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Review

Development of temporomandibular joint arthritis: The use of animal models

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ABSTRACT

Osteoarthritis is the most common joint disease affecting roughly one sixth of the human population. It is also the most common arthritis affecting the temporomandibular joint, often leading to severe pain and the inability to masticate. Animal models are essential to investigate the disease in part because they lend themselves to genetic manipulation and various treatments and also because of the lack of availability of human specimens from various stages of the disease. The wide range of osteoarthritis models alone are a proof of its multifactorial origin. Manipulation of collagen, cytokine, matrix metalloproteinase and small leucine-rich repeat proteoglycan genes can all have an effect on the development and persistence of arthritis. Surgical models also exist, highlighting the importance of normal anatomy and trauma. Here we review the English literature of murine models of temporomandibular joint arthritis with special attention to the genetic and molecular background of osteoarthritis.
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1. Introduction

Osteoarthritis (OA) is the most common joint disease characterized by progressive softening and disintegration of the articular cartilage. The basic characteristics of the disease are similar in many species including humans. Murine models of OA are very important in gaining more information about this disease, especially because the presence of OA can be observed in nearly all inbred strains of laboratory mice as part of the joint tissue's ageing process. Animal models are an excellent tool to investigate the molecular background and development of the disease as these are well conserved in animal models. However, the anatomy of the joint varies in different mammalian groups and so does its morphology and function [1]. Therefore animal models have limited use in studying temporomandibular disorders as they do not show the typical symptoms [2].

The temporomandibular joint (TMJ) is composed of two bones, the mandibular condyle and the glenoid fossa of the temporal bone separated by a fibro cartilaginous disc (Fig. 1). Compared to other joints in the body, TMJ exerts unique properties as it is exposed only to limited load-bearing forces [3] and it has different morphological, functional, biomechanical and biological features [4]. Histologically, the most superficial cellular layer is a fibrocartilage, primarily consisting of type I collagen (CI), whilst the remaining deeper cellular zones contain type II collagen (CII) [5]. This is a unique feature of the TMJ compared to other joints containing hyaline cartilage, which are made entirely of CII. The developmental origin of the fibrocartilage of the TMJ is also different compared to the origin of hyaline cartilage as it develops independently from the chondroskeleton. The cartilage has two roles, it acts as an articular joint cartilage and also as a site for enchondral ossification. Consequently, compared to other joints, it is more likely that cellular events occurring within the TMJ cartilage and subchondral bone may influence tissue homeostasis [6].

In mice, the mandibular condyle reaches skeletal maturity by the eight postnatal week. Until the end of development, the condylar articular surface covers 4-5 rows of flattened fibroblasts. Above and below this level, light microscopic investigations revealed the presence of CI. By 8 weeks, the articular surface presents a smooth outline, but there are marked changes in the internal organization of various cell types including decrease in the number of progenitor cells. Immediately following skeletal maturation, the entire condyle undergoes pronounced remodelling, showing

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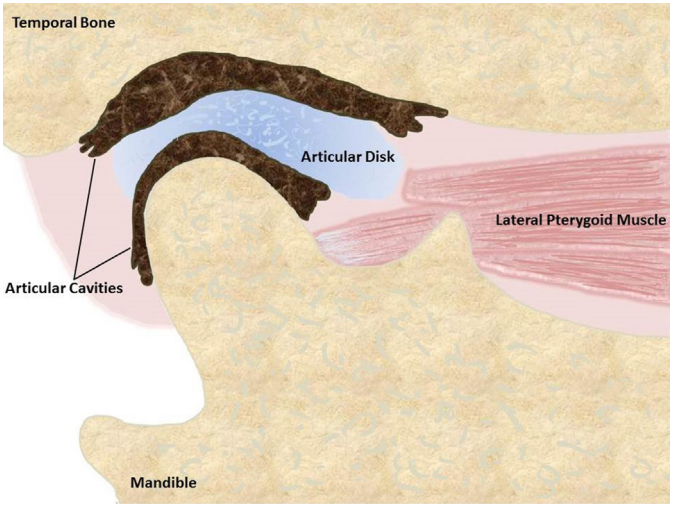

Fig. 1. Anatomical sketch of the temporomandibular joint.

marked alteration of its internal and external architecture. With the advancement of age, there is qualitative decrease in PG content. A layer of amorphous material appears over the articular surface and there is increased surface labelling with colloidal iron accompanied by changes in the appearance of the collagenous component of the tissue. Collagen fibres become closely packed and change their orientation. Light microscopic investigations revealed that with increasing age, the cartilage was reduced to a thin crescentic band. The articular surface at this stage still has a smooth outline, and the number of surface cells reduces and their shape becomes rounded. These cells are still evenly distributed though. In the deeper layer, there are unevenly distributed hypertrophic cells separated by a large amount of extracellular matrix (ECM). The distance between the articular cartilage and the underlying vasculature is decreased. These cells lack deep metachromasia. At 7 months, almost all mice of this strain develop arthropathy in the TMJ [7]. First, there is failure of staining with acidic toluidine blue and clustering of chondrocytes is observed. Later, the articular surface becomes irregular, and superficial clefts appear. In more advanced stages, deeper cracks develop and the articular surface loses fibrocartilage. The articular space decreases as a result of fibrous ankylosis of the joint [8].

2. Murine TMJ OA models

There are multiple TMJ OA models indicating that the pathogenesis of OA has not yet been fully elucidated. These models range from surgical procedures to genetic manipulations. There are also idiopathic models: C57BL/6S mice develop spontaneous OA from 12 weeks of age. At 24–36 weeks, clefts in the cartilage layer is observed along with reduction in the number and irregular alignment of chondrocytes accompanied by detachment or disappearance of the fibrous layer. From 36 weeks, formation of chondrocyte clusters and growth of cells in the synovial membrane toward the surface of the cartilage have been noted. By 72 weeks, deep clefts develop in the bone, the presence of osteophytes and partial detachment of the chondrocyte layer become characteristic feature [9]. It is known that obesity is a major risk factor for the development of OA in both weight bearing and non-weight bearing joints. However, unlike in the knee joint, C57BL/6J mice show no significant cartilage loss in the TMJ when compared to mice on normal diet, indicating that the adipose associated inflammation does not contribute to the OA in TMJ [10].

Partial discectomy of the TMJ results in articular degeneration starting from 4 weeks. Chondrocyte clusters appear at 9 weeks, PG staining and fibrillation of cartilage at 12 weeks and loss of articular cartilage by 16 weeks [11]. Primary OA-like disease develops by the age of 7 months in ICR mice after injection of triamcinolone diacetate for 8 consecutive weeks [8].

Mutations in the genes coding for CII (*COL2A1*), CIX (*COL9A1*, *COL9A2* and *COL9A3*) and CXI (*COL11A1* and *COL11A2*) are responsible for early onset OA associated with variable degrees of chondrodysplasia in humans [12]. Several murine gene-deficient ("knockout" [KO]) models have been produced, which resemble the above diseases. Deletion in the *COL2A1* gene disturbs the assembly and processing of the homotrimeric CII molecule in the cartilage resulting in severe chondrodysplastic phenotype with short limbs, hypoplastic thorax, abnormal craniofacial development and other skeletal deformities. The mutation interferences with normal enchondral ossification [13]. There is reduced number of small chondrocytes in an unorganized setting in the TMJ of these mice, which results in the cartilage being sealed off by bone. By 3 months, the height of the condylar cartilage is decreased, the chondrocytes form clusters and became disorganized. At 6 months, the cartilage is decreased and small areas without chondrocytes become visible and the normal columnar arrangement of chondrocytes in the osteochondral junction is also disturbed. At 9 months, there is intra-articular fibrous adhesion between the condylar articular surface and the disc and vertical splits between chondrocytes became apparent. The columnar appearance is completely diminished by this time. By 15 months, the condyles are largely resorbed and the condylar surface is covered with fibrotic tissue or the joint is fused [14]. CVI-deficient (*COL6A1*-KO) mice also develop early onset OA but other than smaller stature and slower ossification, there are no apparent abnormalities. The collagen of these mice shows significantly reduced mechanical properties [15]. Homozygous mutant mice lacking CIX (inactivated *COL9A1* gene) show no detectable abnormalities, but develop early onset OA in the knee joints [16]. CXI-deficient (*COL11A1*-KO) mice also develop OA-like degenerative changes in the knee and TMJ. These changes start at 3 months but become more severe as time passes. This defect is also associated with increased production of matrix metalloproteinases (MMP-3 and MMP-13) in the joints [12].

Biglycan and fibromodulin are also key players in regulating chondrogenesis and ECM turnover during the development of TMJ OA pathology. As transforming growth factor β1 (TGF-β1) binds to these proteins, in their absence, TGF-β1 accumulates which leads to overactive signal transduction leading to increased chondrogenesis and ECM turnover. As a result, mice lacking these proteins show abnormal growth and differentiation of condylar chondrocytes and accelerated aggrecan content loss in the mandibular cartilage leading to TMJ OA [4,17].

Col1-IL1β^{XAT} transgenic mice overexpress interleukin 1β (IL-1β) in the TMJ. These mice are characterized by most features of OA associated with orofacial grooming and decreased resistance to mouth opening suggesting joint pain and dysfunction [18].

3. The role of cytokines in murine models of TMJ OA

TGF-β is a secretory polypeptide, which acts as a paracrine regulator of cell proliferation and ECM formation [19]. TGF-β1 is a potent regulator of chondrogenesis and plays an essential role during OA pathology [4]. ECM controls the formation and degradation of TMJ condylar cartilage by regulating availability of active TGF-β1. TGF-β1 increases the proliferation of mesenchymal chondroprogenitor cells (MCCs) [20], induces expression of transcription factors *Sox5*, *Sox6* and *Sox9*, which are critical for chondrogenesis. It also stimulates the expression of ECM genes including those of aggrecan (*AGG*), CII (*COL2A1*) and CX (*COL10A1*)

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[4]. In the bone, TGF-β1 increases proliferation and ECM synthesis by osteoblasts, inhibits of the synthesis of cartilage degrading enzymes and induces the production of tissue inhibitors of metalloproteinases (TIMPs). This growth factor also inhibits the destructive effects of IL-1 on the ECM. As described above, biglycan and fibromodulin bind to members of the TGF superfamily and regulate their effects on bone marrow stroma cells, osteoblasts and tendon stem/precursor cells by sequestering the growth factors within the ECM [21]. Mice deficient in biglycan and fibromodulin exhibit sequestration of TGF-β1 in the ECM leading to overactive signal transduction. First, it results in induced chondrogenesis, CII and aggrecan production but ultimately it leads to imbalance in ECM turnover, loss of CII and aggrecan leading to degradation of the cartilage. These changes present earlier in these gene-deficient mice than in their wild type counterparts [4]. Other investigators found that the stimulatory/inhibitory effect of TGF-β1 depended on its concentration: TGF-β1 exerts inhibitory effects at lower concentrations, while it is stimulatory at higher levels [20]. ADAMTS are major aggracanases and play a pivotal role in OA of other joints [22,23]. TGF-β1 also up regulates ADAMTS4 leading to the cleavage of aggrecan [24]. TGF-β1 acts synergistically with other growth factors, such as insulin-like growth factor 1 (IGF-1) [19]. In advanced TMJ OA, IGF-1 is upregulated in order to induce repair processes [25]. Cultures of MCC explants supplemented with TGF-β, TGF-β+IGF-1 or growth hormone (GH) show increased height and area of toluidine blue staining indicating the presence of cartilage production [26].

IL-1α and IL-1β are catabolic cytokines, which has an inhibitory effect on cell proliferation, ECM synthesis and alkaline phosphatase (ALP) production [20]. Increased IL-1β levels have been associated with the development of joint pathology in OA. There may be an inverse correlation between TGF-β and IL-1β production during the development of joint pathology. Low levels of TGF-β have been associated with high levels of IL-1β, and vice versa. This occurs through inhibition of TGF-β expression through the IL-1RI receptor. Abrogation of IL-1β signalling in IL-1RI-KO mice prevented the development of OA [27]. As mentioned above, Col1-IL1β^{XAT} transgenic mice overexpress IL-1β in their TMJ. Pathologic changes in these mice occur the articular cartilage but not the in the bone. These changes include superficial fibrillations, articular surface erosions and chondrocyte cloning accompanied by and apparent loss of PG content. There is induction of mediators of inflammation associated with cartilage destruction including IL-6, cyclooxygenase 2 (COX-2) and MMP-9 [18].

4. The role of biglycan and fibromodulin

As described above, biglycan and fibromodulin are members of the small leucine-rich repeat PG family (SLRPs) and are highly expressed in bone, tendon and cartilage. The ECM is important in maintaining the mandibular condylar cartilage integrity. Biglycan and fibromodulin are important in regulating chondrogenesis and ECM turnover during TMJ OA pathology. These SLRPs are able to maintain ECM structure by interacting with the network of cartilage proteins and can mediate cell metabolism by binding to members of the TGF-β superfamily [21,28]. Both biglycan and fibromodulin bind to TGF-β1 and cause sequestration of this growth factor within the ECM [28]. Deficiency of the *BGN* or *FMOD* gene in mice leads to increased free active TGF-β1 in the condylar cartilage, which results in increased TGF-β1 signalling in MCCs. Abundant TGF-β1 signalling in the absence of *BGN* and *FMOD* increases turnover in mandibular condylar cartilage by increasing both ECM protein synthesis, as well as degradation by MMPs [4,6]. The degradation of CII but not that of aggrecan is a key feature of TMJ OA [6]. The switch to MCC degeneration dominance over formation occurs much earlier than in wild type mice leading to early onset OA in TMJ [4].

BGN- or *FMOD*-KO mandibular condylar cartilage exerts increased cellularity compared with wild-type cartilage and has expanded articular and mature zones. The hypercellularity is likely attributable to increased proliferation of MCCs. The expression of CII is 1.6-fold, while that of aggrecan is 4.2-fold higher than in wild-type MCCs. There is also increased expression of *AGG*, *COL2A1* and *COL10A1* genes. The accelerated loss of aggrecan content is due to increased degradation of this protein by aggrecanases [6]. There is also a redistribution of CII as the expression of CII is localised distally from the articular surface, which indicates that the articular zone is expanded. CI levels are also higher but this is accompanied by more extensive degradation of this protein. Increased toluidine blue and safranin O staining indicates higher amount of PG deposition in the ECM. There is also notable CX expression in gene-deficient, but not in the wild type mice. The glucosaminoglycan (GAG) content is similar in KO and wild type animals at 12 weeks, however, GAG content becomes significantly decreased by 32 weeks in the *BGN*/*FMOD*-KO mice [29]. Apoptosis of chondrocytes in the mandibular condyle is more pronounced in the absence of biglycan and fibromodulin. Suppressed chondrogenesis may not be an important contributing factor in TMJ OA pathology seen in *BGN*/*FMOD*-KO animals. However, there is decreased amount of bone in the subchondral bone region of the TMJ in mice as a result of increased osteoclast (OC) activity and bone turnover. As a consequence of high bone turnover, there is defective trabecular bone structure formation in the subchondral region, which may be a relevant contributor to OA pathology [29] (Tables 1 and 2). Q2

Altogether 22 genes show differential expression in the TMJs of *BGN*/*FMOD*-deficient mice. Down-regulated genes coding for other ECM proteins involved in cartilage degeneration include procollagen type IX α3, procollagen type II α1, procollagen type IX α1, as well as matrilin 3. At least five genes exert differential expression, which are related to osteoclast function/differentiation and bone turnover. These include genes of CART prepropeptide, secreted frizzled-related sequence protein 1 (SFRP1), arylsulfatase K, solute carrier family 4 member 1 (SCF4M1) and protein tyrosine phosphatase receptor type V. CART prepropeptide inhibits bone resorption by modulating RANKL expression, while SCF4M1 is a critical mediator of both osteoclast differentiation and function. The disruption of bone and cartilage metabolism in younger mice could disrupt the overall TMJ tissue homeostasis. This predisposes the mice to late-onset TMJ OA that is associated with osteophyte formation, TMJ subchondral bone sclerosis and cartilage degeneration [6,14,17,29].

5. The role of various types of collagen in murine models of TMJ OA

Several murine gene-deficient models have been developed that resemble OA in TMJ and other joints. Among various types of collagen, deletion in the *COL2A1* gene disturbs the assembly and processing of the homotrimeric CII molecule within the cartilage. Homozygous *COL2A1*-KO mice have short axial skeleton and develop respiratory distress, which results in perinatal death. Heterozygous *Col2A1* +/− mice exert smaller stature, hypo plastic chest, abnormal craniofacial development and other skeletal deformities compared to wild type mice. This mutation interferes with normal enchondral ossification. The amount of cartilage at the cranial base is also reduced. These mice have severe defects in their TMJ. They develop progressive OA lesions from the age of six months. Features of TMJ OA include shorter synchondroses, deranged organisation of cells, reduction of the number and size of chondrocytes and decreased amount of ECM in the TMJs [13,14].

CVI-deficient (*COL6A1* −/− and +/−) mice also develop early onset OA but, other than smaller stature and slower ossification,

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Table 1
Mouse strains and phenotypes.

	Mouse strains	Effect
Type II collagen	*Col2A1* −/−	Homozygous: short axial skeleton; respiratory distress; perinatal death
	Col2A1 +/−	Heterozygous: smaller stature; size of cartilaginous structures of the cranial base reduced; severe TMJ defects, progressive OA lesions from six months; shorter synchondroses; deranged organisation of cells; reduction of number and size of chondrocytes and amount of ECM
Type VI collagen	*Col6A1* −/−, +/−	No apparent abnormalities Lower body weight Reduced mechanical properties of collagen Accelerated age dependent OA Delayed ossification and reduced mineral density Lower linear elastic behaviour
Type IX collagen	*Col9a1* −/−	Early OA starting at the age of three months Normal development
Type XI collagen	*Col11a1* (cho)+/−	Homozygous: lethal Heterozygous: normal development, no skeletal abnormalities at birth; early OA starting at three months of age
TGF-β		In the cartilage: chondrogenesis regulator; increases MCC proliferation; stimulates ECM genes increases expression of transcription factors In the bone: osteoblast ECM synthesis; cartilage degrading enzyme inhibitor; TIMP inductor; inhibits destructive effect of IL-1 on ECM; biglycan and fibromodulin binds to it; up regulates ADAMTS4 leading to cleavage of aggrecan; synergistic with IGF-1
IL-1β	IL-1β KO Col1-IL1β^{XAT}	Inhibitory effect on cell proliferation ECM synthesis ALP production IL-1RI-KO mice: no development of OA; Col1-IL1β^{XAT} mice Overexpress IL-1β Superficial fibrillations Articular surface erosions Apparent loss of PG content
Biglycan and Fibromodulin	Double KO mice	Interacts with the network of cartilage proteins Mediate cell metabolism by binding to members of the TGF-β1 which results in sequestration in the ECM Double KO mice: early onset OA; increased condylar cartilage cellularity (increased proliferation of MCCs); increased expression of AGG, COL2A1 and COL10A1 genes; increased degradation of aggreccan by aggreccanases; CI degradation; redistribution of CII; CX expression; reduced GAG content by 32 weeks; pronounced apoptosis of chondrocytes; decreased amount of bone in the subchondral region as a result of increased osteoclast activity and bone turnover; defective trabecular bone formation

there are no apparent abnormalities. The collagen of these mice shows significantly reduced mechanical properties and lower linear elastic behaviour. Delayed ossification and reduced bone mineral density is also characteristic for these mice [15].

Homozygous mutant mice lacking the CIX (*COL9A1*) gene exert no detectable abnormalities, but develop early onset OA in the TMJ and knee joints starting at the age of three months. Otherwise these animals exhibit normal development [16,30].

CXI (*COL11A1*) homozygous mutation is lethal in mice. Animals showing heterozygous mutations (*COL11A1* +/−) have normal development and they have no skeletal abnormalities at birth, however, they develop early OA-like degenerative changes by three months of age in the knees and TMJs. These changes become more severe with age. This genetic defect has also been associated with increased MMP-3 and MMP-13 production and ECM degradation in the knee joints [12,31].

Table 2
Matrix metalloproteinases.

MMP	Role	Localization
MMP-1	Not present in mice	
MMP-2	Early role in growth and housekeeping of normal cartilage turnover	Young: chondroblastic and hypertrophic zones Old: articular surface, in cartilage
MMP-3	OA if abundant production	Detected at all times: young: immature chondrocytes in the chondroblastic and hypertrophic zones; old: articular surface, chondroblastic zone and in the hypertrophic zone
MMP-8	Collagen cleaving enzyme	Young: chondroblastic and articular surface zones Older: all regions
MMP-9	Removal of denatured collagen fragments	Constant presence in the joint (IL-1 upregulates production): young: articular surface, hypertrophic zones and in the resorption front; old: along articular surface and cartilage
MMP-13	Resorption and bone formation via enchondral ossification at the cartilage-bone interface	Cartilage-bone interface
TIMP-1	MMP inhibition	Young:articular surface, chondroblastic zone and resorption front Old: all zones
TIMP-2	MMP inhibition	Young: not at articular surface Old: articular surface and chondroblastic zones
HTRA1	Degrades molecules of pericellular matrix. Disrupts the pericellular matrix network which alters chondrocyte metabolism resultion in OA	

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6. The role of proteolytic enzymes in murine models of TMJ OA

MMPs are important for the remodelling of ECM by degrading collagen, PGs and other components of the ECM [32]. There are over 20 known MMPs. These proteases are secreted in inactive form and are activated by the ECM milieu. There are three subgroups of these enzymes: 1) collagenases, which degrade CI, CII and CIII (MMP1, MMP8 and MMP13), 2) stromelysins that digest PG and nonhelical regions of collagens (MMP3 and MMP11), as well as 3) gelatinases specific for degraded collagen and also for collagenase-resistant collagens, such as CIV, CV, CXI (MMP2, MMP9) [19,33]. The distribution pattern of the various MMPs shows high variability even within the same class of enzymes, which suggest specific but overlapping functions [34]. Expressions of MMPs are regulated on both transcriptional and post-translational levels by growth factors, cytokines and TIMPs [33,35]. Loss of balance of this regulation can lead to proteolysis and joint degradation. MMP and TIMP activities, as well as the ratio of various MMPs/TIMPs are essential for physiological remodelling of the articular cartilage and for ECM destruction in disease processes. Higher activities of MMPs at younger age are characteristic for rapid growth and differentiation [36].

Among the various MMPs, no MMP-1 mRNA has been detected in the TMJ or knee joints of mice. MMP-2 has a role in the early stages of growth and has a housekeeping function of normal cartilage turnover. Traces of MMP-2 mRNA have been detected in newborns. MMP-2 expression peaks at 2 weeks and decreases thereafter. This decrease in mRNA levels is followed by the decrease of MMP-2 protein expression. Both the active and latent forms of MMP-2 protein were detected in the TMJ and the knee joints from birth. In newborn and young animals, MMP-2 is localized in chondroblastic and hypertrophic zones and can be detected earlier than MMP-9. The activity of MMP-2 is reduced during maturation and aging and at 18 months of age it can be detected along the articular surface and within the cartilage [33,37].

Abundant production of MMP-3 has been associated with OA [38]. In the TMJ, MMP-3 mRNA expression is prominent throughout postnatal development and aging, whilst in the knee joint it is low in newborn and aged animals but high in two-week-old animals. MMP-3 expression is detected at all time points in these joints [39,40]. MMP-3 protein expression at three weeks of age is confined to immature chondrocytes in the chondroblastic and hypertrophic zones, and is less pronounced at the articular surface. At the age of 18 months, MMP-3 is expressed along the articular surface, in the chondroblastic zone and in the hypertrophic zone [12,34,41].

MMP-8 is a collagen-cleaving enzyme, which is present in the connective tissue of most mammals. In young animals, it is localized to the chondroblastic and to the articular surface zones, in older animals it can be detected in all regions of the TMJ [42].

The role of MMP-9 is removal of denatured collagen fragments that increase with deterioration of cartilage in aging joints [33]. The expression of MMP-9 mRNA is consistent with that of MMP-9 protein levels at birth and in young animals. However, while mRNA levels decrease in older animals, MMP-9 protein levels remain high. One reason for that might be the age-related elevation of pro-inflammatory cytokine (e.g. IL-1) production. These cytokines are constantly present in the synovial fluid of aging joints and they may up-regulate the expression of MMP-9 [43]. Compared to the knee joint, MMP-9 levels in the TMJ are higher in newborn and young animals. At this stage, MMP-9 can be detected at the articular surface, in hypertrophic zones and in the resorption front. Levels are lower in the chondroblastic zone. The amount of MMP-9 decreases during later phases of development, when it can be detected along the articular surface and in the cartilage. In general, MMP-9 levels are lower than MMP-2 in the TMJ [34,41].

MMP-13 cleaves CII. It is expressed in skeletal tissues where it participates in both collagen and PG degradation in hypertrophic chondrocyte-calcifying ECM [39,44,45]. In normal cartilage, MMP-13 is expressed at a very low level and it may be associated with resorption and bone formation via enchondral ossification at the cartilage-bone interface [46–48]. High levels of MMP-13 have been described in osteoarthritic cartilage. Constitutive expression of MMP-13 results in OA-like changes in mouse knee joints [11]. Higher expression of MMP-13 has been noted in COL9A1-KO mice [30]. In addition, abundant production of both MMP-3 and MMP-13 has been detected in *COL11A1*-KOmice [12]. MMP-13 mRNA is expressed throughout the development of OA [39,40]. Levels are lower in the knee joint at birth and it peaks at two weeks of age. In older animals, there is lower expression of MMP-13 in all regions [34,41]. In mice experiencing early-onset TMJ OA as a result of partial TMJ discectomy, increased expression of MMP-13 was found likely due to elevated expression of discoidin domain receptor 2 (DDR-2) [49]. DDR-2 is a cell membrane tyrosine kinase receptor that preferentially binds to native CII. Under normal conditions, there is little of no CII around chondrocytes in the pericellular region, which means that there is no contact between chondrocytes and CII in healthy mature articular cartilage [11]. Exposure of the collagen network to chondrocytes will permit interaction of CII with these cells resulting in activation of DDR-2. The activated DDR-2 induces the expression of MMP-13 [11,49,50]. The expression of both MMP-13 and DDR-2 was increased 8 weeks after partial discectomy, when degradation of PG was already evident. This suggests that inhibitors of DDR-2 might be useful for the treatment of OA [11,49]. Mice deficient in CIX and CXI also exhibit early OA as a result of increased DDR-2 and MMP-13 at 6 months of age both in the knees and in the TMJs suggesting that deficiency of these collagens may have deleterious effects on the non-weight-bearing joints as well [30,50]. Expression of high temperature requirement factor A1 (HTRA1) mRNA is increased in the TMJ in CIX-KO and CXI-haploinsufficient mice, as well as in mice that underwent TMJ discectomy. HTRA1 is a serin protease [51] that disrupts the pericellular matrix network, which alters chondrocyte metabolism resulting in OA. Expression of HTRA1 has also been associated with expression of DDR-2 in chondrocytes [52].

TIMP-1 in young mice is located in the articular surface, chondroblastic zone and at the resorption front, while TIMP-2 is not present at the articular surface. In 18-month-old animals, TIMP-1 can be detected in all zones whilst TIMP-2 is confined to the articular surface and to the chondroblastic zones in TMJ [53].

7. TMJ involvement in other murine arthritis models

Mice injected intravenously with *Staphylococcus aureus* develop septic arthritis in the TMJ four days after inoculation. Already at 2 days after inoculation, there are dilated capillaries in the discal attachments, cocci on articular surfaces and neutrophils and macrophages are visible in the condylar marrow. At 4 days, there are acute inflammatory signs, collagen fibers on the surface of the disc and structural changes in the condyles. Two weeks later, there are minor transverse fissures in the fibrous layer of the condyle. Deeper layers of the discs become involved. Later, collagen fibers in the disc and condylar surface become disrupted, and there is lymphocyte infiltration in the bone marrow. Chondrocytes continue to degenerate. Bacteria enter the joint through the synovial vessels [54].

There is little or no synovial inflammation in the TMJ of mice with PG-induced arthritis (PGIA) [55]. Mice with PGIA develop OA-like damage in the cartilage of this joint. The structural damage is mediated by aggrecanases and MMPs through loss of GAG-containing aggrecan. This is thought to be due to the constantly elevated levels of catabolic cytokines in the circulation, which

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results in a pro-inflammatory milieu in the TMJ leading to up regulation of proteolytic enzymes and loss of aggrecan from the cartilage [56].

Adjuvant-induced arthritis (AIA) has originally been described in rats [57], however, injection of Freund's adjuvant also causes TMJ arthritis in mice [53]. In this model, there are microscopic signs of arthritis three weeks after administration of adjuvant to the scalp and to the base of the tail [57].

MRL/l mice develop spontaneous immune arthropathy that resembles rheumatoid arthritis (RA) associated with synovial periarticular and perivascular inflammation, pannus and articular erosion, subcutaneous periarticular inflammation and synovial exudates [58]. Arthritis can also be observed in the TMJ, however, this joint is less often involved and the articular changes are also less severe [59].

Bilharziasis can cause arthropathy in the TMJ. Mice infected with this disease show massive chronic inflammatory cell infiltration, articular disk thickening, hyperplastic changes with narrowing of the joint space and articular surface erosions in the TMJ [60].

8. Conclusions

Osteoarthritis of the TMJ is a multifactorial disease. Different types of collagens, matrix metalloproteinases, SLRPs, cytokines and lifestyle choices all contribute to its early development but ultimately all mice develop osteoarthritis in the TMJs. Further studies are necessary to enhance our understanding of the disease and to develop ways to delay its onset.

Disclosure of interest

The authors have not supplied their declaration of competing interest. Q3

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