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Introduction

Osteoarthritis (OA) is a chronic degenerative disease of diarthrodial joints, predominantly affecting the spine and peripheral joints of the body, particularly the hands, hips, knees and feet. OA most commonly affects people over the age of forty, with the risk of disease increasing with age. OA is a complex heterogeneous disease with different clinical and biochemical phenotypes.

The cause(s) of OA are unknown, and many studies have suggested that the pathobiology of OA is far more complex than a simple cartilaginous or bone disease. It is now acknowledged that OA affects many joint structures, including degeneration of cartilage, abnormal bone remodelling and synovial inflammation. Also, studies have shown that there is a complex interplay between the different joint components, making understanding of the degradative sequence of events involved in OA pathogenesis very difficult to dissect.

The initial onset of OA disease is considered due to an imbalance between the cartilage degradation and repair process. The exact sequence of events that trigger the onset of the disease is however widely debated throughout the literature. One hypothesis, suggests that secretion of pro-inflammatory cytokines into the synovial joint effects human disease. Existing models do not incorporate the important inter-tissue communication between joint components required for disease progression and differences in size, anatomy, histology and biomechanics between different animal models makes translation to the human model very difficult. This narrative review highlights the advantages and disadvantages of the current models used to study OA. It discusses the challenges of producing a more reliable OA-model and proposes a direction for the development of a consensus model that reflects the natural environment of human OA.

We suggest that a human osteochondral plug-based model may overcome many of the fundamental limitations associated with animal and in-vitro models based on isolated cells. Such a model will also provide a platform for the development and testing of targeted treatment and validation of novel OA markers directly on human tissues.

Keywords: Osteochondral plugs, Osteoarthritis, ex-vivo model, in-vivo model, Animal-model

SUMMARY

Osteoarthritis (OA) is a chronic degenerative disease of diarthrodial joints most commonly affecting people over the age of forty. The causes of OA are still unknown and there is much debate in the literature as to the exact sequence of events that trigger the onset of the heterogeneous disease we recognise as OA.

There is currently no consensus model for OA that naturally reflects human disease. Existing ex-vivo models do not incorporate the important inter-tissue communication between joint components required for disease progression and differences in size, anatomy, histology and biomechanics between different animal models makes translation to the human model very difficult. This narrative review highlights the advantages and disadvantages of the current models used to study OA. It discusses the challenges of producing a more reliable OA-model and proposes a direction for the development of a consensus model that reflects the natural environment of human OA.

We suggest that a human osteochondral plug-based model may overcome many of the fundamental limitations associated with animal and in-vitro models based on isolated cells. Such a model will also provide a platform for the development and testing of targeted treatment and validation of novel OA markers directly on human tissues.

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OA a distinct challenge. Human OA tissue samples are usually collected for research once end stages of the disease have been reached, for example during joint replacement, by which time destructive changes in the joint are well established. This makes studying the early disease process very challenging. OA pathology, particularly early OA, is therefore very difficult to study, and so researchers turn to *in vivo* and *ex vivo* preclinical animal models to investigate early pathological changes in OA. These models offer unique advantages as well as limitations for studying human OA. This article will review the different models used for OA research.

### Table I

A summary of the advantages and disadvantages of different *ex vivo* models used in OA research

| Ex-vivo Model | Advantages | Disadvantages | Example of the application of the model in OA research |
|---------------|------------|---------------|-------------------------------------------------------|
| Monolayer culture | - A large number of cells can be easily produced from a single sample | - Limited for certain tissue types such as cartilage, whose phenotype changes once in a monolayer culture environment, introducing inter-experimental variability | - Monolayer cultures can be used to study the effects of cytokine stimulation and osmotic pressure |
| - The configuration of cells cultured in a monolayer layout allows homogenous spread of nutrients and growth factor from the culture medium | - Chondrocytes are very sensitive to their molecular environment and so need to remain in contact with the extracellular matrix to ensure that they reflect natural *in vivo* samples | - Synovial cell cultures useful to study the role of the synovium in OA |
| - Cartilage has low cellularity, therefore, a large sample of cartilage is required to ensure sufficient numbers of cells are present to carry out a reliable experiment | - Cells in monoculture traditionally grow on a flat surface in glass or plastic flasks and so do not allow for growth in all directions, as seen in the natural 3D *in vivo* environment | |
| - Isolating a tissue in culture removes all systemic influences on that tissue, which does not reflect natural joint tissue | - Different conditions are required for culturing each cell type | |
| - The 3D structure provides structural strength to sensitive cells | - Co-culturing cells can result in alterations of phenotype when cells are isolated | |
| - The proliferation rate of cells tends to be slower in 3D cell cultures compared to 2D cultures | - Co-culturing cells traditionally grow on a flat surface in glass or plastic flasks and so do not allow for growth in all directions, as seen in the natural 3D *in vivo* environment | |
| - The structural strength provided to cultured cells depends on the scaffold used | - The structural strength provided to cultured cells depends on the scaffold used | |
| - Co-culturing cells can be used to study the effects of cytokine stimulation and osmotic pressure | - Co-culturing sclerotic osteoarthritic osteoblasts and chondrocytes from osteoarthritic articular cartilage results in an increased shift towards chondrocyte hypertrophy and release of matrix metalloproteinases and aggregases | |
| - Co-culturing synovium and cartilage together produce very different results in terms of the break-down of proteoglycan and matrix structure compared to when cultured alone | - Co-culturing synovium and injured cartilage produces a protective effect on synoviocytes | |
| - Simple, cheap and easy to produce | - Cell death often occurs at the explant edge | |
| - Explant models allow for the natural processes that occur within the extracellular matrix environment to be observed | - Only a limited number of cells can be extracted from a single source | |
| - 3D cell culture allows for culture of different cell lines and important cell-cell interactions | - Limited tissue availability and significant inter-experimental variability | |
| - 3D cell cultures grow as aggregates or spheroids in a matrix, allowing growth in all directions, similar to the natural *in vivo* environment | - Explant based models can be used to study the effects of cytokine stimulation and osmotic pressure, as well as the effects of physical injury and loading on tissue | |
| - The 3D structure provides structural strength to sensitive cells | - A matrix structure of collagens and proteoglycans favours phenotypically normal cartilage | |
| - 3D cell culture can be used to study the effects of cytokine stimulation and osmotic pressure, as well as the effects of physical injury and loading on tissue | - Synovial tissue explants useful to study the role of the synovium in OA |
Table II
A summary of the different animal models used in OA research

| Species/Model | Spontaneous | Surgically induced | Chemically Induced | Examples of the application of the model in OA research |
|---------------|-------------|--------------------|--------------------|--------------------------------------------------------|
| Mouse         | Naturally occurring OA 1,2,34 | - Anterior cruciate ligament transaction (ACLT) 3,4,41-43 | - Mono-iodoacetate (MIA) intra-articular injection 3,40 | - Mouse models widely used for toxicology testing. 1 |
|               | - Genetic models: PAR2 -/+ , CD4 -/- , MMP17 -/- , Tenascin C -/- , Ddr2 -/- , SulPhatase -/- , IGF2, Syndecan 4 -/- , Fg2 -/- , Mmp13 -/- , Hif2a -/- , GDF5 -/- , Osteopontin, Ptgse1, Trnfrsf1b b1/- , Runx 2 -/- , ADAMTS-5 -/- , ADAMTS-7 -/- , ADAMTS-9 -/- , iNOS -/- , Tnf -/- | - Articular groove model 34 | - Steroids, cytokines 3,40 | - Mouse models used to study the molecular basis of OA. 35 |
|               | - Naturally occurring OA 1,2,34 | - Intra-articular tibial plateau fracture, cyclic articular cartilage tibial compression, anterior cruciate ligament, rupture via tibial compression overload 3 | - Ovariectomy 41 | - Genetically modified mouse models used to investigate the genetic factors and specific genes involved in cartilage degeneration, bone remodelling and inflammation 1,18,43-45 |
|               | - Canine - Naturally occurring OA 2,34,41 | - Partial discectomy 44 | - Partial discectomy 44 | - Rat model useful in toxicity testing of pharmaceutical compounds 1 . MMT, medial collateral ligament transaction (MCLT) and iodoacetate induced models used to study pain 30-45 |
|               | - Canine - Abrasion, valgus osteotomy, cartilage defect 1,2 | - Medial meniscal transection 40 | - Medial meniscal transection 40 | - Rat undergone partial medial meniscectomy are useful in cartilage restoration techniques 45 |
|               | - Canine - Articular cartilage 3,4 | - Combination surgery 45 | - Combination surgery 45 | - Syrian hamster OA models are naturally occurring, and transgenic models are used to study pathogenesis of OA 1 |
|               | - Canine - ACLT and removal of medial/lateral meniscus or transection of posterior medial/lateral collateral ligament 34 | - Combination surgery 45 | - Combination surgery 45 | - Transgenic guinea pig models used to study pathogenesis of OA 1 |
|               | - Canine - MCLT, osteotomy, patellarctomy, sciatic nerve crush 34 | - Ovariectomy 41 | - Ovariectomy 41 | - Guinea pig models used to study age and BMI associated risk factors in OA 34 . Dunkin Hartley guinea pig used in therapeutic and pathogenic studies of knee OA 34 . Guinea pigs induced by medial meniscal tear and spontaneous OA models used to study slow and rapidly progressive OA 35 |
|               | - Canine - Combination surgery 45 | - Medial meniscal transection (MMT) 1,34,41,45 | - Medial meniscal transection (MMT) 1,34,41,45 | - Useful in pain studies 2 |
|               | - Canine - Partial discectomy 44 | - Combination surgery 45 | - Combination surgery 45 | - Rabbit models useful in efficacy testing of various compounds such as hyaluronic acid 35 |
|               | - Canine - Partial discectomy 44 | - Partial discectomy 44 | - Partial discectomy 44 | - Partial meniscectomy models used in testing chondroprotective agents 3 |
| Mouse Del1: Short deletion in type II collagen 18 | - Partial medial meniscectomy models used in testing chondroprotective agents 3 |
| Guinea pig    | Naturally occurring OA 2,34,41 | - ACLT 40 | - Intra-articular injection of steroids, cytokines 30 | - Partial meniscectomy models used in testing chondroprotective agents 3 |
|               | - Transgenic models 1 | - MCLT, osteotomy, patellarctomy, sciatic nerve crush 34 | - Collagenase 34-40 | - MIA, papain, collagenase, copper II bisglycinate, lipopolysaccharide, chondromucoprotein 35 |
|               | - Naturally occurring OA in medial compartment of knee joint in Dunkin Hartley guinea pigs 1,18 | - Combination surgery 45 | - Quinolone 34 | - Quinolone 34 |
| Syrian hamster| Naturally occurring OA 2,34,41 | - ACLT 40 | - Mono-iodoacetate (MIA) intra-articular injection 3,40 | - Chymopapain, trypsin, IL-1β, chondroitinase, vitamin A, fibronectin fragments 35 |
|               | - Transgenic models 1 | - Collagenase 34-40 | - Collagenase 34-40 | - MIA, papain, calcium pyrophosphate crystals 34,41 |
| Guinea pig    | Naturally occurring OA 2,34,41 | - Immunoconjugate, papain, collagenase, copper II bisglycinate, lipopolysaccharide, chondromucoprotein 35 | - Allogeneic cartilage particles 66 | - Allogeneic cartilage particles 66 |
| Cat           | Naturally occurring OA 2,34,41 | - MIA, papain, collagenase, copper II bisglycinate, lipopolysaccharide, chondromucoprotein 35 | - MIA, papain, collagenase, copper II bisglycinate, lipopolysaccharide, chondromucoprotein 35 | - MIA, papain, calcium pyrophosphate crystals 34,41 |
| Rabbit        | Naturally occurring OA 2,34,41 | - Intra-articular injection of steroids and cytokines 30 | - Allogeneic cartilage particles 66 | - Allogeneic cartilage particles 66 |
| Canine        | Naturally occurring OA 2,34,41 | - Combination surgery 45 | - Combination surgery 45 | - MMX model useful in toxicity testing and ACLT model used to study slow progression of OA and pathogenesis that mimics naturally occurring disease 1 |
|               | - Abrasion, valgus osteotomy, pelvic osteotomy, cartilage defect 1,2 | - Combination surgery 45 | - Combination surgery 45 | - Canine models that naturally develop OA have been used in |
|               | - Cranial cruciate ligament transaction 57 | - Combination surgery 45 | - Combination surgery 45 | - MMX model useful in toxicity testing and ACLT model used to study slow progression of OA and pathogenesis that mimics naturally occurring disease 1 |
investigation of OA, discuss their advantages and disadvantages, and propose development of a gold standard model for OA that closely reflects natural human disease.

### Current models used in OA research

OA research models can be categorised into either ex-vivo or in-vivo models. Depending on the research question, different models can be used to address different aspects of OA development and progression. Each model has its advantages, yet it has become clear that no single model provides the opportunity to study the disease as a whole. The different models currently used in OA research are discussed below.

#### Ex-vivo models

Ex-vivo models can be categorised into monolayer culture, co-culture, three-dimensional (3D) culture and explant-based culture. Each model has its advantages and disadvantages and so can be used to answer different questions in OA research.
A summary of the advantages and disadvantages of different animal models used in OA research.

| Animal Model | Advantages | Disadvantages |
|--------------|------------|---------------|
| Mouse        | - Mice have a short life span (generally one or 2 years) and so develop OA fairly rapidly, making mice an easy model to study the whole disease process; - Small animal size means the whole joint can be histologically sectioned; - Mice are easily managed, with low maintenance cost, demonstrate rapid disease onset and their complete genome is available for study; - Genetically modified mouse models are easy to produce and are useful to investigate the genetic factors involved in OA pathogenesis, specifically genes involved in cartilage degeneration, bone remodelling and inflammation; - Mouse models can be used in toxicology testing and to establish the molecular basis of OA. | - Huge variation in results observed between different strains of mice; - Disease severity varies with age, with older mice more representative of human disease; - Difficult to ascertain skeletal maturity as growth plates often do not close completely; - Mice are anatomically and histologically different to humans, for example, mice have a thicker layer of calcified cartilage, do not have three distinct chondrocyte layers and have a cartilage seventy times thinner than humans; - Macroscopic lesions and degrees of damage are difficult to identify due to the small anatomical size of mice; - The progression and process of disease is faster in mice than in humans (weeks rather than decades); - The small size of mice makes surgical inducing OA more challenging; - Postoperative management of mice is difficult in surgically induced models. |
| Rat          | - Rat cartilage is thicker than that of mice, so it is possible to induce partial and full-thickness cartilage defects; - Rats rarely experience post-operative infection so are useful animal models to surgically induce OA; - Rats are easily managed and require low maintenance costs; - It is easier to perform surgery in rats than in mice due to their larger size; - The full rat genome is available for study; - MMT, MCL transection and iodoacetate models useful to study pain; - Rat models useful in toxicology testing and studying cartilage restoration techniques. | - Naturally occurring OA is uncommon in rats, variation in results is often observed between different strains of rat and disease severity varies with age, with older rats tending to present with more severe OA; - It is difficult to ascertain the skeletal maturity of rats; - Rats have greater volumes of highly vascularised adipose tissue and muscle in the medial knee region; - Post-operative rats immediately resume load-bearing which accelerates joint degeneration; - Genetically engineered rat models are not available and postoperative management of rats is challenging; - The weight of each guinea pig and whether they are housed alone or in pairs influences the severity of their OA; - Unlike in humans, guinea pigs resume load-bearing post-operatively which accelerates joint degeneration; - The time to guinea pig skeletal maturity is fast. |
| Guinea Pig   | - The guinea pig model has similar OA histopathology to disease in humans; - Guinea pigs are large enough that tissue samples can be easily collected for tests and the whole joint can be histologically sectioned; - Guinea pigs are easy to manage; - Naturally occurring guinea pig models are available and the disease pathogenesis is predictable and similar to that seen in humans; - Hartley guinea pigs can be used to study risk factors for OA such as BMI and age. | - Complete guinea pig genome available; - The full cat genome is available; - The small size of mice makes surgical inducing OA more challenging. |
| Cat          | - Cats are larger in size allowing for tissue and fluid collection; - The full cat genome is available. | - Cats are difficult and costly to manage and there are ethical issues surrounding emotional attachment; - Cats display genetic variability between individuals; - Rabbits have a very different gait compared to humans and only rabbits over the age of eight or 9 months can be used to guarantee skeletal maturity; - The cartilage of rabbits is ten times thinner compared to humans, with a higher chondrocyte density and cartilage zonal layers that varies highly within the same joint; - The rabbit meniscus is more cellular, has less vascular penetration and can heal faster than the human meniscus; - Rabbit cartilage can spontaneously heal and regenerate and there is no complete rabbit genome available for study. |
| Rabbit       | - Naturally occurring OA is very common in rabbits; - Rabbit model useful in studying the efficacy of compounds; - Complete rabbit genome available. | - OA progression varies with the age of the rabbit after surgical OA induction, with faster progression seen in older rabbits; - Canines have different joint biomechanics and gait compared to humans, their skeletal maturity is not reached until 9 to 18 months of age and their cartilage is half the thickness of human cartilage; - There are ethical issues surrounding emotional attachment of dogs and management is costly; - Canines display genetic variability between individuals. |
| Canine       | - Canines have similar anatomy and disease progression to humans; - Canines display a widespread clinical incidence of OA; - Canines are easy to manage and train postoperatively; - Surgical lesions develop slowly in canines, similar to the human model; - Canines have similar gastrointestinal physiology to humans; - The canine model is widely used so comparison across different studies can be made, the larger size of canines allows for tissue and fluid collection and the full canine genome is available; - Naturally occurring OA models are available for intervention preclinical trials; | - Canine cartilage thickness varies between individuals, the skeletal maturity of a goat is not reached until at least 2 years of age and cartilage healing capacity varies with a goat’s age, with better capacity in younger animals; - Cartilage repair outcomes differ in the short and long term and so follow up is required to assess progress; - Naturally occurring OA in goats is uncommon; - The disadvantages of the sheep model are very similar to the caprine model of OA. |
| Caprine      | - Anatomically the caprine stifle joint is very similar to the human knee; - The caprine stifle joint is closest in size to the human knee joint, the larger size of the animal allows for tissue and fluid collection and goat cartilage thickness is close to that of humans; - Goats are cheap and easy to use in studies compared to most large animal models and they can be used to study cartilage repair; - Complete goat genome available. | - Caprine cartilage thickness varies between individuals, the skeletal maturity of a goat is not reached until at least 2 years of age and cartilage healing capacity varies with a goat’s age, with better capacity in younger animals; - Cartilage repair outcomes differ in the short and long term and so follow up is required to assess progress; - Naturally occurring OA in goats is uncommon; - The disadvantages of the sheep model are very similar to the caprine model of OA. |
| Ovine        | - Sheep are cheap and easy to use in studies compared to most large animal models. | - The advantages of the sheep model are similar to the caprine model of OA. |
Ex-vivo models such as monolayer culture and co-culture are easier and cheaper to produce than 3D cell cultures and explant-based models. Monolayer cultures are also easy to produce on a large scale and avoid the challenges associated with culturing different cell types at different conditions. However, monolayer and co-cultures are limited in their use due to the fact that they isolate only one or two tissue components at a time. Many studies have shown that there is a strong interplaying network of communication between different joint components that help regulate and maintain a healthy joint, and so isolation of specific joint components hinders this communication. For example, healthy articular cartilage is dependent upon the release of soluble factors by subchondral bone, and interactions between chondrocytes and synovial fluid ensures the joint is anatomically similar to the human knee and so is produced on the synoviocytes. Similarly, culture of subchondral bone and cartilage separately results in increased chondrocyte death and cartilage degradation as well as decreased protein content in culture media compared to when cultured together. Explant models and 3D cell cultures allow for this inter-tissue communication and so are arguably more useful models available to OA researchers to reproduce natural in-vivo environments. Despite this, these models are more difficult to produce in terms of tissue volume and maintaining cell viability over extended periods of time. Some of the advantages, disadvantages and applications of various ex-vivo models used in OA research are summarised in Table I.

In-vivo models

Many animal models in at least eighteen different species have been developed to study established pathological features of OA such as pain, synovitis, cartilage degeneration and bone remodelling. Animal models used in OA research (see Table II) can be categorised into either induced or spontaneous models. Induced models refer to models where OA disease (or OA like features) have been induced either chemically or surgically. On the other hand, spontaneous models are subcategorised into naturally occurring and genetically modified models that develop OA.

Smaller animal models of OA such as mice, rats, rabbits and guinea pigs are much easier, quicker, cheaper and more readily available than larger animal models such as horses, pigs and dogs. Smaller animals can be handled and housed with greater ease than larger models, but due to their smaller size, tissue samples extracted are much smaller and therefore tend to differ to a greater extent in their anatomical and histological structure when compared to humans. Larger animal models therefore provide many advantages over the use of smaller animal models in terms of their greater anatomical similarity to the human model. A dog’s articular cartilage for example is half the thickness of a humans, whereas that of a mouse is a minimum of 70 times thinner. Additionally, a wider range of tests can be performed on larger animals, such as repeated synovial fluid collection and imaging. They also have a longer life span allowing for slower disease progression and time to end stage OA, as seen in humans. Whilst slow progressive models most accurately reflect human OA, they are however more expensive and time consuming to conduct. There are also greater ethical considerations around the use of larger animal models, such as non-human primates and canines. Based on this, some animal models are therefore better suited to OA research than others, such as the canine, caprine, bovine and porcine models. Some of the advantages and disadvantages of various animal species used in OA research are summarised in Table III.
cartilaginous, and biomechanics and physiology makes translatability between animal models and human disease very difficult. Challenges are posed by species-specific differences in disease pathology and progression, as well as normal joint homeostasis, specifically the repair processes that occur within the joint. Different OA induction methods used in certain animal species also sometimes results in differences in OA presentation. There is therefore a need to reduce experimental variability and increase the reliability of data interpretation. Furthermore, different animal models have been shown to represent different stages of the disease more effectively, making selection of an animal model that completely reflects natural human disease challenging. To add to this, it has become clear that there is much dispute as to what defines OA and which molecules are associated with the disease. This is in part hindered by the fact that current ex-vivo models do not allow for the important inter-tissue communication between different joint components required for natural OA disease processes to be studied. To gain a better understanding of the mechanisms of joint damage in OA, specifically the exact sequence of events and interactions between different joint components, it has been suggested that more focus should be placed on developing 3D cell cultures and explant-based models that allow for these important interactions, providing interesting opportunities for researchers to develop their understanding of OA.

In the ideal animal model, the disease must be induced reliably, with 100% penetrance, and within a suitable time frame, and yet still present with disease characteristics that are comparable to the human condition. Disease progression in the animal model should also allow for the examination of all stages of disease to ensure full detection of any therapeutic effects. The animal must be inexpensive, easy to house and manage but also be of large enough size to allow for a full range of analysis techniques to be performed. The animal must also be anatomically, biomechanically and histologically similar to humans. Some animal species, such as the canine, caprine, bovine and porcine models, are therefore better suited to OA research than others.

A promising model for OA

OA is a disease of the whole joint and therefore the gold standard model for human OA must allow for key communication between different tissues of the joint. An osteochondral (cartilage on bone) model may overcome many of the current challenges and limitations of the various models discussed above. The use of osteochondral plugs provides a model incorporating the key joint tissues affected in OA, maintaining the important interactions between these tissues as seen in human disease. There are a few studies that have used osteochondral plugs from bovine, equine and human samples as ex-vivo models of OA. These osteochondral plug-based models appear very promising and so further studies should be encouraged as the basis for developing a gold standard model for OA. In the model design, cytokines such as interleukin-1 beta (IL-1β) and tumour necrosis factor alpha (TNF-α) may be used as the best method for inducing OA (cartilage damage) and tissue responses that closely replicate the natural disease, as these cytokines are known to contribute to the inflammatory effect of the synovium in the model. However, OA is a complex disease and many cytokines and chemokines have been shown to be expressed in OA synovium and detected in synovial fluid. Therefore, in the model design, investigators should consider using synovial tissue and/or synovial fluid from patients with active disease to induce OA in the osteochondral plugs. Osteochondral plugs can be harvested from joint surfaces, such as the femoral condyle, tibial plateau and patella. Methods of plug extraction available for use include different sizes of graft harvester, biopsy punch, mosaicplasty osteotome, diamond tipped cylindrical cutter or surgical trephine burr. Plugs can be cultured in serum-free culture medium such as Dulbecco's Modified Eagle Medium F-12 (DMEM-F-12, Invitrogen, USA) or α-Minimum Essential Medium (α-MEM, 22,561 Gibco, The Netherlands) for up to 57 days with significant cell viability. Indeed, an early study reported that >99% chondrocyte viability can be maintained in the untraumatized areas at the centre of the osteochondral plugs.

The availability of an osteochondral plug-based model, particularly a human tissue-based one, would be invaluable in screening of new disease-modifying osteoarthritis drugs (DMOADs). Currently, there are many DMOADs under different stages of development. Early studies of these drugs were in animal models, but the availability of this new model will provide an opportunity to directly test these drugs on human tissues. An osteochondral plug system like this may also be used for discovery of novel markers for OA.

Conclusion

It is clear that we are limited in our understanding of OA because we do not have a suitable model that accurately reflects natural human OA. Whilst animal models provide crucial information about disease mechanisms, none of the current models used in OA research recreate the natural in-vivo environment and allow the whole disease process to be studied. Differences in anatomy and biomechanics also makes translatability to the human model a distinct challenge. It is also important to consider the cost and ease of management of using animal models in research. Whilst smaller animal models provide many benefits in terms of availability, handling and management, larger animal models such as canines and pigs are not only more comparable to humans physiologically but also in their progression to disease. Their larger size also allows for performance of a broader range of analysis techniques and investigations.

The models currently used in OA research each have their advantages and disadvantages; however, it has become clear that there are consistent problems with all of these models that hinders our ability to understand the pathogenesis of OA. The only way to achieve greater understanding of the pathological processes that underpin OA is to produce a ‘gold standard’ model for OA. Development of a consensus model will provide greater understanding of the specific stages and interactions involved in OA pathogenesis, as well as a model that can be used to compare data findings between different research groups, test pre-clinical drugs and identify and test possible biomarker targets directly on OA joint tissue. An osteochondral plug-based model could be a “promising” new model for OA, able to provide a reliable throughput model for proof of concept and mechanistic studies, aiding the discovery of targeted OA therapy. The model would also provide an opportunity to reduce the financial, ethical and time restraints associated with using animals in research, shifting OA research to embody the principle of the 3Rs; replacement, reduction and refinement of animal use in research.

Author’s contributions

Conception and design: MS, KO, YL. Drafting of the article: PC, MS, KO. Provision of study materials: PC, YL. Final approval of the article: MS.

Competing interest statement

The authors declare that they have no competing interests.

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