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Review

Non-invasive mouse models of post-traumatic osteoarthritis

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SUMMARY

Animal models of osteoarthritis (OA) are essential tools for investigating the development of the disease on a more rapid timeline than human OA. Mice are particularly useful due to the plethora of genetically modified or inbred mouse strains available. The majority of available mouse models of OA use a joint injury or other acute insult to initiate joint degeneration, representing post-traumatic osteoarthritis (PTOA). However, no consensus exists on which injury methods are most translatable to human OA. Currently, surgical injury methods are most commonly used for studies of OA in mice; however, these methods may have confounding effects due to the surgical/invasive injury procedure itself, rather than the targeted joint injury. Non-invasive injury methods avoid this complication by mechanically inducing a joint injury externally, without breaking the skin or disrupting the joint. In this regard, non-invasive injury models may be crucial for investigating early adaptive processes initiated at the time of injury, and may be more representative of human OA in which injury is induced mechanically. A small number of non-invasive mouse models of PTOA have been described within the last few years, including intra-articular fracture of tibial subchondral bone, cyclic tibial compression loading of articular cartilage, and anterior cruciate ligament (ACL) rupture via tibial compression overload. This review describes the methods used to induce joint injury in each of these non-invasive models, and presents the findings of studies utilizing these models. Altogether, these non-invasive mouse models represent a unique and important spectrum of animal models for studying different aspects of PTOA.

Introduction

Osteoarthritis (OA) currently affects approximately 27 million people in the United States[1], and 630 million people worldwide, and the knee is by far the most commonly affected joint[2]. OA can be classified either as "primary" (or idiopathic), arising from unknown causes and affecting primarily older subjects, or "secondary" (or post-traumatic), arising as a consequence of a joint injury and often affecting much younger subjects. For example, after anterior cruciate ligament (ACL) or meniscus injury, patients are at a much higher risk of developing post-traumatic osteoarthritis (PTOA) within 10–20 years after injury[3,4]. This risk is even greater following high-energy impact joint injuries involving intra-articular bone fracture[5,6]. Altogether, approximately 10–12% of symptomatic OA cases can be considered post-traumatic[7].

Animal models of OA are essential tools for investigating the development and mechanisms of the disease on a more rapid timeline than human OA. Spontaneous animal models of OA[8–11], in which OA will develop in animals without any "injury" to the joint, are believed to be representative of primary (idiopathic) OA. However, the majority of animal models use a joint injury or other acute insult to initiate joint degeneration, making them more

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representative of PTOA. Little *et al.* identified five properties of the "ideal" animal model of OA[12]:

1) The model should induce consistent reproducible disease that occurs in a suitable time frame to allow reasonably high throughput studies.
2) The induced disease should be universally progressive in the time frame of the study to allow investigation of early, mid and late pathophysiology and treatment effects.
3) The animal should be a mammalian species that is tractable, inexpensive, easy to house and manage, large enough to allow multiple analyses/outcome measures, allows genome wide micro-array analysis and proteomic analysis, sequencing *etc.*
4) The disease process in the animal recapitulates the human pathology in all tissues of the articulating joint.
5) The model should be predictive of therapeutic disease modification in humans.

Numerous animal models of PTOA have been described, however it is not yet known if any of these models fully exhibit these "ideal" properties.

Mice are particularly useful model organisms and are commonly used to study OA and other musculoskeletal conditions, so extensive normative data on mouse musculoskeletal growth and metabolism are available. The abundance of available genetically modified or inbred mouse strains provide the unique ability to study molecular mechanisms contributing to OA development[13–19]. However, the use of mice for studies of OA also has important limitations[20] including the small size of the joint and the extreme thinness of the articular cartilage, which is only a few cell layers thick. Therapeutic strategies that are shown to be successful on this small scale may not prove as effective in the larger human joint. Additionally, the small joint size and thin cartilage make surgical repair or treatment of joint injuries unfeasible or impractical.

While numerous mouse models of PTOA have been described, no consensus exists on the injury methods used to initiate the development of OA. This limitation is crucially important, since the observed pattern of joint degeneration likely depends on the injury method used. For this reason, injury methods should be utilized in mice that recapitulate the human injury conditions as closely as possible. However, most mouse models use invasive (i.e., surgical) or non-physiologic methods to initiate joint degeneration.

Surgical and injection mouse models of PTOA

Surgical injury methods initiate joint degeneration by disrupting joint structures such as ligaments and menisci that can alter the stability and biomechanics of the joint. Development of mouse models of PTOA based on this concept follows previous studies in larger animals. One of the first surgically-induced animal models of OA was ACL transection (ACLT), or Pond-Nuki model, in dogs in 1973[21]. The authors noted a histological progression of arthritis similar to naturally occurring arthritis, with gross fibrillation extending deep into the articular cartilage at long time points. This study laid the groundwork for further ACLT studies in dogs[22–26], rats[27–29], rabbits[30–32], cats[33,34], guinea pigs[35,36], sheep[37], and mice[38,39].

Another common method of inducing OA in animal models involves partial or total removal of the medial meniscus[40–44]. Studies have combined meniscectomy and ACLT to model the combination injury seen clinically[39,45,46]. Destabilization of the medial meniscus (DMM) also initiates OA progression in mice[19,38,47–50]; this method has been the most commonly reported for studying OA in mice. DMM produces relatively predictable development of OA, although disease progression may be variable, particularly when the procedure is performed by surgeons with disparate skill or experience. These factors may represent potential drawbacks to the DMM model or any other surgical method. These procedures can be technically difficult to perform, and require specialized equipment and personnel to effectively perform the procedure. Surgical techniques also require opening the joint capsule, which can disrupt the natural environment of the joint, and may therefore come with unintended adaptive and healing processes that are due to the surgery itself, rather than the intended "injury". This consideration is particularly important when studying early time points following an injurious event, and thus require the use of "sham" surgeries and increased numbers of experimental animals.

Degenerative changes in the knee joint can also be achieved by intra-articular injection of degradative agents into the joint space, including proteolytic enzymes such as papain[51–53] and collagenase[53–56], cytokines such as tumor necrosis factor alpha (TNF-α)[57,58], transforming growth factor β (TGF-β)[59,60], and interleukin-1 (IL-1)[55,61], or chemicals such as monosodium iodoacetate (MIA)[53,62–64] and colchicine[65]. Different agents will create pathological changes in the joint by different mechanisms, making these approaches appropriate for studies of particular biological mechanisms. However, these methods do not mimic human injury conditions, suggesting that the translatability of information garnered from these models may not be relevant to PTOA.

Non-invasive mouse models of PTOA

Non-invasive models can initiate PTOA using externally applied mechanical loads, but do not break the skin or disrupt the joint capsule. Non-invasive injury models are therefore completely aseptic, and avoid potential confounding effects caused by the trauma of the surgical/invasive injury procedure.

A particular opportunity afforded by non-invasive injury models is investigating early adaptive processes that are initiated at the time of injury, with time scales of hours or days following injury (Fig. 1). This is a key advantage, as the window of opportunity for treatments aimed at slowing or inhibiting PTOA may be only a few days following injury. Non-invasive models more accurately recapitulate the mechanically-induced mechanisms involved in injuries leading to OA in humans, initiating joint degeneration through direct damage to cartilage, bone, or soft tissue structures of the joint. Additionally, non-invasive models may be simpler, quicker experimental procedures that are straightforward to implement and do not require technically difficult surgical or injury techniques.

Several non-invasive mouse models of PTOA have been described within the last few years. Each model initiates joint degeneration using different methods, and is therefore representative of specific conditions leading to the human disease. However, these non-invasive models represent a unique and important spectrum of animal models for studying different aspects of PTOA.

Intra-articular fracture of the tibial plateau

The first non-invasive mouse model of PTOA was described by Furman *et al.*, in 2007[66]. This model initiates symptoms using intra-articular fracture (IAF) of the proximal tibia, and includes blunt impaction of articular cartilage, fracture of the articular cartilage/subchondral bone layer, fragmentation of the articular surface, residual displacement of the articular surfaces, and exposure of blood and marrow products to the articular surface and synovium. This injury model is representative of higher-energy impact injuries that may be sustained by humans in events such as frontal automobile collisions.