Emerging Ideas

Instability-induced Periprosthetic Osteolysis Is Not Dependent on the Fibrous Tissue Interface

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Abstract

Background Stable initial fixation of a total joint arthroplasty implant is critical to avoid the risk of aseptic loosening and premature clinical failure. With implant motion, a fibrous tissue layer forms at the bone-implant interface, leading to implant migration and periprosthetic osteolysis. At the time of implant revision surgery, proresorptive signaling cytokines are expressed in the periimplant fibrous membrane. However, the exact role of this fibrous tissue in causing periprosthetic osteolysis attributable to instability remains unknown.

Questions/hypotheses We propose an alternative mechanism of periprosthetic osteolysis independent of the fibrous

tissue layer, where pressurized fluid flow along the bone-implant interface activates mechanosensitive osteocytes in the periprosthetic bone, causing the release of proresorptive cytokines and subsequent osteoclast differentiation and osteolysis.

Method of Study An animal model for instability-induced osteolysis that mimics the periprosthetic bone-implant interface will be used. In this model, a fibrous tissue membrane is allowed to form in the periprosthetic zone, and pressurized fluid flow transmitted through this membrane reliably creates osteolytic lesions in the periprosthetic bone. In this study, half of the rats will have the fibrous tissue present, while the other half will not. We will determine whether the fibrous tissue membrane is essential for the release of proosteoclastic cytokines, leading to osteoclast differentiation and periprosthetic bone loss, by measuring the volume of bone resorption and presence of proresorptive cytokines at the bone-implant interface.

Significance We will determine whether the fibrous tissue membrane is crucial for osteoclastogenic signaling in the setting of periimplant osteolysis. In the future, this will allow us to test therapeutic interventions, such as specific cytokine inhibitors or alterations in implant design, which may translate into new, clinically relevant strategies to prevent osteolysis.

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All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research* editors and board members are on file with the publication and can be viewed on request. Each author certifies that his or her institution approved the animal protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research. This work was performed at Hospital for Special Surgery, New York, NY, USA.

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Hypothesis

We hypothesize that fluid flow along the bone-implant interface or “effective joint space” [22] induces a pathologic response in the periprosthetic bone, independent of the fibrous tissue membrane, resulting in the expression of proresorptive cytokines by osteocytes, leading to osteoclast differentiation and osteolysis.

Background

Despite the evolution of new implant designs, materials, and surgical techniques, revision of total joint arthroplasties owing to prosthetic loosening remains a major clinical problem. With an aging patient population and increasing prevalence of total joint arthroplasties, the rate of revision THAs is projected to increase by 123% and the rate of revision TKAs by 412% by 2030 [14]. Mechanical loosening as a result of osteolysis accounts for approximately 19.7% of revision THAs [12]. Therefore, osteolysis in total joint arthroplasty remains a significant concern and osteolysis and aseptic loosening represent the greatest obstacles to excellent long-term function in a total joint arthroplasty.

With prosthetic aseptic loosening, a fibroblast-rich tissue forms at the bone-implant interface [4, 6, 9, 10, 16, 24]. This fibrous layer may serve different roles in the periprosthetic zone: one mechanical, leading to component subsidence, and the other biologic, in which osteoclastogenic cytokines are expressed. At the time of revision surgery, the fibrous tissue has been shown in several studies to have the capacity to produce multiple proinflammatory cytokines such as prostaglandin E₂, collagenase [8–10], and receptor activator of nuclear factor kappaB ligand (RANKL) [18]. This fibrous tissue was found to be heavily infiltrated with particulate cement and polyethylene debris [9], leading to the hypothesis that fibroblasts in the interface membrane respond to particulate wear debris, stimulating the release of osteoclastogenic cytokines [13]. However, all studies analyzing the biologic activity of the fibrous tissue interface have been performed in the chronic setting and at the end stage of aseptically loose implants in patients who presented for revision surgery. Therefore, the exact role of the fibrous tissue interface in actually causing implant loosening and periprosthetic osteolysis remains unclear.

Apart from the suspected biologic role of the fibrous tissue interface, this membrane also may have a mechanical role as a fluid carrier along interface gaps [4, 24], augmenting the transport of wear particles and debris [26, 27]. It is believed that wear debris then directly stimulates macrophages to release proresorptive cytokines, leading to osteoclast differentiation. However, studies have shown that hydrostatic pressure and fluid flow of a clinically relevant magnitude, transmitted through a fibrous tissue membrane but in the absence of wear particles and debris, may induce the formation of periprosthetic osteolytic lesions [2, 3, 5–7, 11, 23, 25]. The pressurized fluid flow velocity along the bone-implant interface has been estimated [7] and calculated [1] to be 10 times larger than that during normal physiologic loading. Elevated pressures, as much as 155 to 776 mm Hg, can be present in patients with loose hip implants before revision surgery

during different mechanical maneuvers [20]. In addition, Schmalzried et al. noted the ability of joint fluid to penetrate along the interface between the prosthesis and bone, and in the periprosthetic tissues, even in well-fixed components [22]. Furthermore, even in the absence of implant motion, elevated pressures have been found in screw holes around well-osseointegrated acetabular cups [26]. Pressure and the associated fluid flow in bone have been shown to alter the biochemical response of osteocytes [21, 28], leading to an increase in the ratio of RANKL to osteoprotegerin (OPG). Therefore, it is highly likely that fluid flow at a higher magnitude can induce pathologic changes in the bone, leading to the expression of proresorptive cytokines.

In the rat model for instability-induced osteolysis, osteoclast differentiation is associated with a lower expression of inflammatory modulators, such as tumor necrosis factor (TNF) α and IL-1 β , than that induced by wear particles, suggesting an alternative or parallel signaling pathway compared with wear-induced osteolysis [19]. However, the mRNA expression of mechanosensitive cytokines, such as inducible nitric oxide synthase, prostaglandin E synthase, and IL-6, was upregulated by mechanical loading in the absence of wear particles. IL-6 is a key regulator of osteoclastogenesis and also has been shown to be activated in bone by loading [15]. Furthermore, polymorphism in the *IL-6* gene has been associated with an increased risk of osteolysis in patients with THA [17]. However, the role of the fibrous tissue membrane in causing these pathologic changes in this instability-induced pathway remains unclear.

Based on the previous observation that instability-induced osteolysis (in the presence of a fibrous tissue membrane) may be induced by a parallel or separate signaling pathway, we propose an alternative to the wear particle-induced, inflammatory pathway (driven by macrophages) (Fig. 1). Specifically, we propose that pressurized fluid flow directly stimulates osteocytes in the periprosthetic bone, independent of the fibrous tissue membrane, leading to osteoclast differentiation. Finding a novel, osteolytic pathway, involving direct activation of signaling in periprosthetic bone and not of fibrous tissue, could be crucial to discovering new target molecules to decrease the prevalence of osteolysis in total joint arthroplasty.

Proposed Program

We propose to determine the role of the fibrous tissue in periprosthetic osteolysis in the absence of wear particles by using a rat model for prosthetic loosening, mimicking the clinical scenario of dynamic fluid fluctuations at the periprosthetic interface in an unstable implant—the instability-induced model of osteolysis [23, 25]. This model studies the

Fig. 1 The schematic drawings show the two parallel pathways in the periprosthetic interface leading to osteolysis. The classic wear particle-induced osteolysis is dependent on macrophages in the fibrous tissue to express proresorptive cytokines, leading to osteoclast differentiation. Pressurized fluid flow could directly influence osteocytes in the periprosthetic bone to undergo apoptosis and/or necrosis, leading to osteoclast differentiation.

effect of implant instability in Sprague-Dawley rats. The rat model imitates the presence of an unstable implant by loading the bone-implant interface via a fibrous tissue layer. A loading device is placed in the proximal tibia, and a fibrous tissue layer is allowed to form during the course of 5 days in the space between the piston and the bone surface. Once loading is initiated, this layer of fibrous tissue is then pushed down toward the bone surface, exerting fluid pressure on the underlying cortical bone (Fig. 2). Pressures generated in the instability-induced model previously were measured using a pressure transducer, and are similar to those reported for loose hip implants in vivo [1, 7, 20]. The loading device never contacts the underlying cortical bone in this model.

For the current study, half of the animals will have the fibrous tissue membrane present under the pressure piston, while the other half will not have a fibrous tissue membrane present (the 5-day latency period will not be allowed). Each group will be divided further into those exposed to loading, and also nonloaded controls, to control for baseline biologic activity and transient responses to the surgical trauma related to implanting the experimental device. Samples will be scanned by micro-CT to assess the volume of bone resorption in two regions for each specimen: the central zone, just beneath the piston, and the peripheral zone, peripheral to the loaded region.

We then will perform immunohistochemistry using cathepsin K antiserum to observe the number of bone-resorbing osteoclasts, and cleaved caspase 3 to observe the

Fig. 2 A schematic diagram shows the experimental setup. Once loading is initiated, fluid pressure is applied at 0.17 Hz for 2 minutes twice daily. FT = fibrous tissue; P = peripheral zone; C = central zone; Ti = titanium plate (the undersurface of the titanium plate is smooth, with no adjuvant surface coating).

number of apoptotic osteocytes. The mRNA expression of cytokine IL-6, the osteocyte-specific gene *SOST* codon for sclerostin, the proresorptive cytokine RANKL, and OPG will be assessed after 24 hours of loading by quantitative PCR in the fibrous tissue interface and the central and

peripheral zones of bone. By using osteoclast number as the primary outcome variable in each group, and an increase of 50% in osteoclast number to be a clinically significant effect size, 16 animals in each subgroup (32 with fibrous tissue, 32 without fibrous tissue) would achieve a power of 80% with an alpha level of 5%. Therefore, a total of 64 animals will be included in this study.

If the fibrous tissue actually plays an important biologic role in the expression of proinflammatory cytokines, leading to osteoclast activation in the periprosthetic bone, we expect the samples with the fibrous tissue present to have the greatest number of osteoclasts and the fibrous tissue to express more proresorptive cytokines than the periprosthetic bone. However, if the fibrous tissue plays more of a mechanical role, we would expect the two samples to have a similar number of osteoclasts and mechanosensitive osteocytes, and the periprosthetic bone to be the source of proresorptive cytokines.

Limitations

The rat model for instability-induced osteolysis reliably shows that pressurized fluid flow in the presence of a fibrous tissue membrane can create periprosthetic osteolysis [23, 25]. However, as with any animal model, it remains unclear how this can be directly translated to have clinical relevance in humans. To our knowledge, this is the only animal model mimicking the mechanical situation around an implant. Other studies focusing on physical factors involved in osteoclast differentiation have been performed in vitro [1, 5]. However, in vitro experiments are limited by the ability to extrapolate their findings to the in vivo environment. One limitation with this study is that we will be measuring gene expression only after 24 hours of loading and the presence of activated osteoclasts after 5 days of loading. We intend to perform measurements at later times to determine whether the source of cytokine signaling and location of osteoclasts vary at different times. A second limitation is that owing to the experimental protocol of this model, the effects of fluid flow are being studied on cortical bone in the extramedullary, rather than intramedullary environment. In the future, a protocol that replicates the intramedullary environment could prove more useful in studying aseptic loosening of arthroplasty components. However, despite the limitations of this animal model, we believe that it is of critical importance to understand the phenomenon of osteolysis in vivo.

Next Steps

As noted above, the next steps in studying the mechanism of instability-induced osteolysis would involve increasing

the number of cytokines measured for mRNA expression, and also varying the times at which these markers are assessed. It will be crucial to note if fluctuations are present in the mRNA expression of cytokines such as RANKL and OPG, and if the source of these cytokines varies with time. Furthermore, the development and validation of a mouse model for instability-induced osteolysis would allow future experiments to involve the use of knockout mice, which would prove useful in determining the specific role of various proinflammatory cytokines.

In addition, the effect of having wear particles and fluid pressure present in the instability-induced model of osteolysis will be studied to determine if a synergistic effect exists between the two mechanisms. Finally, therapeutic interventions such as the TNF α receptor inhibitor etanercept and dexamethasone will be tested to determine their effectiveness in preventing instability-induced osteolysis.

Implications and Future Directions

The information gained from this study will provide crucial information regarding the role of the fibrous tissue membrane commonly seen around loose implants and its role in the mechanism of instability-induced osteolysis. Further understanding of this mechanism may influence the view that osteolysis is not only a response to wear debris but also a consequence of dynamic fluid fluctuations activating cells in the periprosthetic bone.

If we find that instability-induced bone loss is not dependent on the fibrous tissue layer, intracortical signaling and mechanosensitive osteocytes may be more crucial in instability-induced osteolysis. This would be novel since periprosthetic bone loss has been thought to be driven by macrophages and not by osteocytes.

Understanding the osteolytic mechanism and pathway at the established bone-implant interface may lead to identification of new pharmacologic targets and preventive strategies. In addition, it may lead to modification of prosthetic designs with the intent of decreasing periprosthetic fluid pressure and flow and ultimately to reduction in the incidence of aseptic loosening in total joint arthroplasties.

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