HHS Public Access

Author manuscript

Oral Dis. Author manuscript; available in PMC 2016 May 11.

Published in final edited form as:

Oral Dis. 2016 January ; 22(1): 33–38. doi:10.1111/odi.12353.

Mouse genetic models for temporomandibular joint development and disorders

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Abstract

The temporomandibular joint (TMJ) is a synovial joint essential for hinge and sliding movements of the mammalian jaw. Temporomandibular joint disorders (TMD) are dysregulations of the muscles or the TMJ in structure, function, and physiology, and result in pain, limited mandibular mobility, and TMJ noise and clicking. Although approximately 40–70% adults in the USA have at least one sign of TMD, the etiology of TMD remains largely unknown. Here, we highlight recent advances in our understanding of TMD in mouse models.

Keywords

temporomandibular joint disorders; mouse model

Introduction

The temporomandibular joint (TMJ) is one of the most frequently used joints in the human body. The TMJ is a synovial joint essential for hinge and sliding movements of the mammalian jaw. The TMJ consists of the mandibular condyle, the articular disk (or disc), the glenoid fossa, and the capsule (Tanaka *et al*, 2008). The articular disk separates joint space between the glenoid fossa and the condyle into two distinct parts: the upper and lower articular cavities. The upper and lower articular cavities are bounded by the articular fossa and the articular eminence and by the condyle, respectively (Nozawa-Inoue *et al*, 2003). TMJ disorders (TMD) are dysregulations of the muscles or the TMJ in structure, function, and physiology (Naidoo, 1995). Approximately 40–70% of adults in the USA have at least one sign of TMD and at least 33% among those have one symptom, such as pain, limited mandibular mobility, and TMJ noise and clicking (Scrivani *et al*, 2008). However, there are

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Author contributions

J. Iwata made substantial contributions to the conception and design of the article, drafted and revised the article critically for important intellectual content, and involved in the final approval of the version to be published. A. Suzuki revised it for intellectual content and was involved in the final approval of the version to be published. All authors read and approved the final manuscript.

Conflict of interest

None declared.

some important questions which have not been answered yet. Why does TMD occur so often? What determines the occurrence and progress of TMD and osteoarthritis (OA) in the TMJ? What causes differences in the TMJ from other synovial joints in the body?

Unique features of the TMJ

- Unlike the articular cartilage of the knee, the cartilage of the mandibular condyle is considered a secondary cartilage (independent from the chondroskeleton) and has a different embryonic origin [derived from cranial neural crest (CNC) cells] (Shen and Darendeliler, 2005).
- The condyle of the mandible has a lower amount of collagen type I (COLIA1) compared to the other synovial joints (Benjamin and Ralphs, 2004).
- In contrast to the articular cartilage of the other joints, the superficial layer of mandibular condylar cartilage does not express collagen type II (COLIIA1) (Hinton *et al*, 2009).
- The articular surfaces are not composed of hyaline cartilage but of fibrous tissue (Hinton *et al*, 2009).

Animal models including mice and rats are useful to study the development of the TMJ because the process of development/morphogenesis and the molecular mechanism are well conserved in these animal models (Herring, 2003) (Figure 1). In contrast, rodent models (mice and rats) are less useful for a TMD study because of morphological difference in the TMJ among humans and rodents; thereby, rodents do not show typical TMD symptoms (Figure 2).

Morphological features of the TMJ in rodents compared to humans

- The glenoid fossa is shallow and flatted.
- There is no articular eminence.
- The lateral pterygoid muscle is less in the volume and functional force.
- The upper articular cavity forms first, and then, the lower articular cavity forms.
- The articular disk rarely becomes fibrous cartilage with aging.

These anatomical factors cause the limitation of usage of rodent models for TMD study. Until now, some specific devises and methods have been developed to induce TMD in mice and rats. In addition, some genetic animal models for OA are used to understand TMJ OA (known as a severe form of TMD) (Hinton, 2014).

Mouse models for temporomandibular joint disorders (TMD)

Extracellular matrix

The growth of the TMJ is regulated through synthesis and degradation of various components of the extracellular matrix (ECM) (Wang and Detamore, 2007). The changes of ECM composition are associated with pathological processes of cartilage degeneration in

TMJ OA, accompanied by the upregulated matrix metalloproteases (MMPs) expression (Kanyama *et al*, 2000). Elevated MMP activity is responsible for ECM degradation in the processes of TMJ OA. Collagen type II (COLIIA1) is the most abundant protein in hyaline cartilage (Ricks *et al*, 2013). Mice with a disproportionate micromelia (*Dmm*) mutation, a three-nucleotide deletion of the *Col2a1* gene, display mild dwarfism in the heterozygotes (*Dmm*/+ mice). *Dmm*/+ mice also show condylar cartilage abnormalities in the TMJ at early ages. The TMJ of *Dmm*/+ shows fissuring of condylar cartilage as early as 6 months of age (Pace *et al*, 1997). Mice with deficiency of *Col9a1* (*Col9a1*$^{-/-}$) or chondrodysplasia (*Cho*/+) exhibit TMJ OA (Xu *et al*, 2003; Lam *et al*, 2007). *Col9a1*$^{-/-}$ and *Cho*/+ mice develop OA-like changes in the knee and TMJ from the age of 3 months and show a severe OA-like pathology over 9–12 months (Tanaka *et al*, 2008). Both chondrocyte clustering and increased production of proteoglycan in the pericellular matrix have been identified as early OA indicators (Tanaka *et al*, 2008).

A mouse model for progressive ankylosis (*ank/ank* mice) shows narrower and/or ankylosed upper and lower articular cavities filled with fibrous connective tissue throughout the entire articular cavity after 3 months of age (Huang *et al*, 2011). The *ANKH* gene is a human homolog of the murine progressive ankylosis gene, *ank*, and plays a critical role in the transport of pyrophosphate ions (Timms *et al*, 2003). *ANKH* polymorphism seems to be associated with human TMJ closed lock (a permanently displaced disk) (Huang *et al*, 2011).

Mice with inactivation of Golgi-associated *N*-sulfotransferase 1 (*Ndst1*), which catalyzes the constituent sulfation of heparan sulfate proteoglycan glycosaminoglycan chains, exhibit TMJ deformities with a variation of a thicker prechondroblastic cell layer and ectopic ossification with increased proliferation to lack of TMJ (Yasuda *et al*, 2010).

Transcription factors

The *Runx2* (runt-related transcription factor 2; essential for osteoblast differentiation) and *Sox9* (sex determining region Y box 9; essential for chondrocyte differentiation) genes are expressed in the mesenchymal condensation that initiates the formation of the mandibular condyles. Mice with deficiency of *Runx2* (*Runx2*$^{-/-}$ mice) exhibit the absence of the mandibular condylar cartilage (Shibata *et al*, 2004). Mice with the deletion of *Sox9* in CNC cells (*Sox9*$^{F/F}$*;Wnt1-Cre* mice) display the mandibular condylar cartilage agenesis, abbreviated mandibular fossa formation, altered articular disk formation with irregular cell shape, and incomplete articular cavity formation (Mori-Akiyama *et al*, 2003; Wang *et al*, 2011). Mice with the loss of *Trps1*, a transcription factor mutated in human trichorhino-phalangeal syndrome, which is characterized by an abnormal development of various organs including the craniofacial skeleton, exhibit an extremely small condylar process, and the complete absence of the articular disk and articular cavities (Michikami *et al*, 2012). Vitamin D is a prohormone that can be metabolically converted from 25-hydroxyvitamin D by 1α-hydroxylase [1α(OH)ase] to the active form, 1,25-dihydroxyvitamin D [1,25(OH)$_2$D]. 1,25(OH)$_2$D binds to its nuclear receptor and alters transcription activity of target genes. Mice with 1,25(OH)$_2$D deficiency [*1α(OH)ase*$^{-/-}$ mice] exhibit an erosive TMJ OA phenotype starting at 6 months of age, following DNA damage, cellular senescence, and the production of senescence-associated inflammatory cytokines (Shen *et al*, 2013).

Indian hedgehog signaling

Indian hedgehog (IHH) ligands express in mouse condylar cartilage at embryonic day 15.5 (E15.5). Mice with loss of *Ihh* (*Ihh*$^{-/-}$ mice) exhibit the absence of the articular disk and the lower articular cavity, and severe joint deformities at newborn. These defects in *Ihh*$^{-/-}$ mice can be partially restored by the loss of *Gli3* (a negative regulator of IHH signaling pathway) (*Ihh*$^{-/-}$;*Gli3*$^{-/-}$ mice), indicating that IHH inhibits GLI3 expression and function (Shibukawa *et al*, 2007). Mice with deficiency of *Gli2* display aberrant TMJ development including cellular disorganization of condylar cartilage and no articular disk formation (Purcell *et al*, 2009). In addition, a conditional deletion of *Smo*, a receptor for IHH, from chondrocyte progenitors in mice (*Smo*$^{F/F}$;*Sox9-Cre* mice) results in a failure of articular disk separation from the mandibular condyle (Purcell *et al*, 2009). Thus, IHH signaling plays important roles in disk morphogenesis, condyle initiation, and disk–condyle separation. Interestingly, tamoxifen-induced conditional *Ihh* knockout mice (*Ihh*$^{F/F}$;*Col2a1-CreER* mice) at postnatal days 4, 7, 14, and 56 show disorganization and growth retardation of condylar cartilage, and reduced proliferation in a polymorphic zone of the condyle, and abnormal adhesion of the articular disk with the condylar surface and/or glenoid fossa (Ochiai *et al*, 2010). Thus, IHH signaling also plays a crucial role in postnatal TMJ maintenance for proper tissue homeostasis. *Short stature homeobox 2* (*Shox2*) is expressed in condylar chondrocytes and the glenoid fossa of the developing TMJ and is essential for the process of TMJ morphogenesis. *Shox2*-deficient (*Shox2*$^{-/-}$) mice exhibit severe defects in a number of developing organs, as well as the TMJ dysplasia and ankylosis (Gu *et al*, 2008). Mice with overexpression of *Shox2* in CNC cells (*Wnt1-Cre;pMes-stopShox2* mice) show the dysplasia in the condyle and glenoid fossa after 2 weeks of age, following increased apoptosis and the upregulated expression of MMPs and downregulated expression of IHH signaling molecules, COLIA1 and COLIIA1 (Li *et al*, 2014a). Mice with the replacement of the mouse *Shox2* gene with the human *SHOX* gene (*Shox2*$^{SHOX\text{-}KI/KI}$ mice) show increased apoptosis in the articular disk, following the decreased expression of COLIA1 and aggrecan, accompanied by increased MMP activities (Li *et al*, 2014b). Senescence-accelerated 8 (*Samp8*) mice (a spontaneous mouse line) develop early-onset OA-like changes after 4 months of age, following reduced *Ihh* and other IHH signaling mediators expression in chondrocytes and *Col10* in the hypertrophic chondrocyte of the condylar cartilage (Ishizuka *et al*, 2014). This degeneration of condylar cartilage is accelerated by malocclusion in mutant mice, following increasing apoptosis and decreasing cell proliferation (Ishizuka *et al*, 2014). Primary cilium is known to be a sensor for mechanical stresses in many organs and regulates hedgehog signaling (Kinumatsu *et al*, 2011). Mice with deficiency of kinesin family member 3A (*Kif3a*) (*Kif3a*$^{F/F}$;*Col2a1-Cre* mice), which encodes ciliary transport protein, exhibit narrow and flat condyles which are often fused with the articular disk and display an irregular surface (Kinumatsu *et al*, 2011).

Transforming growth factor beta (TGFβ) superfamily signaling

Mice with transgene of TGFβ1 point mutation in bone, a mouse model for Camurati–Engelmann disease (CED), show high levels of active TGFβ1 in bone and result in increased apoptosis and MMPs expression in the hypertrophic zone of the condylar cartilage after 4 months of age (Jiao *et al*, 2014). CED mice exhibit abnormal bone remodeling in the condylar subchondral bone such as microstructure and increased activities of osteoclasts and

osteoblasts without coupling, and cartilage degradation in the condylar cartilage. Bone morphogenetic protein receptor type I (BMPR1A) is expressed in the developing condyle, glenoid fossa, and interzone mesenchymal cells that are all derived from CNC cells (Gu *et al*, 2014). Mice with the deletion of *Bmpr1a* (*aka Alk2*) in CNC cells (*Bmpr1a*$^{F/F}$*;Wnt1-Cre* mice) display defective TMJ development, including a failure of articular disk separation from the condyle, and persistence of interzone cells between the glenoid fossa and the articular disk-like structure (Gu *et al*, 2014). In contrast, augmented BMPR1A signaling in CNC cells (*caBmpr1a;Wnt1-Cre* transgenic mice) inhibits osteogenesis in the glenoid fossa and induces ectopic primary cartilage formation (normally secondary cartilage formation in the developing condyle) in the condylar primordium (Gu *et al*, 2014).

Epithelial growth factor signaling

MIG6 (*aka* ERRFI1) acts as a negative regulator of epidermal growth factor receptor (EGFR) family members. MIG6 is essential for maintaining the integrity of postnatal synovial joints, and loss of *Mig6* (*Mig6*$^{-/-}$) leads to the formation of large osteophytes along with the degradation of articular cartilage and subchondral cyst formation in the joints, including the knee, ankle, and TMJ in mice at approximately 1 month of age (Zhang *et al*, 2005). The onset of the OA-like phenotype in *Mig6*$^{-/-}$ mice likely involves mechanical stress on the joints in life (Staal *et al*, 2014). Osteophyte formation, which appears at the edge of the meniscus as newly formed cartilage rich in proteoglycans and collagens, is the most profound pathological change observed in the knee joints of *Mig6*$^{F/F}$*;Col2a1-Cre* mice, followed by chondrocyte maturation, hypertrophy, and mineralization (Staal *et al*, 2014). The formation of osteophytes is likely the result of inappropriate cell proliferation in the absence of *Mig6*. EGFR signaling is overactivated in chondrocytes of the articular cartilage and in the osteophyte of *Mig6*$^{F/F}$*;Col2a1-Cre* knee joints (Staal *et al*, 2014). Interestingly, *Mig6*$^{F/F}$*;Col2a1-Cre* mice exhibit aggressive OA-like phenotype only in the knee joints (rare in the TMJ and the ankle), suggesting that the other cell types (*Col2a1*-negative cells) may be responsible for the OA-like phenotype in the TMJ.

WNT/β-catenin signaling

β-Catenin (CTNNB1) is critical for the induction of TMJ cartilage degeneration (Wang *et al*, 2014). The conditional constitutive activation of the *Ctnnb1* gene in TMJ cartilage (*Ctnnb1(ex3);Col2-CreER*) leads to an OA-like phenotype in mice after 1 month of age (Wang *et al*, 2014). The deletion of *Mmp13* (matrix metallopeptidase 13; *aka* collagenase 3) or *Adamts5* (a disintegrin and metalloproteinase with thrombospondin motif 5), which are the key enzymes for cartilage degradation, partially restores the OA-like phenotype in *Ctnnb1(ex3);Col2-CreER* mice in the cartilage thickness and area (Wang *et al*, 2014).

Fibroblast growth factor signaling

Mice with a knock-in mutation of *Fgfr3*, which significantly enhances the affinity of fibroblast growth factor (FGF) receptor type III (FGFRIII) to FGF ligands, (*Fgfr3*^{P244R} mice) display early degenerative changes of condylar articular cartilage, abnormal development of the articular eminence/glenoid fossa, and fusion of the articular disk in the TMJ at postnatal day 21, following reduced cell proliferation, diminished *Sox9* and *Col10* expression, and a compromised trabecular bone network underlying the cartilage (Yasuda *et*

al, 2012). The *Sprouty* genes, *Spry1* and *Spry2*, encode intracellular inhibitors of receptor tyrosine kinase signaling pathways, including FGF signaling. *Spry1* and *Spry2* are highly expressed in muscles attached to the TMJ. Mice with combined inactivation of *Spry1* and *Spry2* (*Spry1*$^{-/-}$;*Spry2*$^{-/-}$ mice) exhibit overgrowth of lateral pterygoid and temporal muscles and regression of the developing mandibular fossa, and smaller condylar cartilage compared to controls (Purcell *et al*, 2012).

Parathyroid hormone-related peptide signaling

Parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTHrP) regulate calcium homeostasis; PTHrP further regulates growth and development. Mice with constitutively active PTH/PTHrP receptor expression in bone (*Col1-caPPR* mice) show abnormal growth and disruption of postnatal TMJ. The condylar cartilage is mostly composed of immature chondrocytes and fibroblastic cells, with only an occasional island of hypertrophic chondrocytes (Tsutsui *et al*, 2008).

Discoidin signaling

Disordered cell matrix interactions play a central role in the pathogenesis of OA (Lam *et al*, 2007). Mice with the deletion of discoidin domain receptor tyrosine kinase 1 (*Ddr1*$^{-/-}$ mice) exhibit a high incidence of OA in the TMJ beginning at as early as 9 weeks of age with typical signs of OA, including surface fissures, loss of proteoglycans, chondrocyte cluster formation, upregulated *Col1a1* expression, and atypical collagen fibril arrangements (Schminke *et al*, 2014). Loss of *Ddr1* causes major changes in ECM components. *Ddr1*$^{-/-}$ mice exhibit a greater relative bone mineral density of the subchondral bone. *Ddr1*$^{-/-}$ chondrocytes from the TMJ exhibit decreased expression of *Col2a1, Col3a1, Col9a1, Aggrecan* (*Acan*), and *Sox9*, and increased expression of *Nidogen-2* (*Nid2*) and *Runx2*. Moreover, loss of the superficial cartilage layer, deep surface fissures, and destroyed condylar surface are observed in *Ddr1*$^{-/-}$ mice. Interestingly, expression of hedgehog interacting protein (HHIP), which is overexpressed in human OA and in cartilage from other OA mouse models, is increased in *Ddr1*$^{-/-}$ mice (Schminke *et al*, 2014). In addition, vascular endothelial growth factor A (VEGF-A), which is associated with the wingless in Drosophila (WNT) pathway in OA pathogenesis and angiogenesis, and MMP13 are increased in *Ddr1*$^{-/-}$ chondrocytes, followed by the degradation of collagens (Schminke *et al*, 2014). Thus, the loss of *Ddr1* influences OA pathogenesis through the increased expression of *Mmp13, ColIa1, Runx2*, etc., and results in the change of ECM components.

Conclusion

There are limited numbers of studies using mouse genetic models for TMD and TMJ OA. The molecular mechanism of TMD and TMJ OA is presumably different from the pathogenesis of knee joint OA because of differences in the structure and origin of cells that give rise to TMJ structures. The further characterization of CNC cells (a source of TMJ structures) in the TMJ will facilitate the understanding of normal development of the TMJ and its dysfunction (TMD and TMJ OA). Recent studies suggest that mechanical stress is a key factor to induce and progress TMD with a combination of some intent with genetics.

Acknowledgments

This study was supported by start-up fund to J. Iwata.

References

Benjamin M, Ralphs JR. Biology of fibrocartilage cells. Int Rev Cytol. 2004; 233:1–45. [PubMed: 15037361]

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; 125:729–742. [PubMed: 18514492]

Gu S, Wu W, Liu C, et al. BMPRIA mediated signaling is essential for temporomandibular joint development in mice. PLoS ONE. 2014; 9:e101000. [PubMed: 25093411]

Herring SW. TMJ anatomy and animal models. J Musculoskelet Neuronal Interact. 2003; 3:391–394. discussion 406-7. [PubMed: 15758330]

Hinton RJ. Genes that regulate morphogenesis and growth of the temporomandibular joint: a review. Dev Dyn. 2014; 243:864–874. [PubMed: 24668501]

Hinton RJ, Serrano M, So S. Differential gene expression in the perichondrium and cartilage of the neonatal mouse temporomandibular joint. Orthod Craniofac Res. 2009; 12:168–177. [PubMed: 19627518]

Huang B, Takahashi K, Sakata T, et al. Increased risk of temporomandibular joint closed lock: a case–control study of ANKH polymorphisms. PLoS ONE. 2011; 6:e25503. [PubMed: 22003394]

Ishizuka Y, Shibukawa Y, Nagayama M, et al. TMJ degeneration in SAMP8 mice is accompanied by deranged Ihh signaling. J Dent Res. 2014; 93:281–287. [PubMed: 24453178]

Jiao K, Zhang M, Niu L, et al. Overexpressed TGF-beta in subchondral bone leads to mandibular condyle degradation. J Dent Res. 2014; 93:140–147. [PubMed: 24309371]

Kanyama M, Kuboki T, Kojima S, et al. Matrix metalloproteinases and tissue inhibitors of metalloproteinases in synovial fluids of patients with temporomandibular joint osteoarthritis. J Orofac Pain. 2000; 14:20–30. [PubMed: 11203734]

Kinumatsu T, Shibukawa Y, Yasuda T, et al. TMJ development and growth require primary cilia function. J Dent Res. 2011; 90:988–994. [PubMed: 21566205]

Lam NP, Li Y, Waldman AB, et al. Age-dependent increase of discoidin domain receptor 2 and matrix metalloproteinase 13 expression in temporomandibular joint cartilage of type IX and type XI collagen-deficient mice. Arch Oral Biol. 2007; 52:579–584. [PubMed: 17125729]

Li X, Liang W, Ye H, Weng X, Liu F, Liu X. Overexpression of Shox2 leads to congenital dysplasia of the temporomandibular joint in mice. Int J Mol Sci. 2014a; 15:13135–13150. [PubMed: 25062348]

Li X, Liu H, Gu S, et al. Replacing Shox2 with human SHOX leads to congenital disc degeneration of the temporomandibular joint in mice. Cell Tissue Res. 2014b; 355:345–354. [PubMed: 24248941]

Michikami I, Fukushi T, Honma S, et al. Trps1 is necessary for normal temporomandibular joint development. Cell Tissue Res. 2012; 348:131–140. [PubMed: 22427063]

Mori-Akiyama Y, Akiyama H, Rowitch DH, de Crombrugghe B. Sox9 is required for determination of the chondrogenic cell lineage in the cranial neural crest. Proc Natl Acad Sci USA. 2003; 100:9360–9365. [PubMed: 12878728]

Naidoo LC. Disorders of the temporomandibular joint: a review of anatomical concepts. J Dent Assoc S Afr. 1995; 50:461–466. [PubMed: 8613574]

Nozawa-Inoue K, Amizuka N, Ikeda N, Suzuki A, Kawano Y, Maeda T. Synovial membrane in the temporomandibular joint–its morphology, function and development. Arch Histol Cytol. 2003; 66:289–306. [PubMed: 14692685]

Ochiai T, Shibukawa Y, Nagayama M, et al. Indian hedgehog roles in post-natal TMJ development and organization. J Dent Res. 2010; 89:349–354. [PubMed: 20200412]

Pace JM, Li Y, Seegmiller RE, Teuscher C, Taylor BA, Olsen BR. Disproportionate micromelia (Dmm) in mice caused by a mutation in the C-propeptide coding region of Col2a1. Dev Dyn. 1997; 208:25–33. [PubMed: 8989518]

Purcell P, Joo BW, Hu JK, et al. Temporomandibular joint formation requires two distinct hedgehog-dependent steps. Proc Natl Acad Sci USA. 2009; 106:18297–18302. [PubMed: 19815519]

Purcell P, Jheon A, Vivero MP, Rahimi H, Joo A, Klein OD. Spry1 and spry2 are essential for development of the temporomandibular joint. J Dent Res. 2012; 91:387–393. [PubMed: 22328578]

Ricks ML, Farrell JT, Falk DJ, et al. Osteoarthritis in temporomandibular joint of Col2a1 mutant mice. Arch Oral Biol. 2013; 58:1092–1099. [PubMed: 23518238]

Schminke B, Muhammad H, Bode C, et al. A discoidin domain receptor 1 knock-out mouse as a novel model for osteoarthritis of the temporomandibular joint. Cell Mol Life Sci. 2014; 71:1081–1096. [PubMed: 23912900]

Scrivani SJ, Keith DA, Kaban LB. Temporomandibular disorders. N Engl J Med. 2008; 359:2693–2705. [PubMed: 19092154]

Shen G, Darendeliler MA. The adaptive remodeling of condylar cartilage—a transition from chondrogenesis to osteogenesis. J Dent Res. 2005; 84:691–699. [PubMed: 16040724]

Shen M, Luo Y, Niu Y, et al. 1,25(OH)2D deficiency induces temporomandibular joint osteoarthritis via secretion of senescence-associated inflammatory cytokines. Bone. 2013; 55:400–409. [PubMed: 23624390]

Shibata S, Suda N, Yoda S, et al. Runx2-deficient mice lack mandibular condylar cartilage and have deformed Meckel's cartilage. Anat Embryol. 2004; 208:273–280. [PubMed: 15156401]

Shibukawa Y, Young B, Wu C, et al. Temporomandibular joint formation and condyle growth require Indian hedgehog signaling. Dev Dyn. 2007; 236:426–434. [PubMed: 17191253]

Staal B, Williams BO, Beier F, Vande Woude GF, Zhang YW. Cartilage-specific deletion of Mig-6 results in osteoarthritis-like disorder with excessive articular chondrocyte proliferation. Proc Natl Acad Sci USA. 2014; 111:2590–2595. [PubMed: 24550287]

Tanaka E, Detamore MS, Mercuri LG. Degenerative disorders of the temporomandibular joint: etiology, diagnosis, and treatment. J Dent Res. 2008; 87:296–307. [PubMed: 18362309]

Timms AE, Zhang Y, Bradbury L, Wordsworth BP, Brown MA. Investigation of the role of ANKH in ankylosing spondylitis. Arthritis Rheum. 2003; 48:2898–2902. [PubMed: 14558096]

Tsutsui TW, Riminucci M, Holmbeck K, Bianco P, Robey PG. Development of craniofacial structures in transgenic mice with constitutively active PTH/PTHrP receptor. Bone. 2008; 42:321–331. [PubMed: 18063434]

Wang L, Detamore MS. Tissue engineering the mandibular condyle. Tissue Eng. 2007; 13:1955–1971. [PubMed: 17518708]

Wang Y, Liu C, Rohr J, et al. Tissue interaction is required for glenoid fossa development during temporomandibular joint formation. Dev Dyn. 2011; 240:2466–2473. [PubMed: 21953591]

Wang M, Li S, Xie W, et al. Activation of beta-catenin signalling leads to temporomandibular joint defects. Eur Cells Mater. 2014; 28:223–235.

Xu L, Flahiff CM, Waldman BA, et al. Osteoarthritis-like changes and decreased mechanical function of articular cartilage in the joints of mice with the chondrodysplasia gene (cho). Arthritis Rheum. 2003; 48:2509–2518. [PubMed: 13130470]

Yasuda T, Mundy C, Kinumatsu T, et al. Sulfotransferase Ndst1 is needed for mandibular and TMJ development. J Dent Res. 2010; 89:1111–1116. [PubMed: 20554886]

Yasuda T, Nah HD, Laurita J, et al. Muenke syndrome mutation, Fgf R3P(2)(4)(4)R, causes TMJ defects. J Dent Res. 2012; 91:683–689. [PubMed: 22622662]

Zhang YW, Su Y, Lanning N, et al. Targeted disruption of Mig-6 in the mouse genome leads to early onset degenerative joint disease. Proc Natl Acad Sci USA. 2005; 102:11740–11745. [PubMed: 16087873]

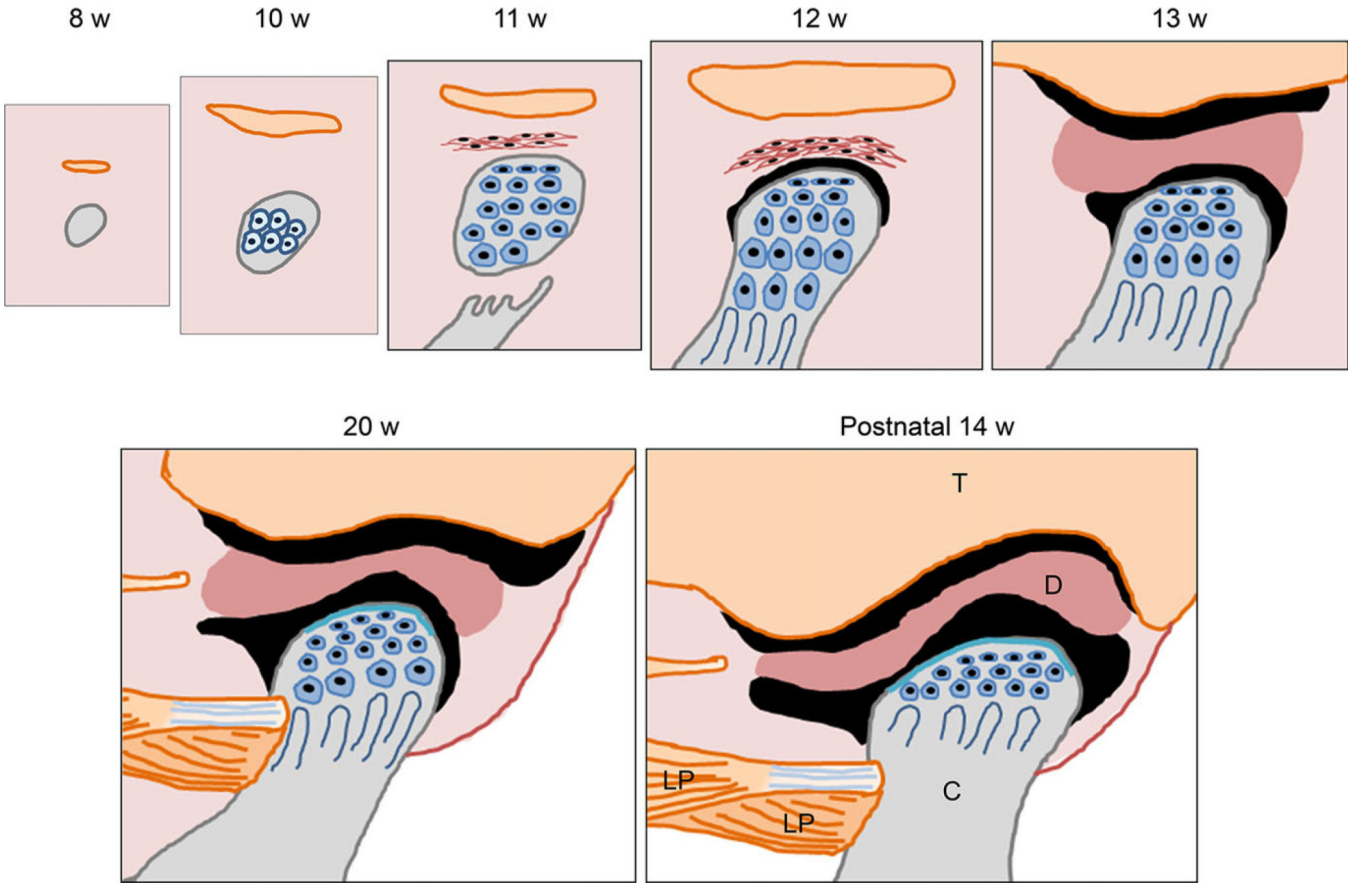

Figure 1.

Time course of temporomandibular joint development in humans. At the 8th week of gestation, mesenchymal condensation forms at the TMJ region. Orange, mesenchymal condensation of the future temporalis bone; gray, mesenchymal condensation of the future mandibular condyle. At the 10th week of gestation, mesenchymal cells differentiate into chondrocytes and start to form the core of cartilage which is the future mandibular condyle. The temporal bone starts intramembranous ossification. During the 11th week of gestation, intramembranous ossification of the ramus of the mandible reaches the base of the future condyle. There are no joint cavities during this stage. The mesenchymal condensation that forms the anlage of the articular disk appears in connective tissue between the anlage of the temporal bone and the mandibular condyle. During the 12th week of gestation, a small space or cleft appears between the anlage of the articular disk and the mandibular condyle that defines the initial formation of the lower articular cavity. During the 13th week of gestation, the organization of the upper articular cavity starts between the temporal bone and the articular disk. At approximately 20th week of gestation, the glenoid fossa of the temporal bone forms, but the articular surface of the temporal bone has a flat surface. At postnatal 14th week, the glenoid fossa and the articular eminence of the temporal bone well form and fit with the shape of the mandibular condyle. T: the temporal bone, D: the articular disk, C: the mandibular condyle, LP: the lateral pterygoid muscle

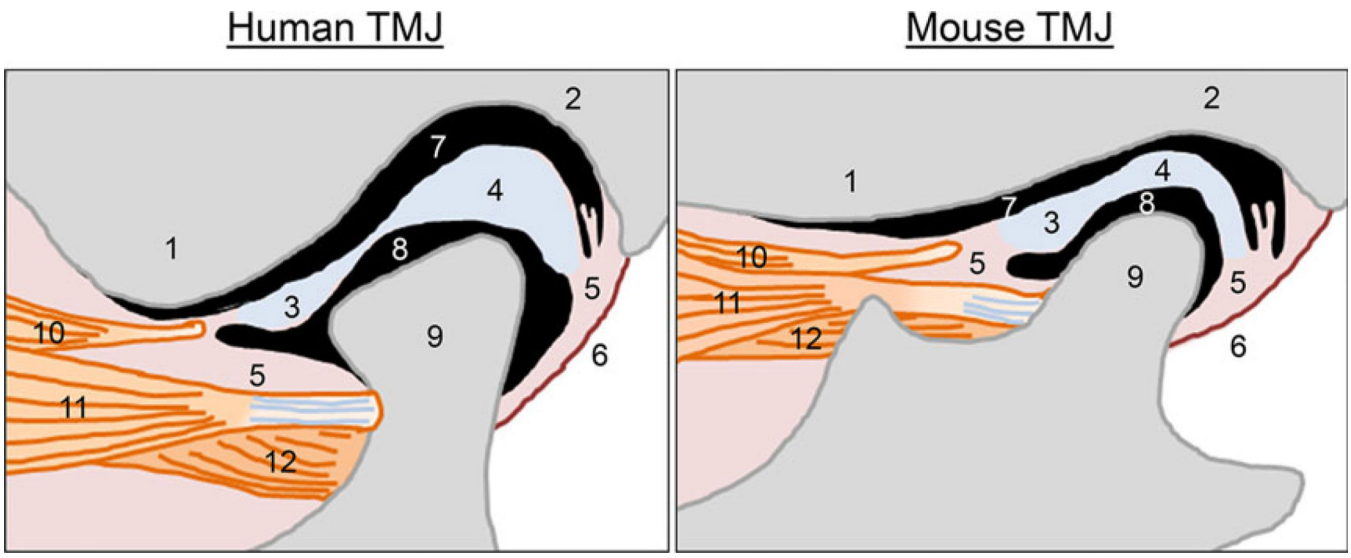

Figure 2.

Comparison of the structure of the temporomandibular joint between humans and mice. TMJ, temporomandibular joint. 1: the articular eminence of the temporal bone, 2: the glenoid fossa of the temporal bone, 3: anterior band of the articular disk, 4: posterior band of the articular disk, 5: connective tissue, 6: the posterior joint capsule, 7: the upper articular cavity, 8: the lower articular cavity, 9: mandibular condyle, 10: a part of upper head of the lateral pterygoid muscle, associated with the articular disk, 11: upper head of the lateral pterygoid muscle, connected with the mandibular condyle, 12: lower head of the lateral pterygoid muscle, connected with the mandibular condyle