Review

Transgenic mouse models for studying the role of cartilage macromolecules in osteoarthritis

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Abstract

The development of transgenic technology has made possible the generation of targeted gene-mutated mouse lines suitable for use in experimental osteoarthritis (OA) research. Transgenic mice harbouring mutations in cartilage collagen types II and IX develop early-onset OA and are therefore promising models of age-related OA, even though the mice often show signs of chondrodysplasia. Also, mouse lines harbouring other engineered mutations of the extracellular molecules have given rise to early OA. The molecular background of a few spontaneous mutations in mice has also been clarified and the characterization of the OA phenotype is now in progress. These mutations cause severe chondrodysplasia and death in homozygous mice, but the heterozygous offspring develop the early-onset OA phenotype.

Osteoarthritis (OA) is the most common joint disease. For the disease to occur and progress, the conditions in the joint must be conducive, i.e. the presence of proinflammatory cytokines, a complement of enzymes degrading the extracellular matrix molecules, and sustained joint loading. OA does not develop in cell or tissue culture. The repair capability of injured articular cartilage is poor. As it has been considered unethical to take cartilage biopsies from patients, most of the clinical studies on OA have relied on non-invasive methods [1]. Therefore, it is understandable why there is such a great need for suitable and valid animal models of OA for biomedical research [2–6].

It has been estimated that the genetic background contributes to the prevalence of the disease in 38–65% of OA patients [7]. Currently, mutations of only a few human genes, particularly those coding for cartilage-specific collagens, have been shown to be responsible for evoking OA (Table 1). In addition to the appearance of early-onset OA, other severe cartilage and bone involvements have resulted from these mutations, i.e. chondrodysplasias [8]. In fact, OA changes in joints have been regarded as among the mildest phenotypes caused by collagen gene mutations [9]. It is possible, even probable, that any defect in a structural gene encoding a cartilage matrix constituent can disturb the normal properties of the tissue and lead to early-onset OA [10].

An animal model has been defined as ‘a homogeneous set of animals which have an inherited, naturally acquired, or experimentally induced biological process, amenable to scientific investigation, that in one or more respects resembles the disease in humans’ [11]. The greater the similarity of the changes with the human disease, in this case OA, the more suitable the model is for experimental purposes [2, 3]. This requirement implies that an animal model of human disease must be characterized thoroughly. OA can result from a primary localized or generalized insufficiency of cartilage properties, or it may be secondary to a traumatic insult, congenital disease or developmental malformation, a metabolic, endocrine or calcium deposition disease, other bone and joint diseases, neuropathic arthropathy or some endemic disorders. Therefore, it is not surprising that no animal model can fully mirror all the variants of human OA. Also, due to the different properties of animal cartilage, results obtained with animals cannot be translated directly to human cartilage and disease [2, 3]. There are several features which make mice attractive experimental animals. Mice are small and easy to handle, their breeding ability is usually good, their life span is 2–3 yr, and housing costs, though high, are lower than those of larger animals.

Spontaneous OA develops in most mouse strains. For example, STR/ort and C57BL mice show spontaneous
development of OA at an early age [12, 13]. The molecular background of OA in these mice remains unknown, however. In addition to gene mutations, conditions such as patellar displacement and chondro-osseous metaplasia in tendinous structures have been claimed to augment the disease process. Mutations in genes encoding type II and XI collagens, aggrecan and the multipass transmembrane protein (ANK) that controls pyrophosphate levels in cells have been detected in some mouse strains, and they lead to the development of severe syndromes if present in the homozygous state [14]. However, the heterozygous offspring of these mice appear to develop early-onset OA [15]. Even though they are not transgenic mice, we have included in this review a description of the phenotype of these animals because the predisposing factor to OA is a defined mutation in a gene (Table 1).

Recent progress in transgenic technology has created great interest in the use of gene-mutated mice as experimental animals in OA research [9, 16–19]. Here we use the term ‘transgenic’ to refer to animals in which new genetic material has been introduced into the germ line. Usually the DNA is injected into one pronucleus of the fertilized egg (Fig. 1) [20]. Integration of the DNA takes place at a random location in the genome. After birth, the mice are screened for incorporation of the gene in question by Southern blotting or the polymerase chain reaction. When producing knockout mice, i.e. animals in which specific genes have been inactivated, the targeting construct usually consists of genomic DNA for the region to be replaced (it also incorporates a neomycin-resistance gene) and a flanking copy of the thymidine kinase gene. Embryonic stem cells transfected with this construct and selected by

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### Table 1. Transgenic mouse models of osteoarthritis

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Transforming growth factor (TGF)-βR2, TGF-β receptor 2.
their resistance to neomycin and ganciclovir (indicating correct integration of the construct) are injected into host blastocysts, where they are able to create chimeric mice carrying foreign DNA that disrupts the gene of interest (Fig. 2) [20]. Subsequent matings produce homozygous mice that do not express the gene. Mating the homozygous mice with wild-type animals generates heterozygous knockout offspring. This article provides an overview of mouse lines that develop OA either as a result of transgenesis or because they carry a spontaneous, known gene mutation, and gives information about their properties and their use as animal models in OA research.

Spontaneous mouse mutation models for the study of osteochondrodysplasias and OA

Osteochondrodysplasias are a heterogeneous group of skeletal disorders associated with disturbances in cartilage and bone growth and development. Well-known models of murine osteochondrodysplasias involve the collagen and aggrecan genes. Recently, mouse models of these syndromes, especially their genetic background, have been reviewed extensively [9, 14, 16–19]. The manifestation of osteochondrodysplasias is not solely dependent on mutations of the major constituents of the articular cartilage matrix. For example, a mutation which alters the structure of a transmembrane receptor protein, fibroblast growth factor receptor 3, causes achondroplasia, and another human mutation, which changes the structure of a sulphate transporter, reduces the sulphation of glycosaminoglycans in diastrophic dysplasia [21].

Chondrodysplasia

Autosomal recessive chondrodysplasia in mice (cho) is attributable to the loss of $\alpha_1$(XI) collagen chains in cartilage. This loss results from a single-nucleotide deletion in the $\text{Col11a1}$ gene, leading to a frame shift and premature termination of translation. Type XI collagen, which is a minor component of collagen fibrils in cartilage, is a heterotrimer composed of $\alpha_1$(XI), $\alpha_2$(XI) and $\alpha_3$(XI) collagen chains. In the cartilage of cho mice, the mutation leads to the appearance of abnormally thick collagen fibrils and increased extractability of proteoglycans from the cartilage. Homozygous mice have shortened snouts and other abnormalities in the cartilage of the ribs, limbs, mandible and trachea, such that the mice die at birth due to breathing difficulties [22]. Interestingly, in mice heterozygous for the cho mutation (cho/+) OA-like changes in the joints can be observed several months earlier during ageing than they appear in control animals (Table 1) [9, 15]. Morphological OA changes include alterations in the organization and number of chondrocytes, the staining of the matrix and the extent of fibrillogenesis. The recessive cho mutation apparently causes haploinsufficiency of collagen $\alpha_1$(XI), which explains the phenotype of these mice [15].

Disproportionate micromelia

Mice with disproportionate micromelia have a three-nucleotide deletion in the C-propeptide globular region of type II procollagen. This leads to the substitution of asparagine for the two amino acids lysine and threonine
[14, 23]. As this region is involved in the formation of intra- and interchain disulphide bonds, the mutation disturbs the formation of type II collagen molecules by stabilizing the structure of an abnormal C-propeptide trimer. Homozygous mice (Dmm\textsuperscript{Dmm}) show severe dwarfism, reduced bone length, cleft palate and disorganized growth plates. Electron microscopy reveals a reduced amount of normal-looking thin collagen fibrils in the extracellular matrix. The disturbance of C-propeptide trimerization causes retention, and possibly also degradation, of the abnormal z1(II) chains and type II procollagen molecules. The mice die at birth due to respiratory difficulties. Heterozygous mice (Dmm\textsuperscript{+}) are viable and develop early-onset OA (Table 1) [15]. Cartilage erosion is typically observed in the superficial zone but it also extends into the transitional zone. The dominant negative effect of the Dmm gene appears to predispose articular cartilage to more severe early-onset OA than the cho gene [15]. Because the z1(II) and z3(XI) chains are encoded by the same gene, it can be predicted that the formation of type XI collagen should also be disturbed in chondrocytes.

**Cartilage matrix deficiency**

Cartilage matrix deficiency (cmd) of mice is caused by a deletion of seven base pairs (bp) in the aggrecan gene, resulting in a premature stop codon in the mRNA and the loss of aggrecan core protein from the matrix [24, 25]. Homozygous cmd/cmd mice die soon after birth because of breathing difficulties. The cartilage matrix is reduced in amount and contains tightly packed chondrocytes. Heterozygous cmd/+ mice may show more OA during ageing than normal mice. No human condition resulting from the loss of aggrecan core protein has ever been identified. However, multilevel and severe intervertebral disc degeneration has been observed in women with a shorter length of VNTR (variable number of tandem repeat) in the aggrecan gene than in those with a normal length of VNTR [26]. This suggests that there is an association between the aggrecan gene polymorphism and lumbar disc degeneration.

**Progressive ankylosis**

Progressive ankylosis in mice results from a mutation (ank) in the transmembrane protein ANK, which regulates the pyrophosphate (PP\textsubscript{i}) concentration in cells and extracellular matrix. The mutation is caused by a single-nucleotide, guanine→thymine substitution in the ank gene, creating a nonsense mutation in the open reading frame. The autosomal recessive ank mutation causes an abnormal, flat-footed gait in young mice due to decreased mobility in the ankle and toe joints. With age, a generalized progressive form of arthritis develops, accompanied by mineral deposition, bony outgrowths and joint destruction and rigidity, and death occurs at the age of about 6 months [27]. The human counterpart of the condition has been suggested to be familial chondrocalcinosis.

**Transgenic mice with collagen mutations**

Genetic predisposition to chondrodysplasias and advanced OA has been linked to mutations affecting different collagen types. The mutations exert their effects on the skeletal system, the eye and the inner ear. Conceivably, milder mutations, e.g. those affecting the level of expression of a cartilage matrix component or the structure of any of its interacting domains, could predispose individuals to diseases that become apparent only later in life, and possibly only in association with some other predisposing factor(s). The developmental regulation and the balance of synthesis of type II, IX and XI collagens are still poorly understood. However, the chondrocyte-specific expression enhancers for Col2a1 and Col11a2 show a high level of homology, which explains why type II and XI collagens can be co-expressed in cartilage [28].

**Mutations in type II collagen**

Several lines of transgenic mice have been produced harbouring mutations in the type II collagen gene. These include a line expressing a human COL2A1 transgene with a large internal deletion [29] and another expressing a murine Col2a1 transgene with a Gly85Cys substitution in the triple helical domain [30]. These two transgenic mouse lines develop phenotypes resembling human chondrodysplasias; the former strain also demonstrates more frequently OA in ageing mice (Table 1) [31]. However, an OA phenotype can also be produced by increasing the expression rate of the normal Col2a1 gene, which leads to disruption in the regulation of type II collagen fibril assembly [32].

**Homozygous and heterozygous knockout of Col2a1 gene**

Targeted inactivation of Col2a1 in its homozygous form prevents the formation of endochondral bone but does not hinder the development of membranous bone [33]. The absence of type II collagen fibrils in the matrix of homozygous mice leads to death shortly before or at birth. Heterozygous Col2a1 allele inactivation contributes to minimal phenotypic changes, including slightly retarded growth, shortened limbs and alterations in the craniofacial skeleton [33]. Quantitative microscopy shows that the same mice develop changes in the collagen network of articular cartilage and subchondral bone. However, no striking changes are seen in qualitative microscopic analyses [34]. Thus, the observed softening of the articular cartilage and the higher prevalence of OA in ageing mice probably result from the inactivation of one allele of the Col2a1 gene (Table 1) [34, 35].

**Del1 mouse model for OA**

The transgenic mouse line Del1 harbours six copies of a Col2a1 transgene with a 150-bp deletion of exon 7 and intron 7, removing sequences coding for the 15 amino
acids at the amino-terminal end of the triple helical domain [36]. Homozygous Del1 mice carry 12 copies of the transgene, develop severe chondrodysplasia during embryogenesis and die at birth due to respiratory distress. Heterozygous Del1 mice express the type II collagen transgene mRNA at a level comparable to that of mice carrying only the wild-type alleles [36, 37]. These mice develop early-onset human OA-like lesions, usually confined to the knee joint (Table 1) [37]. In older animals, cartilage erosion has been demonstrated in the mandibular articular cartilage, but also in the tarsal and metatarsal joints [37, 38]. Superficial fibrillation of articular cartilage begins in the knee joints at the age of 3 months. The superficial defects progress rapidly into erosions, penetrating first into the uncalcified and later into the calcified cartilage, accompanied by bony sclerosis, degeneration of the menisci, mineralization of various joint structures, cyst formation and exposure of the subchondral bone. Non-transgenic littermates also develop osteoarthritic lesions, but these appear significantly later and are less severe than those seen in heterozygous Del1 mice. OA is more severe in male than in female Del1 mice, and the lateral condyles of both the tibia and femur are more severely affected than the medial condyles.

As in human OA, synthesis of the cartilage oligomeric matrix protein (COMP) is up-regulated during the early stages of OA in Del1 mice, and its release from the articular cartilage into serum increases [39]. Simultaneously, up-regulation of the expression of MMP-13 (collagenase-3) mRNA is seen in the epiphyses. Little of the protein can be demonstrated in the articular cartilage, whereas the deep calcified cartilage and the adjacent subchondral bone are rich in MMP-13, suggesting involvement of the subchondral bone in the OA process. A possible secondary response to cartilage erosion is observed in the synovial tissue, which appears to be hyperplastic and rich in MMP-13 protein, the enzyme possibly being there in order to digest and remove the released fragments from the joint cavity [40].

Articular chondrocytes retain only limited repair capacity in the adult articular cartilage. In Del1 mice, this includes expression in the chondrocytes of Sox9, a transcription factor regulating the chondrocyte phenotype, and the reappearance of the prechondrogenic type IIA procollagen at sites of cartilage repair. In some areas, spontaneous repair through formation of granulation tissue can be observed. In this tissue, the cells do not exhibit a chondrocyte phenotype, as they are fibroblast-like in shape and embedded in a proteoglycan-poor matrix filled with tangentially oriented type III collagen fibrils. In the border areas of the defects, chondrocytes do attain their terminal differentiation and cease production of Sox9 [41].

Point mutations of type II collagen

Molecular epidemiology has revealed single-base substitution mutations of the human COL2A1 gene that contribute to osteochondrodysplasias and/or OA. The Arg519Cys point mutation in COL2A1 is a candidate of interest for OA research. In humans, this mutation leads to a mild spondyloepiphyseal dysplasia phenotype and generalized OA [42]. However, there are still no reports published describing experiments with transgenic mice carrying this mutation.

Mutations in type IX and XI collagens

Mice transgenic for type IX collagen mutations

Type IX collagen is a heterotrimer consisting of α1(IX), α2(IX) and α3(IX) polypeptide chains, and it has both collagennous and glycosaminoglycan domains. It binds covalently to the surface of type II collagen fibrils and appears to anchor them to the surrounding matrix. Homozygous transgenic mice carrying a central in-frame deletion mutation that codes for truncated α1(IX) chains develop mild chondrodysplasia and progressive OA with ocular involvement [43, 44]. Young mice harbouring the mutation show a cartilage phenotype close to that of normal animals, but they exhibit increased prevalence of OA from the age of 6 months onwards (Table 1). Altered spine morphology and spine degeneration, including osteophyte formation and clefting of the intervertebral discs and endplates, can be observed at the age of 12 months [45].

It seems that the presence of type IX collagen in tissue is not an absolute prerequisite for the formation of collagen fibrils in the articular cartilage and spinal tissues. On the other hand, expression of the α1(IX) chain appears to be necessary for the synthesis of functional type IX collagen molecules [46]. Homozygous inactivation of the Col9a1 gene does not disturb the appearance of the normal phenotype of articular cartilage at birth but it does lead to early-onset OA (Table 1) [47]. Interestingly, blocking of synthesis of the α1(IX) pro-alpha chain by elimination of Col9a1 gene activity prevents the formation of the type IX fibrils, although the mRNA expression of α2(IX) and α3(IX) chains remains unaltered [46].

Mice transgenic for type XI collagen mutations

Disturbances of protein synthesis by Col11a1 and Col11a2 genes have very different effects on the susceptibility of mice to OA. In contrast to the OA changes seen after premature termination of α1(XI)-chain mRNA translation in heterozygous cho/+ mice [9, 15], transgenic mice with targeted disruption of the Col11a2 gene do not show the OA phenotype [48]. In mice lacking the α2(XI) chain, disturbance of the histology of the growth plate is discernible, but the long bones and articular cartilage are devoid of visible pathology and there does not appear to be any increased OA susceptibility up to 1 yr of age [48].

Mutations in type X collagen

Transgenic mice with mutations of type X collagen do not primarily offer a model for OA research. The structural role of type X collagen was demonstrated
when a mutation in the \textit{COL10A1} gene was found in patients with Schmid metaphyseal dysplasia [49]. A large number of \textit{COL10A1} mutations causing this chondrodysplasia are now recognized (http://www.ncbi.nlm.nih.gov/Omim/). Genetically, they all seem to represent haploinsufficiency, as the mutations result in the production of truncated zI(X) chains unable to associate into type X collagen molecules.

Studies involving transgenic mice have produced somewhat contradictory results. Rosati \textit{et al.} [50] reported that type X collagen-null mice developed no gross phenotypic changes. In contrast, Kwan \textit{et al.} [51] described a mild skeletal phenotype involving the chondro-osseous junction in their knockout mice. This phenotype resembled Schmid metaphyseal chondrodysplasia in its abnormal trabecular bone architecture. In particular, the mutant mice developed coxa vara, a phenotypic change common in human disease. Other consequences of the mutation were the reduction in the thickness of the growth plate resting zone and articular cartilage, altered bone content, and atypical distribution of matrix components within the growth plate cartilage [51]. It is possible that these mice will demonstrate OA as they grow older.

\section*{Transgenic models of OA with mutations in non-collagenous molecules}

Bigglycan and fibromodulin are small extracellular proteoglycans that are co-expressed in tendons, cartilage and bone. Currently, the exact physiological role of these molecules remains unknown. Mice with a single knockout of either fibromodulin or bigglycan have irregular collagen fibrils in their tendons [52, 53]. Bigglycan-deficient mice also develop osteoporosis. Fibromodulin and bigglycan single knockouts and mice deficient in both proteoglycans develop OA changes in the knee joints from 3 months of age onwards [54]. OA is most severe in double knockouts, and these mice also generate gradual gait impairment and ectopic sesamoid bones (Table 1). The double-deficient mice show striking similarities with STR/ort mice, which also develop spontaneous ectopic ossification and OA in the knee joints [12].

Involvement of matrix metalloproteinases, particularly MMP-13, has been demonstrated in the degradation of cartilage and the development of human OA lesions [55]. This finding has been utilized in the design of a novel animal model in which transgenic mice express the human MMP-13, which is specifically targeted to hyaline cartilage by the type II collagen promoter, and expression takes place under tetracycline-regulated transcriptional control [56]. These mice develop cartilage lesions with histological similarities to human OA (Table 1).

\textit{\alpha}l Integrin is an important collagen receptor in chondrocytes. Mice deficient for this receptor develop age-associated OA in their knee joints (Table 1) [57]. Accelerated cartilage degradation, loss of glycosaminoglycans and an inflammatory synovial response have been observed in these animals at the age of 9 months. This model provides the possibility of studying the cell–matrix interactions of chondrocytes in both apoptosis and the pathogenesis of OA.

Expression of the bovine growth hormone fusion gene under the transcriptional control of the phosphoenolpyruvate carboxykinase promoter results in abnormalities of the knee joint structures [58]. The changes in the synovial membrane resemble those seen in inflammatory arthritis, whereas damage in the joint cartilages has an osteoarthritic appearance (Table 1). In transgenic mice, expression of the truncated, kinase-defective transforming growth factor \(\beta\) (TGF-\(\beta\)) type II receptor promotes terminal differentiation of chondrocytes and the development of OA [59].

\section*{Future issues and perspectives}

Research on extra- and intracellular signalling pathways has resulted in the production of a number of cytokine- and transcription factor-deficient mice, which demonstrate changes in cartilage and bone development [60–62]. Perhaps not unexpectedly, many of these mouse lines show either abnormal cartilage development with various degrees of chondrodysplasia or pathological conditions with similarities to OA. Their value as models for OA research remains to be determined, but the initial analyses of these mice have highlighted the critical role of research on signalling pathways in increasing our understanding of cartilage development and growth. These models may prove to be extremely useful in the search for mechanisms to repair cartilage.

Although the genetic constitution of laboratory animals is basically similar to that of humans, with great similarity in gene structure and the tissue distribution of gene products, differences from humans do arise with respect to body size and stature. In small mammals walking on four feet, the distribution of load across the joints is quite different from that in humans. Each species has characteristic biological properties of its articular cartilage, such as the high chondrocyte density in the cartilage of mice compared with the low density characteristic of human tissue. This creates discrepancies between the animal models and the human disease. As regards human ‘idiopathic’ OA, with late onset and slow progression, it is perhaps wise not to be overly enthusiastic about animal models that show severe chondrodysplasia and very early OA. A model requiring a somewhat longer follow-up time and showing a milder and more slowly progressive OA phenotype might better mimic the pathogenesis seen in the idiopathic human OA disease. It is possible, however, that the early-onset and late-onset models will both prove to be useful in testing new pharmacological agents, for example. It is fast, cheap and reliable to use a well-characterized transgenic or spontaneous mouse model to test the ability of an agent to prevent, retard the progression of or reverse the morphological changes of OA. If the results of such tests are positive, suggesting
that the agent has disease-modifying properties, further tests with other experimental animals and finally with humans are warranted.

Transgenic mice are useful models for biomedical research [20, 60]. The technology allows the design of distinct genetic changes and the possibility of engineering the manifestation of altered molecules in the organism. This also provides the possibility of developing unique models for OA research. It is to be hoped that these models will find a place in drug-screening programmes and therapeutic trials. However, no studies in which transgenic mice have been used in drug trials for OA treatment have yet been entered into the PubMed database. This is probably due to the fact that such models have been unavailable for testing until recently. One reason for this is that there are still only a few transgenic mouse models that have been thoroughly characterized. Today, it is relatively easy to generate a transgenic mouse line, but characterization of the phenotype is laborious, time-consuming and expensive, and requires cooperation between researchers in different fields.

Acknowledgements

Support from the Research Council for Health of the Academy of Finland, the Finnish Graduate School for Musculoskeletal Diseases and the Ministry of Education in Finland is gratefully acknowledged.

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