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JOINT SURFACE DEFECTS: CLINICAL COURSE AND CELLULAR RESPONSE IN SPONTANEOUS AND EXPERIMENTAL LESIONS

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Abstract

Joint surface defects (JSD) involving the articular cartilage and the subchondral bone are a common clinical problem in rheumatology and orthopaedics. The recent availability of accurate imaging for diagnosis and efficacious therapeutic options has stirred new interest in their natural history and biology. The evidence that some of these lesions can heal spontaneously whereas others precipitate osteoarthritis has raised important questions as to which lesions should be treated, when, and how. Evidence of repair of some of these lesions has also stimulated research into which factors contribute to successful healing and which ones determine chronic evolution and development of osteoarthritis (OA). Older anatomical observations, together with novel molecular tools and experimental models, have revealed a complex cellular and molecular response of cartilage to focal defects, which could explain differences in healing responses between individuals, and may provide clues to stimulating intrinsic tissue repair. In the first part of this review we will discuss clinical aspects of these lesions in the patient, with particular emphasis on their biology and natural history. In the second part we will summarize the data coming from *in vitro* and *in vivo* models of cartilage injury and regeneration, focussing on the molecular control of cartilage homeostasis after creation of cartilage surface defects.

Keywords: Joint surface defect, cartilage biology, cartilage repair, regeneration, osteoarthritis, Wnt, FGF, animal models.

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Clinical Aspects

Prevalence and aetiology

Joint surface defects (JSDs) are focal lesions of the articular cartilage. They are very common, being reported in about 20 % of all arthroscopic procedures (Curl *et al*., 1997; Hjelle *et al*., 2002). They are clinically important as they can be symptomatic and disabling, with pain and/or locking of the joint, and can predispose to further cartilage loss and development of osteoarthritis (OA) (Ding *et al*., 2008). Awareness of these lesions has increased with the development of non-invasive imaging for diagnosis (MRI), and the recent emergence of efficacious therapies for cartilage repair.

Chondral lesions vary greatly in their morphology and topography, and this variation influences their outcome and clinical manifestations. Broadly speaking, JSD can be superficial, partial thickness cartilage defects, which do not involve the subchondral bone, and full thickness lesions which cross the osteochondral junction. Superficial cartilage defects rarely represent a clinical problem since they are usually asymptomatic and there is little evidence to indicate that they predispose to OA (Messner and Maletius, 1996; Shelbourne *et al*., 2003; Ding *et al*., 2005a; Smith *et al*., 2005). Indeed, chondral surgery, such as autologous chondrocyte implantation or microfracture, is indicated for full thickness, chronic, symptomatic, chondral or osteochondral defects (Brittberg *et al*., 1994; Peterson *et al*., 2000; Brittberg *et al*., 2003; Smith *et al*., 2005; Brittberg, 2008). This distinction may be somewhat artificial because longitudinal studies have shown that full thickness lesions can become partial thickness and *vice versa* (Cicuttini *et al*., 2005; Nakamura *et al*., 2008).

Trauma has traditionally been regarded as the most important aetiological factor in the development of focal chondral or osteochondral defects (Morscher, 1979). However, in a large study of 1000 consecutive arthroscopies, 39% of patients with a focal defect in their knee cartilage failed to remember a previous traumatic episode to their joint (Hjelle *et al*., 2002). Moreover, up to 43% of healthy subjects without a family history of OA have knee chondral lesions as evaluated by MRI (Ding *et al*., 2005b). These data point to the fact that chondral or osteochondral defects are more common than previously thought, are not necessarily of traumatic origin, and need not be symptomatic. Therefore, the ability to identify which lesions become progressive and require intervention is of paramount importance.

Natural history

Over 250 years ago Hunter stated that "If we consult the standard Chirurgical Writers from Hippocrates down to

the present Age, we shall find, that an ulcerated Cartilage is universally allowed to be a very troublesome disease and when destroyed, it is never recovered." (Hunter, 1743). This statement still probably stands true for symptomatic defects that have acquired a chronic course, such as those that reach the attention of the doctor or the surgeon. Until a few years ago, this was also assumed to be true for all JSDs, and was linked to the observation that the risk of developing OA by the age of 65 was 13% in individuals with a history of trauma and 6% in those without a history of trauma (Gelber *et al*., 2000). Clearly, many factors other than JSDs account for the modestly higher relative risk of OA in patients with previous knee trauma, including lesions to ligaments and menisci.

In 1996, Messner and Maletius (1996) reported that 22 out of 28 young athletes with an isolated chondral injury in a weight bearing part of their knee diagnosed by arthroscopy had good or excellent knee function at 14 years of follow up as evaluated clinically and radiographically. No specific treatment had been preformed except, in 3 cases, Pridie drilling (similar to microfracture) and occasional debridement. 21 patients were able to return to pre-injury level sports activities after trauma and arthroscopy. The overall level of activity decreased at the later time points of follow up (14 years) in relation to a decline in engagement in competitive team sports, but since there was no control group it is impossible to determine whether this declined was influenced by the injury. Although at the end of follow-up 12 patients had some radiographic joint space reduction, no control group was included and therefore we do not know whether joint space reduction would have occurred in the absence of a JSD, particularly since this cohort was composed of professional athletes (Messner and Maletius, 1996). There was no significant difference with the contralateral knee in terms of signs of OA. In this study, all patients had an isolated Outerbridge grade 2 (most cases) or grade 3 chondral defect (diameter >1cm) at presentation, without any damage to other joint structures including menisci, ligaments, and the remaining cartilage. The Outerbridge scale categorises superficial defects as grade I; deeper lesions not reaching the subchondral bone as grade II; fissuring to the level of subchondral bone as grade III, and lesions exposing the subchondral bone as grade IV. No patient had instability, or a previous history of knee surgery. What we learn from this study is that isolated chondral or osteochondral lesions, in young active patients, in otherwise healthy knees, have a favourable natural outcome leading to long term functional restoration. We do not know whether (good) structural repair is required for functional outcome or whether these lesions become asymptomatic or repair with scar tissue. In either case, such a good outcome after 14 years follow up in 78% of lesions suggest, at least, that an aggressive approach to treatment of all such lesions is not justified.

The above study followed individuals with focal chondral defects in otherwise normal knees. However, the majority of symptomatic patients who have chondral defects detected on arthroscopy, have additional joint pathology, including lesions affecting the menisci or ligaments (Brittberg, 2008). In a longitudinal study, Shelbourne *et al*. (2003) asked the question whether the presence of a chondral injury detected in young athletes undergoing ACL reconstruction modifies the clinical outcome and requires chondral repair. In this study the clinical outcome of patients that had either a single chondral or osteochondral injury at the time of arthroscopy, was compared with that of age and sex matched patients who underwent ACL reconstruction but had no chondral injury. The cartilage injury was left untreated, and the clinical outcome was monitored for 8.7 years, clinically and radiographically. Although the symptoms of patients with a chondral injury were slightly more severe, 79% of them returned to pre-injury levels of sports activities involving jumping, twisting and pivoting. The radiological score was not different in the 2 groups. There was no correlation between the size of the defect and the outcome. In each individual patient, the severity of symptoms fluctuated significantly during the follow-up (Shelbourne *et al*., 2003). Again, there was no information as to whether structural repair of the chondral injury was a prerequisite for the good clinical outcome.

The recent improvement of imaging of the articular cartilage with 3D fast spin-echo, or fat suppressed spoiled gradient-echo MRI has allowed detection of chondral lesions with sensitivity and specificity approaching 95% and 100% respectively, when compared to the arthroscopic rating (Broderick *et al*., 1994; Disler *et al*., 1995; Recht *et al*., 1996; Kawahara *et al*., 1998; Bredella *et al*., 1999). MRI imaging has therefore allowed monitoring of chondral defects to obtain prospective clinical and structural data in symptomatic and asymptomatic groups. These studies have yielded surprising results.

In a longitudinal study, Ding *et al*. (2006) reported that 43% of the subjects without a family history of OA, and 57% in subjects with a family history of OA (Ding *et al*., 2005b) have chondral defects detectable by MRI. At 2.3 years follow up, 33% of all subjects had a worsening of the defects as graded by MRI, 37% had improvement, and the rest remained stable. A worse outcome was associated with female sex, age, and body mass index at baseline. In separate studies, bone geometry (Davies-Tuck *et al*., 2008) and features of bone remodelling such as the size of "bone marrow lesions" (Wluka *et al*., 2008) were found to significantly influence the natural history of JSD. Although factors associated with the reproducibility of the MRI grading may have contributed to the defect variation, in general, measurement error was considered to be very low. Importantly, only 18% of subjects with a cartilage defect had a history of knee trauma. These data show 3 very important points. Firstly, that chondral defects, including full thickness ones are often asymptomatic; secondly, that the majority of these lesions may not be related to traumatic injury as previously thought; finally, and most importantly, that a number of these lesions can improve (and possibly heal) spontaneously. An important caveat for the interpretation of these data is the relatively short follow-up, which may be insufficient to discern different long term outcomes in patients who have chondral defects in the absence of OA. Indeed, the presence of chondral defects

in these patients predicted a rate of loss of cartilage volume assessed by MRI of 2-3% per annum which was nearly double that in subjects without chondral defects (1-2% per annum) (Ding *et al*., 2005a). Since the rate of cartilage loss is an independent predictor of joint replacement in patients with OA (Cicuttini *et al*., 2004), it is arguable that at least a number of such asymptomatic defects may predispose to osteoarthritis.

The spontaneous healing of chondral defects has been confirmed arthroscopically by Nakamura *et al*. (2008) in patients with co-existing ACL lesions. In this recent paper, the authors compare the Outerbridge grading of chondral defects complicating ACL rupture at first look arthroscopy, with that observed 6-52 months later. In addition, this study revealed a location specific propensity to healing, whereby lesion to the femoral condyles were those most likely to heal, whereas healing to the patella-femoral joint or to the tibial plateaus was exceptional. One interesting feature of this study was that a large proportion of the lesions that healed were partial thickness (Outerbridge grade I and II; 69% at the medial femoral condyle and 88% to the lateral femoral condyle). This is in keeping with previous longitudinal studies in humans (Messner and Maletius, 1996; Ding *et al*., 2008), but at odds with some animal models in which partial thickness defects fail to heal spontaneously (Mankin, 1982) (see below). Besides important differences related to species specificity and location of the lesion, one possible explanation is that experimental lesions are often induced by very sharp instruments that do not induce an injury response which is as strong as that occurring in natural injuries or following blunt trauma (Redman *et al*., 2004), and, therefore, may be insufficient to activate healing responses. This study confirmed the clinical and MR observation that many such lesions heal spontaneously, without the need for specific cartilage repair intervention.

The natural history and consequence of JSDs in established OA joints has also been investigated. Davies-Tuck *et al*. prospectively recorded chondral lesions in a cohort of patients with osteoarthritis (Davies-Tuck *et al*., 2008). In this cohort, chondral injuries worsened in 81% of the cases and improved in only 4% over 2 years. In a similar prospective study, Wluka showed that the presence of cartilage defects in patients with established symptomatic OA was associated with disease severity and was a predictor of joint replacement within 4 years (Wluka *et al*., 2005). This worse outcome may reflect factors that reduce the intrinsic repair capacity of cartilage, including low-grade inflammation associated with OA or altered joint biomechanics as a consequence of joint deformity, or ligamentous/meniscal injury. We can summarise these data by saying that cartilage defects may be due to acute mechanical injury and can complicate and accelerate the course of OA; however such lesions may be present in otherwise normal knees, where, at least in some cases, they accelerate the physiological rate of cartilage loss that takes place after the age of 40 years. Importantly, particularly in the absence of OA, some of these defects may undergo healing, and, although age, gender, body mass index, the size and the location of the defects significantly and in combination influence progression (Table 1), it is not presently possible to predict the outcome of one individual defect and there is no "threshold" of any of these parameters that determines unequivocally the outcome. Of course some of these risk factors and others such as malalignment may on one hand hamper repair, and on the other predispose for new cartilage lesions.

These considerations have important clinical consequences in deciding whether, when, and how to treat a chondral defect. Owing to the relative paucity of strong experimental data, and despite attempts to rationalise the current therapeutic approaches (Behrens *et al*., 2004), recommendations and guidelines vary dramatically from country to country, particularly in Europe. Although general common sense would suggest that chronic, symptomatic, isolated defects are a good indication for interventions such as microfracture or autologous chondrocyte implantation, this is not so obvious for acute defects or when there is other joint pathology. As a consequence, the identification of biomarkers for disease subsets and outcome prediction is being actively pursued. If it were possible to predict the outcome of JSDs accurately, this would not only be valuable for the daily clinical practice but would also facilitate patient selection into clinical trials to increase the power of such studies. Indeed, the identification of a subset of patients who are going to progress would avoid the commonly observed floor effect due to a number of patients who might improve spontaneously in the absence of treatment.

Novel biomarkers for targeting JSD outcome are likely to emerge from cellular and molecular discoveries, in *in vivo* and *in vitro* models of experimental cartilage injury. Such models have been used as a platform upon which to study the natural progression of experimental joint surface defects, as well as to determine which molecular pathways are involved in such injury responses and which of these might promote tissue repair. Below we will describe some of the studies of experimental cartilage surface injury from basic histological observations that were first made in the 19th century, to more recent studies involving genetically modified mice in which the molecular pathways of the injury response are beginning to be elucidated. Rather than presenting a systematic review of the innumerable variants of each model, already reviewed elsewhere (Mankin, 1982), we will highlight features and aspects that are particularly relevant to the modern research targets including molecular mechanisms and therapeutic target identification.

Experimental joint surface defects

When charting the morphological and histochemical response of articular cartilage to scarification or other forms of injury in experimental models *in vivo*, it is possible to measure not only the early response of the cells in the vicinity of the damage, but also the subsequent attempt at tissue repair. From such studies, a distinction can be drawn between the response of the joint to superficial lesions (those that do not breach the integrity of the osteochondral junction), and those that are full thickness (extending into the underlying subchondral bone). Superficial defects lead to an early, intense, but transient reaction in the cartilage surrounding the lesion. This reaction is characterized

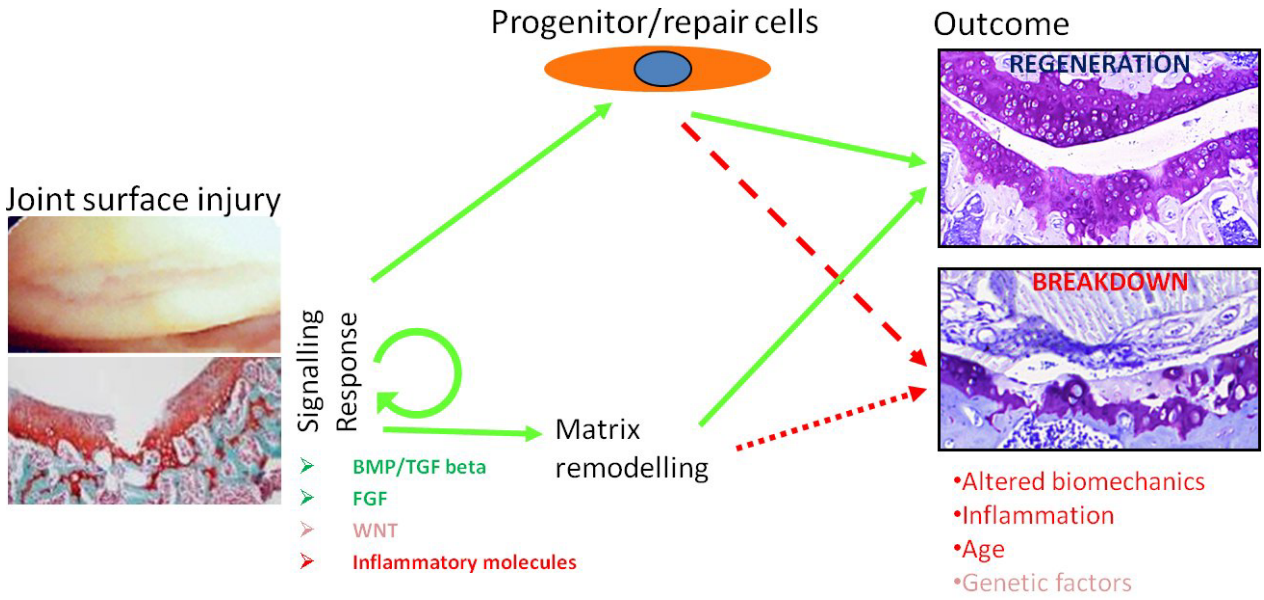

Fig. 1. Acute joint surface injury (e.g., trauma) or chronic mechanical stress (e.g., due to joint malalignment) elicits a molecular response involving several signalling molecules and growth factors. This molecular response activates remodelling and may recruit repair cells, either intrinsic or extrinsic to the joint. Whether this response results in tissue regeneration or breakdown leading to OA likely depends upon other poorly understood contributors including mechanical environment, inflammation, genetic factors and type of cartilage defect e.g., full or partial thickness. In green we have indicated factors presumed to promote a favourable outcome, in red factors that impede it, and in brown factors that are likely to influence the repair responses in different ways, depending on circumstances.

initially by chondrocyte death, and then by a wave of proliferation leading to clustering and intense extracellular matrix production and simultaneous degradation (Mankin, 1982). The efficiency of repair of these lesions is variable (Calandruccio and Glimer, 1962) perhaps in part reflecting differences in experimental conditions, but superficial lesions seldom heal, nor do they evolve into a condition resembling OA (Fisher, 1923; Shands, 1931; Bennett *et al*., 1932; Calandruccio and Glimer, 1962; Redfern, 1969; Redfern, 1969; Mankin, 1982; Shapiro *et al*., 1993; Wei *et al*., 1997). Full thickness defects also stimulate a similar response from the cartilage tissue itself, but in contrast, are more likely to stimulate in addition, an extrinsic repair response, which appears to originate from a fibrous clot at the base of the osteochondral lesion (Meachim, 1963). Others have subsequently studied the origin of these repair cells. Shapiro *et al*. (1993) generated small osteochondral defects in young rabbit cartilage, which were filled by mesenchymal cells within 2 weeks. Using tritiated thymidine pulse chase experiments they showed labelling first in the bone marrow underlying the defect and subsequently in the repair tissue, but not in the adjacent "healthy" cartilage. The authors concluded that the cells contributing to the repair tissue were derived from the bone marrow (Shapiro *et al*., 1993). Subsequently, others have identified potential repair cells in other tissues of the joint such as the synovium (Hunziker and Rosenberg, 1996; De Bari *et al*., 2001a; De Bari *et al*., 2001b;) and the articular cartilage itself (Dell'accio *et al*., 2003; Dowthwaite *et al*., 2004). Ankaru *et al*. performed a detailed characterization of the early events of repair of full thickness defects in rats (Anraku *et al*., 2009). This analysis revealed a striking similarity between the patterning and morphogenetic events taking place during repair and those observed during embryonic joint morphogenesis and endochondral bone formation (Karsenty and Wagner, 2002), perhaps explaining why allelic variants of genes playing a role in embryonic skeletogenesis predispose to OA and are regulated in adult articular cartilage following mechanical injury (Dell'accio *et al*., 2008).

The nature of the repair tissue has also been studied in some detail. Features of both hyaline and fibrocartilagenous cartilage may be present in the repaired lesion (Bennett *et al*., 1932; Shands, 1931), and this doubtless influences the long term outcome. Indeed where studies have been extended beyond the first few months, such lesions frequently display features of OA, with chondrocyte clustering, depletion of interterritorial proteoglycans and increased proteoglycans around individual cells (Campbell, 1969; Mitchell and Shepard, 1976). The conclusions of many of these early studies were that (i) injury causes strong activation of chondrocytes, (ii) there is some attempt at repair, especially when the osteochondral junction is breeched, and (iii) that this repair is often fibrocartilagenous and most likely from cells extrinsic to the cartilage e.g. derived from bone marrow or other tissues (Campbell, 1969; Mankin, 1982).

Studying molecular pathways of cartilage injury responses

The development of *in vitro* models of cartilage injury has helped to dissect the molecular response of adult articular cartilage to mechanical injury. It is hypothesized that some of the pathways and genes modulated by injury may function to activate repair processes (Fig. 1), and could

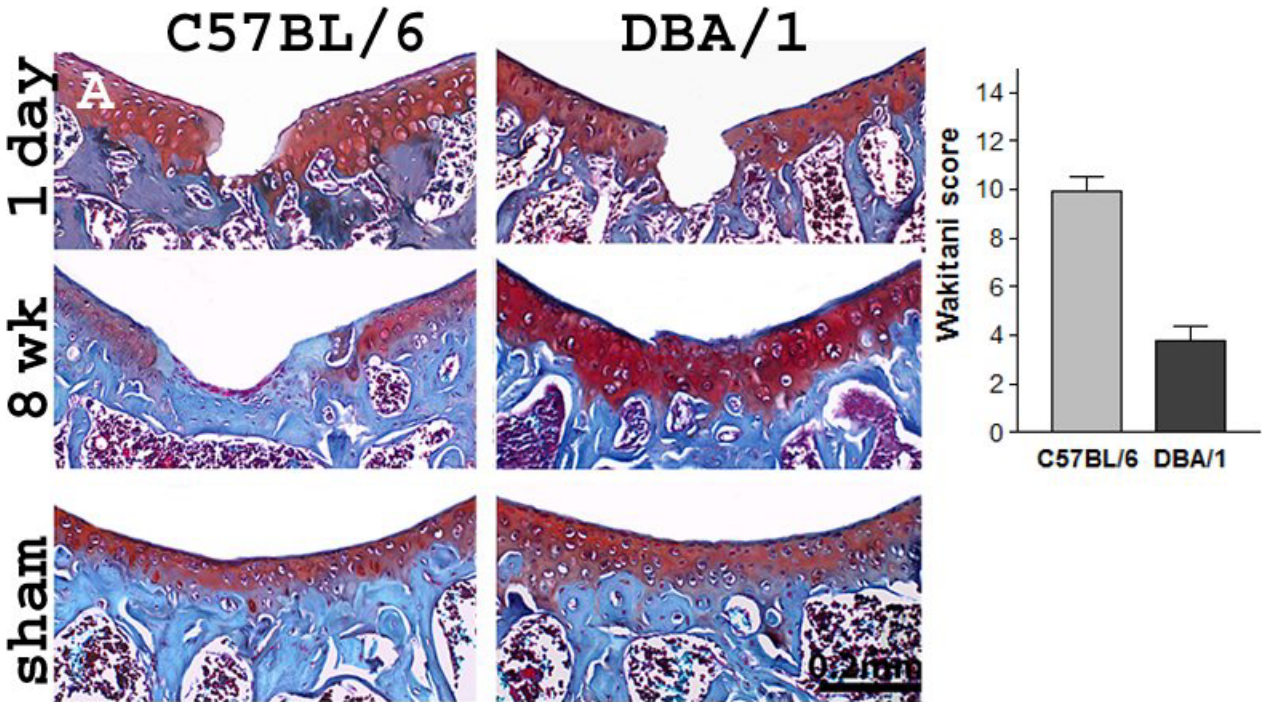

Fig. 2. A controlled full thickness joint surface defect acute mechanical injury to the patellar groove of young-adult mice heals spontaneously in the DBA/1 strain but not in the C57BL/6, thereby demonstrating that there is a genetic component to cartilage healing. On the right, a semi-quantitative repair score. A higher score represents a worse repair outcome. Adapted from (Eltawil *et al*., 2009), with permission of the publisher.

therefore represent novel therapeutic targets. The converse is also the case that some pathways may promote catabolic activities leading to tissue degradation, and could be negatively targeted to prevent progression to osteoarthritis. From *in vitro* studies a number of pathways have been identified as being key to the cartilage injury response. These include FGF2 (Vincent *et al*., 2002), BMPs (Lories and Luyten, 2005) and Wnts (Dell'accio *et al*., 2006;Dell'accio *et al*., 2008). Although the function of these pathways specifically in joint surface healing have yet to be tested *in vivo* in models of cell surface injury, some of them have been studied in models of chronic cartilage injury such as that induced by destabilization of the medial meniscus (DMM) (Glasson, 2007, for review). Using this model, Chia *et al*. were able to confirm the chondroprotective effect of FGF2 *in vivo*, by showing that FGF2 null mice develop accelerated disease following surgical induction of OA (Chia *et al*., 2009). Such models, where injury is continuous (due to joint destabilisation) are complex, because they potentially observe both degradation as well as repair occurring at the same time. Eltawil *et al*. (2009) recently reported on a novel model of joint surface injury in young adult mice, which specifically observes full thickness cartilage injury responses. In this model, a controlled and reproducible full thickness injury is generated in the patellar groove in an open knee procedure. The cartilage was examined histologically after eight weeks. Their results revealed that young-adult DBA/1 mice consistently healed the joint surface defect whereas age-matched C57BL/6 mice failed to repair and developed features of OA such as proteoglycan loss and surface fibrillation, in the cartilage surrounding the lesion (Figure 2). Interestingly, aged DBA/1 mice failed to repair, but did not develop OA, thereby on one hand confirming the age-dependent efficiency of repair reported in humans (Ding *et al*., 2007) and animal models (Mankin, 1982; Wei *et al*., 1997). The different outcome was associated with a specific pattern of tissue responses involving apoptosis, proliferation and matrix remodelling (Eltawil *et al*., 2009) Such MMP-mediated remodelling has also been observed in focal cartilage defects in larger animals (Hembry *et al*., 2001). The strain variability demonstrates that, at least in mice, there is a genetic contribution to cartilage repair responses and a specific pattern of molecular events following injury that is associated with efficient repair. The obvious and great advantage of this model over historical injury models is that such studies can be performed in genetically modified mice and thus directly address the role of specific pathways and molecules in successful cartilage repair.

Concluding Remarks

Joint surface defects are common and may be disabling. The recent explosion of cell based therapies and the advent of novel accurate cartilage imaging techniques has allowed the natural progression of these lesions to be studied. Such prospective studies have revealed that, contrary to what was previously thought, a percentage of JSDs actually heal spontaneously. This is especially the case for superficial lesions and those in otherwise healthy joints. JSDs are much less likely to heal in OA joints, and their presence is a poor prognostic indicator. The increase in sophisticated

molecular genetic models and tools, in conjunction with suitable *in vitro* and *in vivo* model systems is progressively taking us closer to a molecular understanding of repair mechanisms in adult mammals and to the chance of take this knowledge to clinical fruition.

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Discussion with Reviewer

Reviewer I: From a biological point of view, is there a limiting threshold for a endogenous repair or regeneration, which then would lead to further cartilage degeneration?
Authors: The experimental data available, as well as the observational clinical data, suggest that the outcome of regeneration depends on the interaction of different variables including age, body weight, sex, co-morbidity, and genetic background. As a consequence, whereas in animal models, in controlled conditions, changing only one variable at a time, is relatively easy to establish thresholds, in real life it is not currently possible to formulate accurate predictions a priori. For instance, whereas a large number of relatively large JSD were shown to heal in young healthy patients (Ding *et al*., 2006, text reference), even small lesions very rarely heal in patients with pre-existing osteoarthritis (Davies-Tuck *et al*., 2008, text reference), or in specific sites such as the patella (Nakamura *et al*., 2008, text reference). This is the reason why we hope that the identification of biomarkers reflecting the ongoing repair process may represent a significant advance in outcome prediction. Until then, we feel that, particularly for small lesions in otherwise healthy joints, the current practice to clinically monitor JSD and intervene when a chronic course is established is justified.