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Review

The STR/ort mouse and its use as a model of osteoarthritis

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History of the STR/ort Mouse

The parent STR/1N strain was isolated by Dr George E. Jay, Jr in 1951 as a spontaneous piebald (white and red/brown) mutant of STR/1N arising in the F29 generation[1]. STR/ort mice were derived from the parent STR/1N strain following a period of non-inbreeding. After initiating inbreeding again they were designated as the sub-strain STR/ort[2].

General pathology

In a series of papers, Silberberg and Silberberg presented evidence that the development of osteoarthritis (OA) in mice is influenced by a variety of nutritional and hormonal factors[3–10]. In a survey of 18 mouse strains, Sokoloff and Jay[11] reported that the highest incidence of naturally-occurring OA occurred in strain STR/1N. Overall, male mice had a higher incidence of degenerative joint disease than female mice and the medial condyles were affected to a much greater degree than the lateral condyles[12]. However, in a pilot study of ovarectomized, castrated, and sham-operated STR/ort mice of both sexes, we found no evidence to suggest that the development of OA was dependent on sex hormones in this model[13]. In a study of the genetics of degenerative joint disease in mice, including STR/1N, the disease was shown to be polygenic with indications of recessive inheritance, but there was no evidence of sex linkage[14].

Another characteristic of the STR/1N strain is spontaneous obesity, even while receiving a standard diet. Like the STR/1N mice, the STR/ort mice have a high body weight compared to other laboratory strains[14,15]. Both STR/ort sexes grow at a faster rate and they reach a peak of growth 3 months before their CBA counterparts[2]. STR/1N mice also have increased susceptibility to periodontal disease[16], a high incidence of hepatomas, and a low level of hemoglobin[14]. Both STR/1N and STR/ort mice have an increased incidence of obstructive ureteric disease and in the STR/1N strain this could be prevented by castration[1,17].

Morphological studies

In our experience, degeneration of the cartilage in the STR/ort strain occurs first at the interface of the cruciate ligament and the medial tibial articular cartilage and, as in the STR/1N strain, the histological lesions closely resemble those of human OA[18] (Fig. 1). Lesions develop in the medial plateau and range in severity from mild erosion of the cartilage surface to complete loss of the tissue and exposure of the subchondral bone[18]. We have used a six-point grading system to describe the severity of osteoarthritic lesions in the STR/ort mouse[19].

Schunke *et al.* described the histopathological characteristics of osteoarthritic cartilage lesions in the knee joint of male STR/1N mice[20]. The lesion first appeared on the medial tibial plateau and as the disease progressed there was a loss of cartilage which resulted in a pronounced instability of the knee joint and a varus deformity. This was followed by medial patellar subluxation. The authors concluded that cartilage degeneration in the medial tibial condyle develops spontaneously due to an unknown pathogenesis and it is this event that is responsible for secondary patellar subluxation. This conclusion was supported by the findings of Dreessen and Halata[21] who showed an age-related osteoarthritic degeneration in the tempero-mandibular joint (TMJ) of male STR/1N mice, suggestive of a systemic basis of the disease.

Walton[22] surgically stabilized the patellae on the left legs of young male STR/ort mice and used the right legs as controls. None of the nine stabilized knee joints had histological signs of OA, whereas the control legs showed a normal range of joint damage. Walton concluded that patella subluxation was the primary cause of OA in the STR/ort mouse. Nevertheless, of 59 STR/ort mice with OA (grades 1–4), 19 had normal patellae, which does not accord with this conclusion. In a more recent report, Evans *et al.*[23] made a radiological assessment of OA progression in the knee and ankle joints of the STR/ort mouse. The

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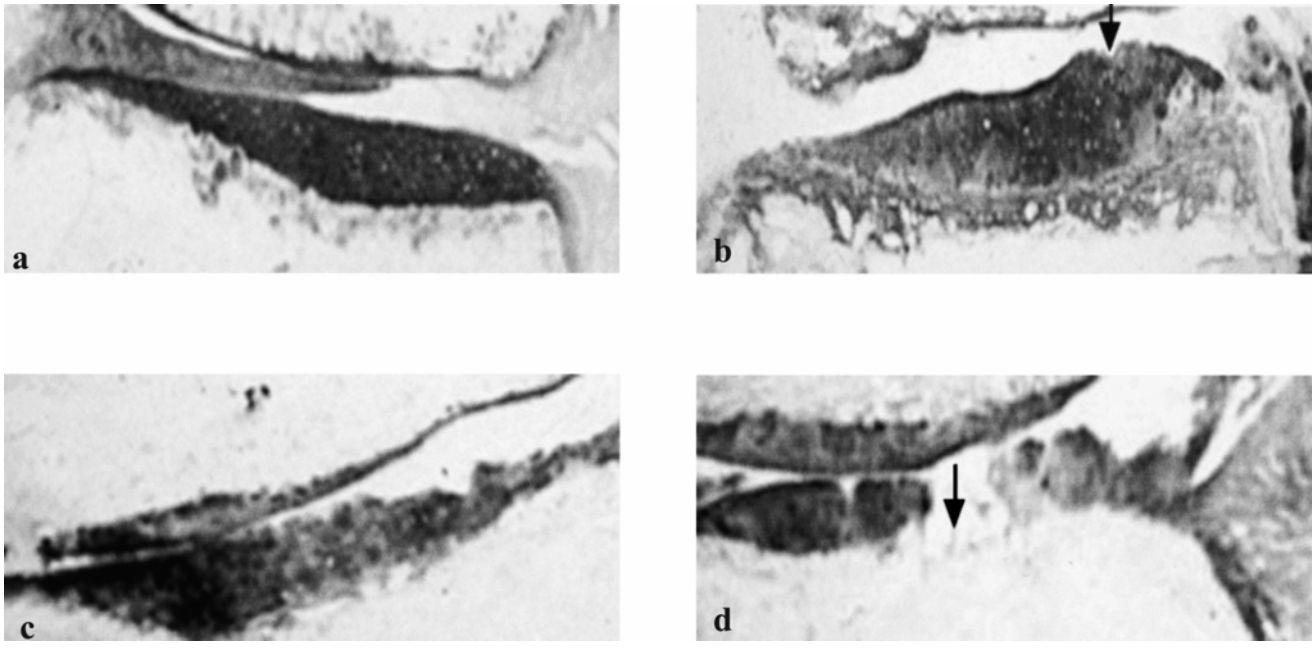

Fig. 1. Medial tibial cartilage of male STR/ort mice stained with Alcian blue (AB) showing varying stages of histological OA. (a) Normal cartilage with smooth surface and uniform AB matrix staining. (b) Early OA with loss of AB stain and small surface lesion (↓). (c) Advancing OA with marked loss of AB staining and extensive surface roughening and fibrillation. (d) Severe OA with loss of AB staining and loss of articular cartilage down to the subchondral bone (↓). Original magnification ×10.

results failed to support Walton's contention that patella displacement was the primary event in the development of OA in this strain. However, it is of interest that Evans *et al*.[23] reported that soft tissue calcification may be an earlier event than cartilage erosion, a finding that was substantiated by a further report[24]. Walton also noted soft tissue calcification[25]. In our experience the degree of calcification in these structures varies between STR/ort colonies maintained in different institutes. Local environmental changes may account for these differences. Our colony has only a low level of calcification in the periarticular tissues. Soft tissue changes may also occur in the absence of calcification. Anderson-Mackenzie *et al.* noted decreased strength of the anterior cruciate ligament and increased collagen remodelling before any radiological evidence of OA in the STR/ort knee joint[26]. Thus, while it seems unlikely that subluxation of the patella is the primary factor inducing OA, it cannot be ruled out that changes in soft tissues in or around the knee destabilize the joint and induce changes in the tibial cartilage.

Walton[15] also investigated whether obesity was an etiological factor in the development of OA in STR/ort mice. He concluded that there was no positive correlation between obesity and OA. We also found no correlation between the weight and severity of OA in individual STR/ort mice (Fig. 2) and Sokoloff *et al.* reported genetic dissociation between obesity and susceptibility to OA in the STR/1N strain[14]. Figure 2 also draws attention to two other features of OA in STR/ort mice. First, mild histopathological lesions are often evident in one or other knee joint at 10 weeks of age. Occasionally these are severe. By 20 weeks most animals have lesions in one or both knees, but it is clear that the age of onset and the severity of lesions is quite variable between different mice. Second, the medial tibial cartilage is generally affected while the lateral is usually spared, or only mildly affected, as in some other murine OA of the knee joint[12]. Male STR/ort mice are also known to develop a spontaneous ankle deformity, but it was reported that there was no correlation between this and the presence of OA[27].

Das-Gupta *et al*.[28] described a histological evaluation of the patello-femoral joints of 37 male STR/ort mice and reported the presence of an acute and chronic synovial inflammatory infiltrate. However, Collins *et al.*[24] found no significant inflammatory changes in the synovial tissue and no alteration in the sub-synovial tissue was detected in animals with established OA. Likewise our own observations over several years have not detected significant synovial inflammatory infiltrates in the STR/ort mouse. It is likely that the particular STR/ort colony studied by Das-Gupta *et al*. was atypical and that the findings described by these authors are not a universal feature of the strain.

Cytochemical studies

CHONDROCYTE METABOLISM

Chondrocytes depend on anerobic respiration for the re-oxidation of NADH generated during glycolysis. Apart from its requirement in glycolysis, NAD is also required as a co-enzyme for two oxidative reactions involved in the biosynthesis of UDP-sugars needed for glycosaminoglycan synthesis. Histochemical studies by Altman[29] suggested a deficiency of lactate dehydrogenase activity in chondrocytes of the medial tibial cartilage of STR/ort mice. This occurred before any histological evidence of degeneration. He proposed that this would lead to increased levels of NADH in chondrocytes which would compromise glycolysis and glycosaminoglycan synthesis. Studies by Dunham *et al*.[30] indicated a decline in glucose-6-phosphate dehydrogenase (G6PD) activity with

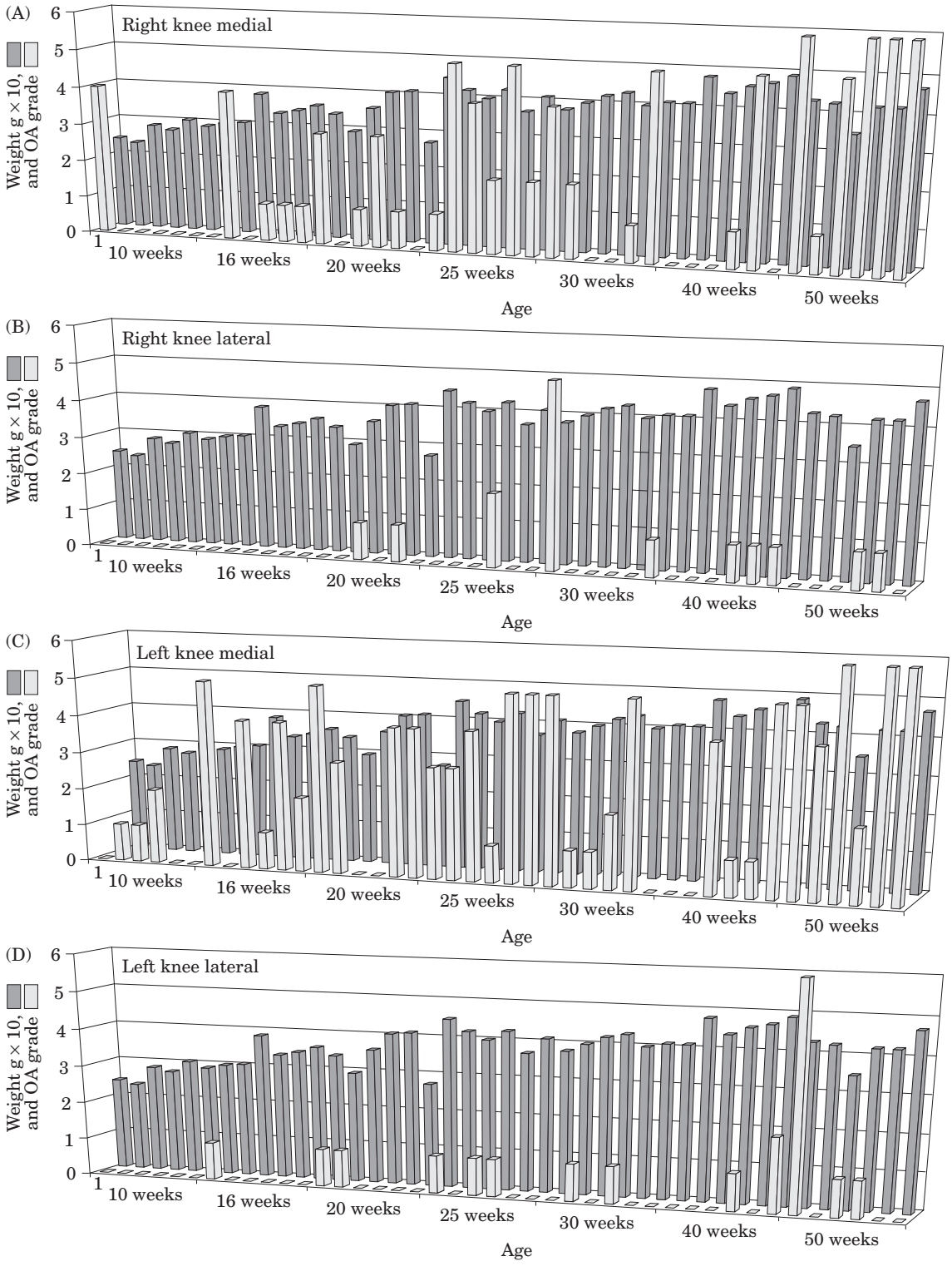

Fig. 2. Severity of OA lesions in the tibial plateau in relation to age and body weight of male STR/ort mice. Data are shown for the medial and lateral tibial cartilage of the right and left knee. Body weight, dark shaded bars; OA grade, light shaded bars. Grade 0, normal; 1, roughened articular surface and small fibrillations; 2, fibrillation down to the layer immediately below the superficial layer (zone 2) and some loss of surface lamina; 3, loss of surface lamina and fibrillations extending down to the calcified cartilage; 4, major fibrillations and cartilage erosion down to subchondral bone; 5, major fibrillations and erosion of up to 80% of the cartilage; 6, greater than 80% loss of cartilage.

age in the medial tibial plateau of STR/ort mice. They surmised that this too contributed to the development of OA.

5′-Nucleotidease, an enzyme on the purine degradation pathway converting inosine 5′ phosphate to inosine, is normally expressed in the superficial zone of murine

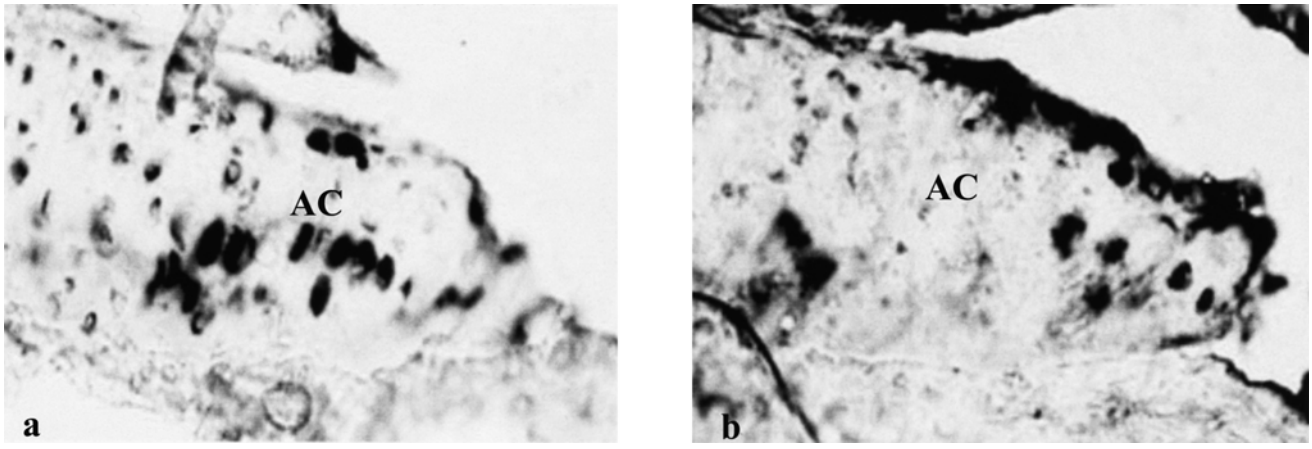

Fig. 3. Aggrecan cleavage neoepitopes in OA medial cartilage of STR/ort mice. (a) Neutral matrix metalloproteinase-generated neoepitope (VDIPEN); (b) aggrecanase-generated neoepitope (NITEGE). AC=articular cartilage.

articular cartilage. In the STR/ort mouse enzyme activity is markedly increased in cells adjacent to a lesion throughout the full cartilage depth[31]. The chondrocytes in the area of the lesion also show other changes. For example, *in-situ* hybridization studies indicate an absence of aggrecan transcripts in these cells[32]. Moreover, cytochemical assays for activity of UDP-glucose dehydrogenase, a key enzyme in generating UDP-glucuronate for chondroitin sulfate synthesis, show a marked reduction in the chondrocytes close to the lesions (unpublished results). These findings, taken together, indicate that aggrecan synthesis in these cells is likely to be severely compromised, contributing to the matrix proteoglycan depletion in the same area which is detected by Alcian blue staining. Chondrocytes in the lesional area may have generally low levels of metabolic activity since the TUNEL assay suggests that many of them are undergoing apoptosis. Indeed, we have shown that there is a linear correlation between the number of TUNEL positive cells in this area and the severity of the osteoarthritic lesion[33]. Electron microscopy confirms the apoptotic nature of these cells which have morphological features identical to those reported by Hashimoto *et al.* for apoptotic chondrocytes[34]. Interestingly, the distribution of monoamine oxidase, an enzyme normally localized to mitochondria, is changed in the medial tibial cartilage of STR/ort mice where activity was detected in the extracellular matrix[35]. One possible explanation is enzyme leakage from apoptotic chondrocytes.

CARTILAGE DEGRADATION

Chambers *et al*.[19] investigated whether there were changes in the expression of systemic factors which are known to influence matrix catabolism. Analysis of gene expression for IL-1α and -β, IL-6, IGF-1 and TGFβ showed that transcripts for all were present in the STR/ort chondrocytes. However, they could not be detected in the age- and sex-matched control CBA mice. Furthermore, anabolic growth factors predominated in pre-lesion cartilage, whereas catabolic cytokines were more strongly expressed in the later stages of the disease. These findings are consistent with a disease mechanism in which the chondrocyte is primed to increase the synthesis of matrix macromolecules prior to the appearance of the tissue lesion. This response ultimately fails and cartilage erosion follows. The cytokine changes would be expected to induce proteinases responsible for matrix degradation. An *in-situ* hybridization study[36] showed that collagenase 3 expression is increased in normal areas of STR/ort tibial cartilage compared to age-matched CBA mice which do not develop OA. However, collagenase 3 expression is frequently lost in STR/ort chondrocytes adjacent to osteoarthritic lesions. We also investigated collagenase 3 in STR/ort tibial chondrocytes by immunohistochemistry following incubation of the knee joint in a medium containing monensin to block secretion of the enzyme from cells. However, even with this method the enzyme was not consistently detected in STR/ort chondrocytes in all animals tested[36]. Nevertheless, it should be noted that a study carried out by Brewster *et al*.[37] indicated that tibial cartilage degeneration in the STR/ort mouse could be inhibited with a selective collagenase inhibitor. It should be noted that some other proteases can also cleave the triple helical region of collagens. We also examined whether collagen cleavage neoepitopes are generated in STR/ort tibial cartilage using the Col 2-3/4C short antibody which detects such cleavage[38]. Such neoepitopes appear only when cartilage fibrillations are present[39].

The degradation of aggrecan in STR/ort tibial cartilage was mapped by Chambers *et al*., using anti-sera which recognized the neoepitopes generated by proteolytic enzymes cleaving the molecule between amino-acid residues Asn^{341}-Phe^{342} [metalloproteinase(s)] and Glu^{373}-Ala^{374} [aggrecanase (ADAMTS)][40]. Both of these fragments were detected in tibial cartilage of CBA and STR/ort mice[41]. In some areas the localization overlapped, suggesting that the enzymes may act together as well as independently (Fig. 3). Immunostaining of the matrix adjacent to the cartilage lesion suggested that MMPs and aggrecanase may have been released into the matrix, promoting tissue degradation.

Biochemical and molecular studies

Dunham *et al*.[42] showed that the birefringence of Alcian blue stained proteoglycans in the medial tibial cartilage of the STR/ort mouse declined as the severity of the disease increased. This suggested progressive disorganization of the proteoglycans which, together with a dysfunctional collagen network, would contribute to the altered biochemistry and physicochemical properties characteristic of osteoarthritic cartilage. Biochemical investigation of individual tibial plateau of mice is extremely difficult. However,

Rostand *et al*.[43,44] used the Beckman-Airfuge to isolate and characterize articular cartilage proteoglycans from the STR/1N mouse. No qualitative changes in the structure of aggrecan were observed in the diseased animals. However, these authors found that a greater proportion of ^{35}S-labeled proteoglycans were extractable from the cartilage of OA mice than from normal mice, suggesting that the restraining collagen network may have been disrupted in the former. More recent work showed that the chondroitin sulfate content of the tibial plateau cartilage was elevated in the 18- to 20-week STR/ort mouse[45]. Similar findings were also reported by Collins *et al*.[24] for the proteoglycan content of the STR/ort patellae. Gaffen *et al*.[46] used quantitative RT-PCR to measure aggrecan mRNA levels in the tibial cartilage of 18- to 20-week male STR/ort mice and showed that they were higher than those in CBA control mice. This and the elevated concentration of chondroitin sulfate in the cartilage at this age suggest that matrix synthesis is stimulated at this stage of the disease. The 4-sulfated isomer of chondroitin sulfate was dominant at all ages in both the STR/ort and CBA articular cartilage[45]. It was shown that the osteoarthritic mice synthesized a normal spectrum of proteoglycans and that most of them were aggrecan[46].

Initial comparative studies of two different colonies of STR/ort mice suggested that one developed more severe osteoarthritic lesions than the other[47]. However, genetic fingerprint analysis showed a high degree of homogeneity both within and between the two colonies. Moreover, a more extensive analysis showed that the colonies did not in fact differ in the rate at which they developed the disease or the severity of lesions which developed. Rather, the findings indicate that there is a marked range in the severity of lesions found in any one group of STR/ort mice at any one age. Clearly this is a factor which must be taken into account in any study of disease-modifying agents in these animals.

Biochemical markers of disease activity

It has been reported that type X collagen expression in human articular cartilage is a marker of osteoarthritic disease activity[48]. However, type X collagen expression occurs in both normal CBA mice and osteoarthritic STR/ort mice and is not therefore a marker of disease activity in the murine model[32]. Others have also reported expression of type X collagen in normal murine articular cartilage[49].

Other potential biochemical markers may be better indicators of disease activity in the mouse. For example, no BSP-1 protein was detected in the hyaline or calcified cartilage in the knee joint of normal CBA mice or in very young STR/ort mice free of osteoarthritic lesions. However, BSP-1 immunostaining was detected at the junction of the calcified cartilage and subchondral bone of the medial tibial plateau of STR/ort mice with the appearance of mild osteoarthritic lesions in the articular cartilage (unpublished results). COMP-1 expression provides a further potential marker of disease activity in the STR/ort mouse. In this case immunostaining for the protein is lost with onset of mild osteoarthritic lesions in cartilage (unpublished results).

Concluding remarks

The STR/ort strain of mouse is an acceptable animal model for studying the development of OA. The disease is a naturally occurring one. About 85% of all male mice develop OA in the medial tibial plateau. The histological lesions resemble those of human OA. A number of biochemical features of the murine disease such as matrix proteoglycan depletion by matrix metalloproteinase and aggrecanase are also similar to changes found in human osteoarthritic cartilage[40]. It is unlikely that an animal model would express all of the features observed in the human disease. Such models are best used to explore temporal changes in individual processes. The STR/ort model provides a unique opportunity to investigate the events involved in the initiation of OA and its progression, to identify candidate genes associated with it, and to investigate the effect of new therapeutic agents on the disease process. There are currently few well-defined small animal models of OA available for assessing new drugs. Murine models are an advantage since mice are readily inbred to produce large numbers of genetically homogeneous animals for such studies. The time frame for development of OA in models should be well defined and short enough to enable trials to yield results within a reasonable period. The STR/ort mouse has many of these features. We would recommend initiating trials from an early age (e.g. 8 weeks) and continuing them until at least 30 weeks of age. Since OA develops as a focal disease in the STR/ort mouse, the whole knee joint should be examined by serial sectioning to grade the cartilage histopathology at the conclusion of any trial. Although time consuming, this seems to us to be the most reliable read-out to assess the potential effect of any new therapy. Although well defined biochemical or other markers of disease activity in the STR/ort mouse may be developed in the future, none is available at present.

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