzad H, Shahrokhi Rad A, Keshvad A. Evaluation of signs, symptoms, and occlusal factors among patients with temporomandibular disorders. Cranio. 2018;30:1–6. https://doi.org/10.1080/08869634.2018.1449781.
3. Anthwal N, Joshi L, Tucker AS. Evolution of the mammalia midde ear and jaw: adaptations and novel structures. J Anat. 2013;222:147–60. https://doi.org/10.1111/j.1469-7580.2012.01526.x.
4. Reichert KB. Uber die Visceralbogen der Wirbelthiere im Allgemeinen und deren Metamorphosen bei den Vogeln und Saugethieren. Arch Anat Physiol Wissensch Med. 1837:120–220.
5. Gaupp E. De Reichertsche Theorie. Arch Anat Physiol Suppl. 1912:1–416.
6. Khojastepour L, Vojdani M, Forghani M. The association between condylar bone changes revealed in cone beam computed tomography and clinical dysfunction index in patients with or without temporomandibular joint disorders. Oral Surg Oral Med Oral Pathol Oral Radiol. 2017;123(5):600–5.
7. Hinton RJ. Genes that regulate morphogenesis and growth of the temporomandibular joint: a review. Dev Dynam. 2014;243:864–74. https://doi.org/10.1002/DVY.24130.
8. Blackwood HJ. Growth of the mandibular condyle of the rat studied with tritiated thymidine. Arch Oral Biol. 1966;11(5):493–500.
9. Helm NB, Padala S, Beck FM, D'Atri AM, Huja SS. Short-term zoledronic acid reduces trabecular bone remodeling in dogs. Eur J Oral Sci. 2010;118(5):460–5.
10. Detamore MS, Orfanos JG, Almarza AJ, French MM, Wong ME. Athansiou. Matrix Biol. 2005;24:45–57.
11. Landesberg R, Takeuchi E, Puzas JE, et al. Cellular, biochemical and molecular characterization of the bovine temporomandibular joint disc. Arch Oral Biol. 1996;41:761–7.
12. Almarza AJ, Bean AC, Baggett LS, Athanasiou KA. Biological analysis of the porcine temporomandibular joint disc. Br J Oral Maxillofac Surg. 2006;44:124–8.
13. Mizoguchi I, Nakamura M, Takahashi I, Kagayama M, Mitani H. A comparison of the immunohistochemical localization of type I and type Il collagens in craniofacial cartilages of the rat. Acta Anat (Basal). 1992;144(1):59–64.
14. Kato T, Takahashi S, Domon T. Effects of liquid diet on the temporomandibular joint of growing rats. Med Princ Pract. 2015;24:257–62.
15••. . Utreja A, Dyment NA, Yadav S, Villa MM, Yingcui L, Xi J, et al. Cell and matrix response of temporomandibular cartilage to mechanical loading. Osteoarthr Cartil. 2016;24(2):335–44. **Transgenic mice expressing fluorescent proteins to identify areas of gene expression in the mandibular condyle have documented the cell lineage progression in response to TMJ loading.**
16. Krupnik VE, Sharp JD, Jiang C, Robison K, Chickering TW, Amaravadi L, et al. Functional and structural diversity of the human Dickkopf gene family. Gene. 1999;238(2):301–13.
17. Kuboto T, Michigami T, Ozono K. Wnt signaling in bone metabolism. J Bone Miner Metab. 2009;27(3):265–71.
18. Outani H, Okada M, Yamashita A, Nakagawa K, Yoshikawa H, Tsumaki N. Direct induction of chrondrogenic cells from human dermal fibroblast culture by defined factors. PLoS One. 2013;8(10):e77365. https://doi.org/10.1371/journal.pone.0077365.
19. Takahashi I. Mechano-reaction of chondrocytes in the mandibular condyle during orthopedic-orthodontic interaction. In: Ngan PW, Deguchi T, Roberts WE, editors. Orthodontic treatment of class III malocclusion. Mumbai: Bentham Books; 2014. p. 37–60.
20. Koyama E, Saunders C, Salhab I, Decker RS, Chen I, Um H, et al. Lubricin is required for the structural integrity and post-natal maintenance of TMJ. J Dent Res. 2014;93(7):663–70.
21. Ito MM, Kida M. Morphological and biochemical re-evaluation of the process of cavitation in the rat knee joint: cellular and cell strata alterations in the interzone. J Anat. 2000;197:659–79.
22. Badel T, Savic-Pavicin I, Zadravec D, Marotti M, Krolo I, Grbesa D. Temporomandibular joint development and functional disorders related to clinical otologic symptomatology. Acta Clin Croat. 2011;50:51–60.
23••. . Shibata S, Sakamoto Y, Yokohama-Tamaki T, Murakami G, Cho BH. Distribution of matrix proteins in perichondrium and periosteum during the incorporation of Meckel's cartilage into ossifying mandible in midterm human fetuses: an immunochemical study. Anat Rec. 2014;297:1208–17. **This reference documents that the articular surface of the mandibular condyle is covered with periosteum and not cartilage.**
24. Shibata S, Sato R, Murakami G, Fukuoka H, Rodriguez-Vazquez JF. Origin of mandibular condylar cartilage in mice, rats and humans: periosteum or separate blastema? J Oral Biosci. 2013;55:208–16.
25. Liang W, Li X, Gao B, Gan H, Lin X, Liao L, et al. Observing the development of the temporomandibular joint in embryonic and post-natal mice using various staining methods. Exp Therapeut Med. 2016;11:481–9.
26. Zhang H, Zhao X, Zhang Z, Chen W, Zhang X. An immunohistochemistry study of Soxp9, Runx2, and Osterix expression in the mandibular cartilages of newborn mouse. Biomed Res Int. 2013; https://doi.org/10.1155/2013/265380.
27. Huang Q, Opstelten D, Samman N, Tidman H. Experimentally induced unilateral tooth loss: expression of type II collagen in temporomandibular joint cartilage. J Oral Maxillofac Surg. 2003;61:1054–60.
28. Gu Z, Jin X, Feng J, Shibata T, Hu J, Zhan J, et al. Type II collagen and aggrecan mRNA expressions in rabbit condyle following disc displacement. J Oral Rehabil. 2005;32:254–9.
29. Natiella JR, Burch L, Fries KM, Upton LG, Edsborg LE. Analysis of the collagen 1 and fibronectin of temporomandibular joint synovial fluid and discs. J Oral Maxillofac Surg. 2009;67:105–13.
30. Toriya N, Takuma T, Arakawa T, Sasano AY, Takahashi I, et al. Expression and localization of versican during postnatal development of rat temporomandibular joint disc. Histochem Cell Biol. 2006;125:205–14. https://doi.org/10.1007/s00418-005-0020-1.
31. Shibata S, Suda N, Suzuki S, Fukuoka H, Yamashita Y. An in situ hybridization study of Runx2, Osterix, and Sox9 at the onset of condylar cartilage formation in fetal mouse mandible. J Anat. 2006;208:169–77.
32. Shibata S, Suda N, Yoda S, Fukuoka H, Ohyama K, Yamashita Y, et al. Runx2-deficient mice lack mandibular condylar cartilage and have deformed Meckel's cartilage. Anat Embryol. 2004;208:273–80.
33. Fukuoka H, Shibata S, Suda N, Yamashita Y, Komori T. Bone morphogenetic protein rescues the lack of secondary cartilage in *Runx2*-deficient mice. J Anat. 2007;211:8–15.
34. Vortkamp A, Lee K, Lanske B, Segre GV, Kronenberg HM, Tabin CJ. Regulation of rate of cartilage differentiation by Indian hedgehog and PTH-related protein. Science. 1996;273:613–22.
35. Vortkamp A, Pathi S, Peretti GM, Caruso EM, Zaleske DJ, Tabin CJ. Recapitulation of signals regulating embryonic bone formation during postnatal growth and in fracture repair. Mech Dev. 1998;71:65–76.
36. Minina E, Wenzel HM, Kreschel C, Karp S, Gaffield W, McMahon AP, and Vortkamp A. BMP and Ihh/PTHrP signaling interact to coordinate chondrocyte proliferation and differentiation. Development 2001:128:4523–4534.
37••. . Purcell P, Joo BW, Hu JK, Tran PV, Calicchio ML, O'Connell DJ, et al. Temporomandibular joint formation requires two distinct hedgehog-dependent steps. Proc Natl Acad Sci U S A. 2009;106:18297–302. **An in-depth examination of Hedgehog signaling in TMJ development.**
38. Shibukawa Y, Young B, Wu C, Yamada S, Long F, Pacifici M, et al. Temporomandibular joint formation and condyle growth require Indian hedgehog signaling. Dev Dynam. 2007;236:426–34.

39••. . Gu S, Wu W, Liu C, Yang L, Sun C, Ye W, et al. BMPR1A mediated signaling is essential for temporomandibular joint development in mice. PLoS One. 2014;9:e101000. **This paper integrates information on IHH and BMP signaling in the development of the TMJ**

40. Frommer J. Prenatal development of the mandibular joint in mice. Anat Rec. 1964;150:449–61.

41. Gu S, Wei N, Yu L, Fei J, Chen Y. Shox2-deficiency leads to dysplasia and ankylosis of the temporomandibular joint in mice. Mech Dev. 2008;125(8):729–42.

42. Tang GH, Rabie A, Hagg U. Indian hedgehog: a mechanotransduction mediator in condylar cartilage. J Dent Res. 2004;83:434–8.