New animal models of wear-particle osteolysis

Jean Langlois · Moussa Hamadouche

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Abstract Particle debris resulting from in vivo degradation of total joint replacement components are recognised as the major factor limiting the longevity of joint reconstruction and the overall success of the procedure. Better understanding the complex cellular and tissue mechanisms and interactions resulting in wear-particle osteolysis requires a number of experimental approaches, including radiological monitoring and analysis of retrieved tissues from clinical cases, in vitro experiments, and also animal-model investigations. In consideration of both their advantages and drawbacks, this paper provides an historical overview of numerous animal models that have been developed over the last three decades to investigate the pathogenesis of wear-particle osteolysis and to facilitate the preclinical testing of new treatment options. The authors also focus on recent studies in order to provide a better understanding of the current state of the art on this subject and propose some perspectives regarding technical and fundamental questions.

Introduction

Total joint replacement has been very successful and cost effective in restoring quality of life [1] to a multitude of patients worldwide since its advent more than 30 years ago. With improvements in prophylaxis against infection, component fatigue strength, and skeletal fixation, wear and its sequelae have become the primary limitation to its longevity (75% of all failures). Clinically, periprosthetic osteolysis can lead to aseptic loosening of components, massive bone loss that renders revision surgery technically more challenging, and periprosthetic pathological fracture [2]. Evidence in support of the role of prosthetic implant wear includes four areas.

1. Radiological correlation between osteolysis and higher wear rates [3]: Dumbleton et al. found a revision inferior to 30% rate at 20 years, which was significantly correlated with a polyethylene wear rate >0.1 mm per year [3]. To date, wear remains the only positive correlation with aseptic osteolysis and implant loosening.
2. Explant examination: Vast numbers of wear particles are found associated with the periprosthetic interfacial membrane removed during revision surgery [4–6]. The limitation is that the outcome measures represent the end stage of the process.
3. Cell involvement: In vitro, several cell populations have been implicated in the initiation and development of periprosthetic osteolysis in response to wear debris [7–9]. However, these models do not mimic the complex network and general environment in which multiple cell interaction occur.
4. Experimental models: Experimental systems have demonstrated that particulate debris can induce osteolysis in a variety of animal models. For these models,

J. Langlois (✉)
Resident in Orthopaedic and Trauma Surgery,
Department of Orthopaedic
and Reconstructive Surgery Service A,
Centre Hospitalo-Universitaire Cochin-Port Royal,
27 Rue du Faubourg St Jacques,
75014, Paris, France
e-mail: jeangast@hotmail.com

M. Hamadouche
Orthopaedic Surgery, Department of Orthopaedic
and Reconstructive Surgery Service A,
Centre Hospitalo-Universitaire Cochin-Port Royal,
27 Rue du Faubourg St Jacques,
75014, Paris, France

the choice of species, the mechanical environment of the stimulated bone, and many other factors are critical to allow relevant extrapolation to the clinical situation.

This paper provides a concise historical overview of animal models in particles osteolysis, stresses their main advantages and limitations, discusses some of the more recent animal models directed at understanding this biological cascade of events, and provides future perspectives. Involvement of other potential contributors to osteolysis and aseptic loosening [10], including mechanical factors, are beyond the scope of this review and are not discussed.

Historical overview

Animal models have played a critical role in many areas of medicine and biology. These can generally be categorised into three domains: (1) fundamental discovery, (2) feasibility and bioactivity testing, and (3) clinical modelling and efficacy prediction. Our subject (periprosthetic osteolysis from a mechanistic and fundamental therapeutic point of view) mainly concerns the two first domains.

Fundamental discovery Questions related to fundamental discovery involve characterisation of biological mechanisms. These are inevitably addressed in highly defined animal models (both genetically and immunologically) that provide a high level of reproducibility. This kind of research also demands animal systems in which reagents (e.g., antibodies and probes) are readily available and where turnover of individuals (breeding) and the occurrence of biological events (e.g., morphogenesis, disease development, injury repair, and aging) are rapid. Therefore, the study of animals with short development and life cycles (days to months) provides the best opportunities for detecting and observing the process under study. That it why in fundamental studies (such as ours) on bone tissue, small vertebrates such as *Mus musculus* (mouse) and *Rattus norvegicus* (rat) are the most relevant.

Feasibility and bioactivity testing Feasibility and bioactivity testing takes one step toward clinical translation by asking: Is this mechanism a possible therapeutic target? In the setting of an implant, the anatomical location and tissue at the site of implantation will generally match the type of tissue, if not the exact location, in which therapeutic use is expected. However, in the case of bone formation or repair, subcutaneous, epimuscular, intramuscular, periosteal, and intraosseous sites of implantation (both cranial and long bone) have been used. As with model systems used for fundamental discovery, these testing models benefit from the use of inbred strains of mice and rats, where outcomes

can be determined after relatively short periods of observation and where the variation in radiographic, imaging, histological, or biochemical outcome between individuals is small (thus reducing the number of animals needed to achieve a statistically significant assessment). In some settings, feasibility studies must be advanced into a larger animal, such as a rabbit, dog, sheep, pig, or—rarely—horse. For example, this is necessary when the surgical procedure involved cannot be performed reproducibly in a smaller animal (e.g., spinal fusion procedures or tendon–rotator cuff repair procedures) or when the size of the implant or device under study exceeds the volume capacity of a smaller animal (e.g., assessment of an implant >1–4 cm, depending on the tissue site).

For obvious reasons, the early models of aseptic loosening involved an implant (of stainless steel or titanium) in association with different types of particles. However, once an implant is integrated into bone to achieve true fixation, clinical aseptic loosening takes at least six months (even with a modified rat model that incorporated a running wheel for two hours per day for five days per week) [11]. Based on the limitations of the implant models, investigators decided to focus on the biology of wear-debris-induced osteolysis independent of the critical mechanical and biomechanical components of aseptic loosening. To this end, they have developed many nonimplant models that shorten and multiply the experiences.

No model is ideal for every stage of testing. Each experimental approach has its own set of advantages and limitations, and it is of major importance to know them in order to fit the scientific question with an experimental approach.

Larger animals

Larger animal models allow for more clinically relevant implants that can be subjected to appropriate physiological loads, but their cost is often prohibitive, especially when multiple therapeutic interventions are being considered. Sufficient power can be difficult to obtain. Distinction between implant and nonimplant models is one of the most relevant.

Rabbit models

Historically, some of the first investigations were supported by rabbit models, the smallest animal to have the Haversian system in its bone. Use of an in vivo model avoided the primary difficulty of examining polyethylene particles in cell culture. Indeed, polyethylene particles float at the top of culture media, leading to physical separation between particles and cells. Goodman et al. developed the “particle size effect” principle using New Zealand rabbits: when

implanted in bulk form, medical polymers and metals are surrounded by an incomplete fibrous-tissue layer. When implanted in particle form, these same materials induce an inflammatory reaction, including macrophage infiltration, foreign-body giant cells, and fibrous tissue similar to that seen around loose implants [12]. Nonimplant rabbit models [such as bone harvest chamber or bone groove with polymethylmethacrylate (PMMA) plug] have been very useful to delineate the effects of different particle types and concentrations on bone ingrowth and to explore the effects of different pharmacological interventions [13–18]. Kubo et al. [19] evaluated the response to a variety of particles of differing sizes by inserting a PMMA plug with a groove for particle placement into rabbit femora. They found a marked histiocytic response around particles of ultra-high-molecular-weight polyethylene, stainless steel, and cobalt–chromium. A less intense histiocytic response was found surrounding particles of alumina ceramics and titanium. Although not ideal in term of size, a variety of implant systems with rabbits have been investigated, including poorly cemented tibial hemiarthroplasty [20], or by directly placing particles around the implant [21]. Subsequent tissue-culture supernatants from this model demonstrated elevated prostaglandin E₂ (PGE₂) levels in association with loose implants [20]. Others have used implants to study the effect of hydroxyapatite seals around an implant to prevent polyethylene particle ingress into the bone–implant interface [22].

Canine models

Spector et al. developed a canine model of aseptic loosening by loosely implanting a femoral component into a bed of preinserted cement particles. They isolated and cultured periprosthetic cells from these animals and found an elevated secretion of interleukin 1 (IL-1) and PGE₂. The secretion of these mediators paralleled the radiographic appearance of loosening. The PGE₂ response was partially suppressed by in vitro administration of naproxen [23]. Turner et al. reported on aseptic loosening of cemented total hip prostheses in a canine model. They found thick, fibrous, and granulomatous membranes at the failed cement–bone interface, with sheets of histiocytes and occasional foreign-body giant cells. They identified granulomatous cortical erosions with evidence of particulate debris. Dowd et al. also used an in vivo canine hip arthroplasty model to study the effects of motion and particles. The prosthesis was designed with a reservoir for particles. In addition, a midshaft ball joint allowed motion between the proximal and distal portions of the prosthesis. The histological and biochemical characteristics of the experimentally induced membranes were similar to those of tissues retrieved at revision surgery [25]. The canine model has been implemented in other investigations: Shanbhag et al. demonstrated

a significant reduction in implant loosening when dogs were treated with alendronate [26]; Rahbek et al. recently demonstrated that hydroxyapatite coating prevents osteolysis associated with the injection of intra-articular particles [27].

Sheep models

Several total hip replacement and nonloaded implant models have been developed in sheep [28, 29]. One advantage of this species is that the implants and the forces on the implants and surrounding bone more closely resemble those in humans.

These early canine, rabbit, and sheep in vivo models have confirmed the results of in vitro cell-culture studies, demonstrating that various particle compositions can induce an inflammatory response and osteolysis. Unfortunately, none of the animal models truly demonstrated the radiographic findings that the orthopaedic surgeon associates clinically with osteolysis. Despite this limitation, many other outcome measures (histological, cellular, molecular, biological, and mechanical features associated with the clinical phenotype) can often be precisely quantified, providing useful approaches for assessing preventive or therapeutic intervention.

Smaller animals

Excepting their small size and volume, tricky access to bone, and limited cancellous bone, murine models present many advantages: controlled source available; inexpensive to purchase and house; high physiological turnover; homogenous and established genetic background; immunocompromised, transgenic, or knock-out models available; growing proven track records on bone and immunological mouse system. However, many of these studies are nonimplant models; major differences remain in physiological time courses between humans and a murine model (murine life span two years, for example), difficulties in evaluating bone and implants in loaded situations (gait and weight differences).

Rat models

The nonimplant rat models were first developed by Howie et al., who demonstrated osteolysis after injection of polyethylene particles around an acrylic plug placed in the femora of rats [30]. Gelb et al. used a subcutaneous air-pouch rat model to quantitatively demonstrate the in vivo effects of the size, morphology, and surface area of PMMA particles on the acute inflammatory response [31]. One of the earliest implant rat models was developed by Allen et al. [32] and then used to investigate the effects of alendronate on particle-induced osteolysis [33]. They

demonstrated that intra-articular injection of polyethylene particles caused substantial bone loss around a loaded implant and that alendronate effectively prevented the particle-induced periprosthetic bone loss.

Mouse models

More recently, three types of murine models of wear-debris-induced osteolysis were distinguished:

1. Air-pouch model: Several types of subcutaneously generated air-pouch models have been used in which bone tissue is implanted and then undergoes resorption [34]: particles of metal, polyethylene, and PMMA bone cement are then introduced into the pouch to promote inflammation and osteolysis. Gene therapy with the anti-inflammatory cytokines IL-1Ra or viral IL-10 protects mice from the inflammatory response to particles [35] and, importantly, also reduces osteolysis of bone fragments introduced into the air pouch [36], suggesting that the inflammatory response to particles contributes to the eventual bone loss characteristic of osteolysis. Another gene transfer (adeno-associated virus-mediated osteoprotegerin) succeeded in protecting against bone resorption [37].
2. Exposed calvarium model: The second mouse model to gain prominence involves direct application of particulate matter to the exposed calvarium. Merkel et al. first adapted this model to prove that titanium particles on the calvaria leads to profound inflammation, osteoclast formation, and bone resorption [7]. Schwarz et al. developed a method to quantitatively measure bone loss, allowing assessment of the potential various genetic approaches and biological agents to prevent bone loss [38]. Recently, the use of micro computed tomography has provided an additional highly quantitative method of assessing the degree of bone loss. This calvarial model was also used to study the involvement of a key proinflammatory cytokine, tumour necrosis factor (TNF)-alpha. Interestingly, inhibiting TNF-alpha action by deleting the genes encoding TNF receptors [7, 39] or by treatment with etanercept—a TNF antagonist [40]—diminishes particle-induced inflammation and osteolysis. The calvarial model was also used to show that the anti-inflammatory cytokine viral IL-10, a selective cyclo-oxygenase (COX)-2 inhibitor (celecoxib), or osteoprotegerin (OPG) can suppress wear-debris-induced osteolysis [41–43]. Strengths of this model include the possibilities of using transgenic and knockout models, rapidity of the development of osteolysis (about ten days), relatively low cost, and ability to screen a large number of compounds and doses of various agents. However, weaknesses are

Table 1 Selected literature regarding osteolysis in a murine model

Author	Animal (strain, age, no.)	Type of particles	Bone studied	Implantation time (weeks)	Outcome measures	Novelties	Drawbacks
Ren et al. [46]	<i>mus musculus</i> (nude, 12w, 13)	conventional UHMWPE	distal femur intramedullary injection (no implant)	1, 2	bioluminescence imaging and immunohistology	to observe the homing of circulating macrophages	short-term delay (adverse effects of systemic growth of the cells injected)
Ma et al. [47]	<i>mus musculus</i> (C57BL/6Jw, 5)	polystyrene (blue-dyed)	femur (intramedullary titanium tubing followed by silicone tubing connected to an osmotic pump)	4	volume of serum particles infused and rapid histology	Continuous infusion of particles over an extended period of time	only 50% delivery efficiency (based on an extremely approximative method); no clinically relevant particles; no bone loss proven yet
Yang et al. [48]	<i>mus musculus</i> (BALB/c, 10–12w, 13)	titanium (intramedullary injection at implantation + monthly intra-articular injections)	proximal tibia (intramedullary pin of stainless steel or titanium alloy)	2, 4, 12, and 26	histology + immunohistology microCT, biomechanical	long-term study, presence of an implant, on a weight-bearing joint, pull-out test, in vivo exogenous locoregional gene transfer	implantation implant + particles at the same time, delicate surgical technique, no quantitative measure of gene transfer
Zhang [49]	<i>mus musculus</i> (BALB/c, 10–12w, 18)	titanium (intramedullary injection at implantation + monthly intra-articular injections)	proximal tibia (intramedullary pin of stainless steel or titanium alloy)	2, 4, 12, and 24	microCT, histology + immunohistology, transgene product assessment	periparticular gene transfer or “therapy”	

UHMWPE ultrahigh molecular weight polyethylene, CT computed tomography

related to the fact that this model represents an acute (rather than chronic) effect, lack of an implant, and lack of other nonbiological factors likely related to osteolysis (oscillatory fluid pressures or mechanical forces).

3. Load-bearing implant introduced to long bones: The two first murine models suffer from a number of features that distinguish them from the analogous situation experienced by patients with osteolysis, the most significant being the absence of a loaded implant, and the use of implanted bone slices (air-pouch model) or flat bones (calvarial model) as opposed to long bones with the periosteum removed. In response to these concerns, a third class of mouse osteolysis model was developed in which load-bearing implants are introduced to the long bones and the effects of particles around the implant are studied. Early results from these models are promising and have confirmed that particles around the implants induce a proinflammatory response in the periprosthetic tissue [44].

A limitation of these small-animal models is that the temporal pattern of osteolysis is different from the long-term osteolysis that occurs in patients. However, an accelerated time scale is an essential feature of any experimental model of osteolysis. Moreover, substantial bone formation and repair occurs in osteolytic regions in patients with loose implants [45].

Selected recent short reviews

Overall picture

We selected four papers from the recent literature that we believe provide innovative insight into osteolysis animal models. These papers are summarised in Table 1 [46–49].

Respective discussion

Exploring one of the most initial processes (macrophage homing) to find a way to minimise osteolysis, Ren et al. [46] found an elegant way to improve the murine model by

using noninvasive in vivo imaging (confirmed by immunohistology). As they confirmed the short time course in this model (edge around day eight for a single introduction of particles), they also demonstrated that there may be “systemic signalling” (macrophages activated elsewhere than around the first injection site). However, once again, this model is a one-shot-stimulated model: it could be postulated that more locally originating macrophages would play a part in the reaction if the stimulation had been continuous. In order to reach a more realistic model with regards to the time course, Ma et al. [47] showed that continuous delivery with an osmotic pump, of particles into the intramedullary space in a mouse model was feasible. Moreover, they associated a stable intramedullary implant and a continuous infusion of particles. However, this can be judged as a preliminary study, as no bone loss has been quantitatively proved (polystyrene particles used), only a few animals were included, the exact number of particles delivered could only be grossly extrapolated, and—surprisingly—no particles were observed on any histological bone section. We consider that major improvements were provided by Yang et al. [48] and Zhang et al. [49]. These authors used an effective long-term implant (pin implanted into proximal tibia to form a contiguous surface with the articular cartilage); an implant that stays well fixed after six months without particle challenge; monthly intra-articular injections for six months to achieve a long-term course (chronic reaction); pull-out tests as additional outcome measure; and most of all, in vivo gene transfer (using adenoassociated virus) to improve the delivery system of OPG-related therapy. Attempts have also been made to look for any general toxic effects of this new therapy.

Conclusion and perspectives

The use of animal models has always allowed researchers to perform well-controlled studies with standardised models to elucidate the complex biological response of both bone and soft tissues to particles. Quality criteria for animal studies could be summarised as shown in Table 2.

Table 2 Summary of possible quality criteria for animal studies

Criterion	Description
Appropriate controls	Sham and/or vehicle treatment, matched in age, sex, and strain, to experimental group. No historic control
Study population well described	Details on species, strain, substrain, sex, age, and initial body weight
Sample size appropriate	Large enough to achieve statistical power
Treatment well described	Details on administration of compounds (dosage, frequency, and route of administration)
Follow-up period suitable	Long enough to expect changes; details on dropouts or lost samples
Reliable outcome measurements	Outcome measures validated or generally accepted
Blinded outcome assessment	Especially for subjective measurements

The perfect model should refer to relevance to humans in terms of physiology, anatomy, and biomechanics. However practical considerations should also be discussed, including cost; availability of facilities, equipment, and skilled personnel; surgical access; timing issues; and relevance to outcome measures. However, experimental qualities (such as an original model) remain inferior to a relevant clinical question (such as novel hypothesis to one clearly stated clinical problem). Because the clinical phenotype of osteolysis remains multifactorial and complex, it will be unlikely that any single approach will ever be able to truly replicate the clinical scenario. A rational approach would be to screen strategies in small animals, then use larger animals for confirmation (such as pharmacological testing), and ultimately, controlled human clinical trials to document long-term efficacy. As the ultimate goal is to improve the treatment of patients with osteolysis, one of the largest research directions consists of testing new drugs to reduce already active osteolysis. Yet another way research can solve the problem is to prevent osteolysis: using alternative surface bearings, it remains important to expose them and, more specifically, their debris in experimental animal situations. Ultimately, a better understanding of individual sensibility to wear-debris particles using genetic research will probably help us to make more rational choices than those based only on age, bone stock, and—most of the time—the surgeon's own experience. Future research should probably be based on small animals using long, loaded, and implanted bones, over a rather long time period, using more relevant outcomes measures such as micromechanical testing, real-time imaging, or new biochemical marker analysis [proteomics by enzyme-linked immunosorbent assay or transcriptomics by reverse transcriptase polymerase chain reaction].

Conflicts of interest Authors declare no conflicts of interest

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