The most frequent cause of failure after total hip replacement in all reported arthroplasty registries is peri-prosthetic osteolysis. Osteolysis is an active biological process initiated in response to wear debris. The eventual response to this process is the activation of macrophages and loss of bone.

Activation of macrophages initiates a complex biological cascade resulting in the final common pathway of an increase in osteolytic activity. The biological initiators, mechanisms for and regulation of this process are beginning to be understood. This article explores current concepts in the causes of, and underlying biological mechanism resulting in peri-prosthetic osteolysis, reviewing the current basic science and clinical literature surrounding the topic.

Total hip replacement (THR) improves quality of life, including both pain and function, and has been shown to perform well for periods in excess of 30 years in patients with primary osteoarthritis, inflammatory arthropathies including rheumatoid arthritis, ankylosing spondylitis, avascular necrosis, post-septic arthritis, haemophiliac arthropathy, developmental dysplasia and fractures of the hip.

The natural history of THR is that of an increasing rate of failure as the interval from implantation increases. The mode of failure also changes with duration in situ, with infection and dislocation predominating in the initial stages, but aseptic loosening (osteolysis) and peri-prosthetic fracture becoming more common over time. Rates of revision are continuing to increase: in the United Kingdom, the National Joint Registry reported an 8.2% annual increase to 7852 revision procedures in 2010 and in 2008, 36 000 revision THRs were performed for 200 000 primary procedures in the United States; a lifetime incidence of revision of at least 18%. In every published registry, aseptic loosening is the leading cause of failure.

Initiation of osteolysis
Osteolysis is an active biological cascade that can be induced as a response to particulate wear debris, metastatic disease and primary bone tumours. It is a cell-mediated biological process that results in the loss of bone as a direct response to stimulation of macrophages by biologically active particles.

It is commonly accepted that this process begins with mechanical wear of the articulating surface releasing particulate wear debris. This debris is phagocytosed, activating the macrophages and osteoclasts, resulting in bone resorption. This mechanism, and the existence of an underlying biological process of aseptic osteolysis was first hypothesised by Willert and Semlitsch.

Early in the development of joint replacement bone cement was adopted as the fixation method of choice for both the femoral and acetabular components. The earliest descriptions of osteolysis were following revision of cemented THRs. Areas of bone loss and osteolysis were found in association with large granulomas filled with polymethylmethacrylate (PMMA) particles. It was assumed incorrectly that osteolysis was due to the cement. Although originally described as ‘Cement Disease’, any particulate debris may initiate an osteolytic reaction. Particles of ultra-high-molecular-weight polyethylene (UHMWPE), PMMA, cobalt-chrome (Co-Cr), titanium alloys, aluminium oxide (Al₂O₃) and zirconium dioxide (ZrO₂) have all been shown to act as biologically active wear debris.
The size rather than the type of wear particle probably has a greater effect on the biological activity. Most polyethylene wear particles are submicron (< 1 μm) in size, making visualisation with light microscopy difficult because of the wavelength of visible light (0.4 μm to 0.7 μm). This led to an initial underestimation of the number and volume of particles in peri-prosthetic tissues. The use of proteolytic enzymes on peri-prosthetic tissues and subsequent density-gradient centrifugation in conjunction with electron microscopy studies have allowed visualisation of smaller particles and more accurate estimation of particle numbers and size.

The initial supposition that osteolysis was due to cement particles led to a large number of in vitro experiments with PMMA particles. These may be phagocytosed by macrophages when < 7 μm, resulting in release of tumour necrosis factor-alpha (TNF-α). Further investigation has established that all types of metal (stainless steel, Co-Cr-molybdenum, titanium-oxide), polyethylene and ceramic debris invoke a similar cell-mediated response. Some types of wear debris have been shown to be more cytotoxic than others. Current evidence suggests that all wear particles provoke a similar immunologically mediated response, and that the response is independent of the type of initial stimulus.

Contrary to original thinking, 90% of particles are considered to be small (< 10 μm). These particles are less likely to be cytotoxic and are therefore more likely to be responsible for a macrophage-initiated and possibly -mediated response. Kubo et al demonstrated higher levels of biological activity to polyethylene particles of 11 μm than larger controls. The activity of macrophages in response to polyethylene debris has been shown to be both size and concentration dependent with induction of apoptosis at concentrations of > 150 particles per macrophage.

Process of osteolysis
There is currently no universally agreed consensus as to the mechanism, precipitating factors or regulatory factors of this cascade. There are, however, many studies examining the process from different perspectives including histology, gene expression analysis and animal models. This cascade...
of interactions starts with stimulation of the macrophage, with the subsequent release of cytokines. This causes release of receptor activator of nuclear factor kappa-B ligand (RANK-L), which binds to the RANK receptor and results in bone resorption by the osteoclast, the final common pathway. A summary of the recognised signalling pathways and cascade of osteolysis is shown in Figure 1.

Cell lineages involved
Histopathological studies have shown infiltration of macrophages, osteoblasts, osteoclasts and fibroblasts into peri-prosthetic tissues\(^{45}\) and the interstitial membrane.\(^{33,46}\) Each of these cells plays a role in the web of interactions that govern peri-prosthetic bone loss.

Macrophages. Activating macrophages is central to the initiation of an osteolytic response.\(^{46}\) In vitro studies using cultured monoclonal cell lines have shown that macrophages phagocytose wear debris,\(^{45-49}\) resulting in the production of pro-inflammatory signal molecules. A dizzying array of inflammatory mediators are then produced, including prostaglandin E\(_2\) (PGE\(_2\)), TNF-\(\alpha\),\(^{50}\) interleukin-1 beta (IL-1\(\beta\))\(^{51,52}\) and interleukin 6 (IL-6).\(^{47}\) In addition to regulation of immunomodulators, matrix proteins have been demonstrated to be regulated in response to wear debris,\(^{53}\) and high levels of expression of matrix metalloproteinases (MMPs)\(^{54,55}\) have been found in peri-prosthetic tissues.

Osteoblasts. Osteoblasts differentiate from the osteoprogenitor cells in the periosteum under the influence of bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), platelet-derived growth factors (PDGFs) and transforming growth factor beta (TGF-\(\beta\)). Although not traditionally associated with bone loss, osteoblastic differentiation is controlled by growth factors released in response to wear debris. As osteoblasts play a role in bone turnover, remodelling and mineralisation of the bone matrix, it is logical to assume their involvement in osteolysis. There are only a few studies exploring the role of osteoblasts in osteolysis despite the potential for inhibition of osteoblast function to result in bone loss.\(^{56}\) Lohmann et al\(^{57}\) established that osteoblasts can phagocytose wear debris, which promotes differentiation and cytokine expression. Exposure to UHMWPE reduces production of bone matrix by down-regulating both collagen type I and III production.\(^{58,59}\) There is also some evidence from cell culture studies that certain types of particulate debris may also inhibit osteoblast differentiation.\(^{30}\)

Osteoclasts. Osteoclasts are derived from a common cell lineage with macrophages and are multinucleated cells derived from osteoclast precursor cells in the general circulation. As osteoclasts are the only cells capable of active bone resorption\(^{60}\) much research has been directed at establishing their function in aseptic loosening. Osteoclasts are recruited through expression of monocyte chemotactic protein (MCP-1) and macrophage inflammatory protein (MIP-1\(\alpha\)); the expression of both of these is up-regulated in peri-prosthetic tissues.\(^{56,61,62}\) Modulation of osteoclastic function is via signal pathways from activated macrophages,\(^{57}\) chiefly through up-regulation of IL-1, TNF-\(\alpha\),\(^{63-65}\) and IL-6.\(^{66}\)

Much emphasis has been placed on the importance of RANK and its ligand (RANK-L) in osteolysis.\(^{67,68}\) The RANK receptor is a membrane receptor found predominantly on osteoclasts. Ligand binding at this receptor is the initiator for osteoclast differentiation. Osteoprotegerin (OPG) is the antagonist for this pathway.\(^{69,70}\) It is secreted by osteoblasts and regulates osteoclast activity by providing an alternative binding site for RANK-L. The RANK pathway is a key modulator of bone turnover,\(^{69,70}\) and is the ‘on-switch’ for bone loss.

RANK-L expression is increased in osteolytic tissue surrounding loose components, and expression has been localised to macrophages, giant cells and fibroblasts.\(^{70-73}\) Modulation of RANK-L activity through increased expression of OPG\(^{74,75}\) or use of knock-out mice with a deficient RANK receptor\(^{67}\) inhibits osteolysis in a mouse model. Further, exposure of fibroblasts,\(^{68}\) osteoblasts\(^{76}\) and a murine calvarial model to particulate wear debris resulted uniformly in an increase in the RANK/OPG ratio. These observations confirm the central role of the RANK/ RANK-L/OPG pathway in osteolysis.

Alternate activation pathways
Macrophages are able to respond to a stimulus through the activation of many signalling pathways. The classical or M1 macrophage activation pathway results predominantly in TNF-\(\alpha\) and IL-1 production. It is seen in response to type 1 T-helper cell responses (Th1) and promoted by the Th1 group of cytokines (typically IFN-\(\gamma\)), which are more normally produced in response to microbial stimulation.\(^{77}\)

However, macrophages are capable of a broad spectrum of responses and these alternative (or M2) responses are responsible for activation of alternative pathways such as nuclear factor kappa-B (NFkB, an apoptosis pathway), and the mitogen-activated protein kinases (MAP kinases; intracellular signalling pathways responsible for stress and inflammatory signal transduction).\(^{66,78}\) This M2 activation results in the production of other mediators such as prostaglandin (PGE2), and has a modulatory effect on the inflammatory cascades. The alternative activation pathway is driven by response to the Th2 cytokines (predominantly IL-4 and IL-13).

There is accumulating evidence that these alternative pathways are important in the host response to conditions such as Gaucher’s disease,\(^{79-81}\) multiple sclerosis,\(^{81}\) atherosclerosis\(^{77}\) and tuberculosis. Whilst evidence surrounding the role of alternative macrophage activation in osteolysis is far from complete, there is evidence that this process may have a role. Koulouvaris et al\(^{82}\) demonstrated high levels of alternative macrophage activation markers chitotriosidase and the chemokines (particularly chemokine motif ligand-18, CCL-18) when comparing
peri-prosthetic tissue from failed hips with primary controls. These same markers have been implicated in alternative macrophage activation in Gaucher’s disease and sarcoidosis. Macrophages are responsible for the formation of giant cells in granulomatous diseases and both dendritic cell specific transmembrane proteins (DC-STAMP) and triggering a receptor expressed on myeloid cells (TREM2) have been found to be elevated in peri-prosthetic tissue, indicating macrophage-mediated giant cell formation.

It seems likely that the M2 responses play as crucial a role in the osteolytic response as they do in other granulomatous and macrophage driven diseases. The implication of M2 responses may help to explain difficulties in reproducing the in vitro cell culture experiments in vivo or ex vivo. Recent work has shown that in prolonged incubation with wear debris macrophages move through an M1 (TNF-α and IL-6) response that peaks at an hour and returns to normal within 24 hours. Further incubation periods appear to result in a gradual increase in M2 cytokines with a slow increase in markers such as chitotriosidase. It seems possible that the balance between these two responses may play a role in the differential activation of the osteolytic cascade seen from patient to patient.

Despite much credible published scientific work investigating the process of osteolysis the majority of in vitro experiments have been performed using monoclonal macrophage cell lines, and the observed response presumed to be generalisable to humans. Giant and Jacobs investigated the effects of different cell lines to the same wear debris. They demonstrated significantly different responses between macrophage populations. This is a worrying observation, as our understanding of osteolysis is based for the most part on cell culture studies. If different cell lines give a different response, how do the published data relate to what is occurring within the joint? Gordon et al. from retrieval of peripheral blood monocytes, have shown that individuals with radiological evidence of osteolysis have a marked increase in inducible expression of a range of cytokines (IL-1α, IL-1β, IL-1Ra, IL-6, IL-10, IL-18) in response to wear debris. This and similar observations have given rise to the concept of ‘sensitive’ or ‘inducible’ individuals who may be particularly responsive to wear debris load. Although there is little work on the genetics of osteolysis these observations are supported by observations of single nucleotide polymorphisms between individuals with osteolytic change.

Conclusions
The cellular mechanisms resulting in osteolytic change are only now beginning to be understood. Many studies have begun to characterise the complex cellular interactions that result in bone loss. However, it is still not clear why some patients undergo early osteolysis and in others the process may be delayed by many years or never occur. It seems most likely that the answer lies in the biology. Although there is some evidence supporting a biological or genetic predisposition to aseptic loosening, there is little consensus of opinion and the majority of studies are of too small sample size to be conclusive. The pathways are well described, but mainly in animal models and monoclonal cell culture studies. It is most likely that the observed differences between patients represent differential sensitivity to generated wear debris, or differences in ability to mount a wear debris response.

To further our understanding of the process of osteolysis, the basic science studies must be translated to clinical studies and eventually clinical practice. Osteolysis is a biological process; a clear understanding of the biology in human subjects is required to further our knowledge.

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References