Targeting autophagy to inhibit wear debris-induced osteolysis

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Wear debris-induced osteolysis and aseptic loosening

Arthroplasty surgery has become one of the most efficient procedures to restore joint function. However, implant failure due to bone loss is a major complication of joint replacement, with severe consequences both for the individual patient and for health-care systems. Peri-prosthetic loosening without concurrent infection or trauma is called aseptic loosening. It is estimated that up to 20% of all prosthetic implants will induce aseptic osteolysis, generally leading to implant loosening and surgical revision (1).

Although the pathophysiology of aseptic loosening is not completely understood, it is generally accepted that implant wear and subsequent release of biomaterial wear particles to the bone microenvironment are its main cause. The specific biological reactions are dependent on particle type, shape, size and quantity, as well as the patient's individual genetic variability (2). However, inflammation, formation of foreign body granulomas and bone resorption represent the main hallmarks leading to osteolysis (3).

Biological mechanisms involved in wear debris-induced osteolysis

The stimulation of innate immune response by the release of biomaterial wear particles at the interface between bone and implant is the first event leading to local inflammation, which is mediated by monocytes/macrophages (4). These cells produce several pro-inflammatory cytokines and chemokines, such as TNFα, IL-6, IL-8, IL1, IL-18, PGE2 or M-CSF, as well as enzymes such as metalloproteinases (MMPs). In turn, these secreted factors favour chronic inflammation, tissue fibrosis/necrosis and osteoclasts activation responsible for the osteolysis process around the implants (4). Indeed, macrophages, fibroblasts and mesenchymal stem cells can contribute to bone resorption in aseptic loosening (3), but osteoclasts were shown to be excessively activated at the implant site by wear debris from materials such as titanium (Ti), polymethyl methacrylate, polyethylene and cobalt chromium (5). In addition, wear debris not only increase bone resorption by activating macrophages and osteoclasts but also directly impairs bone formation by inhibiting the function of osteoblasts (OB) and osteocytes (OST), normally responsible of implant osseointegration. In OB, wear debris were shown to trigger IL-6 and IL-8 secretion, to decrease proliferation and to increase apoptosis (6,7). Wear particles also affect OB function by suppressing collagen synthesis and inducing MMP production (8,9). OST represent the terminally differentiated state of the OB lineage and express higher levels of OPG and RANKL than OB, which modulate bone resorption directly. Although OST are the most abundant cells in bone, the effect of wear debris on OST has been poorly explored. Several studies demonstrated that wear debris could promote osseointegration by upregulating pro-osteoclastogenic factors in OST. Lohmann *et al.* reported that ultra-high molecular weight polyethylene particles dose-dependently stimulated OST to secrete prostaglandin E2, which has been shown to stimulate osteoclasts and suppress OB (10). Wear debris were also shown to cause OST apoptosis and Akt inactivation in MLO-Y4 cells (11).

More recently, polyethylene wear particle were shown to stimulate RANKL production and osteocytic osteolysis resulting in loss of OST perilacunar bone (12).

Role of autophagy in wear debris-induced osteolysis

Autophagy is a cell cleaning process highly conserved in eukaryotic cells consisting in lysosomal degradation of unnecessary or damaged organelles and misfolded proteins. In addition to its basal role in cell homeostasis, autophagy is also a stress-responsive mechanism for survival purposes. Autophagy can be upregulated in response to various stresses such as starvation, oxidative stress, hypoxia, or toxicant exposure, where it acts primarily as a protective mechanism (13). In addition, autophagy is triggered by various metals and controls inflammation through regulatory interactions with innate immune signalling pathways (14). In this context, autophagy appears as a good candidate to be involved in response to wear debris in cells of the peri-prosthetic region. The work of Wang *et al.*, which is the subject of this commentary, showed that Ti-alloy particles (TiPs) promote osteoclastogenesis by downregulating the anti-osteoclastogenic factor IFN-β via autophagy in OST (15). First, these authors showed that in control conditions, OST-conditioned medium inhibited osteoclast differentiation from bone marrow monocytes via IFN-β. The presence of TiPs induced an autophagosome number increase in OST *in vitro* and *in vivo*, which results in decreased IFN-β production, leading to osteoclastogenesis derepression. In addition, pharmacological or genetic autophagy inhibition restore IFN-β levels and prevented the TiPs-induced osteoclastogenesis. Although the mechanism bridging autophagy activation and decreased IFN-β production is still unknown, Jounai *et al.* demonstrated that Atg5–Atg12 conjugate negatively regulates the type I IFN production pathway by direct association with the retinoic acid-inducible gene I (RIG-I) and IFN-β promoter stimulator 1 (IPS-1) through the caspase recruitment domains (CARDs) (16). In addition, it was demonstrated that hepatitis C virus require the unfolded protein response and autophagy pathways to repress innate antiviral immunity and in particular, IFN-β production (17). Moreover, the measurement of the autophagic flux after a prolonged treatment of OST with TiPs would be of interest. Indeed, autophagy is a dynamic mechanism in which vesicles are formed and rapidly degraded by fusion with the lysosome, in a process called "autophagic flux". Several studies have shown that metal exposure can first trigger autophagy and then block this process, likely due to lysosome impairment (18). Nevertheless, the work of Wang *et al.* suggests that autophagy could be a therapeutic target in OST to inhibit wear debris induced osteolysis. Interestingly, the same group already demonstrated that an autophagy upregulation was observed in OB and macrophages both *in vitro* and *in vivo* in the presence of respectively, CoCrMo metal particles or TiPs (7,19). In OB, autophagy was involved in apoptosis upregulation. In macrophages, autophagy inhibition dramatically reduces TiPs-induced TNF-α expression. In both studies, inhibition of autophagy with 3-MA decreased the severity of osteolysis in animal models. Thus, autophagy seems to be triggered by the presence of wear debris in the three main cell types involved in aseptic loosening, i.e., OST, OB and macrophages. In addition, autophagy was also shown to be involved in osteoclast differentiation (20). Altogether, these reports suggest that transient and local autophagy modulation could be a new therapeutic option to prevent wear debris-induced osteolysis. This could be performed by including autophagy modulators within the prosthetic biomaterials, allowing the local and slow release of these pharmacological agents. However, additional studies will be required to establish the long-term benefits of such a strategy.

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Footnote

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