J Musculoskel Neuron Interact 2004; 4(4):390-392

Review Article

Hylonome

Bone implant interface, osteolysis and potential therapies

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Keywords: Periprosthetic Osteolysis, Anti-TNF Therapy, 3D-CT

Although total hip replacement (THR) is amongst the most successful and beneficial medical procedures to date, long-term outcomes continue to suffer from aseptic loosening secondary to periprosthetic osteolysis. Extensive research over the last two decades has elucidated a central mechanism for osteolysis in which wear debris generated from the implant stimulates inflammatory cells to promote osteoclastogenesis and bone resorption[1]. Osteolysis can be found in up to 20% of patients 10 years after primary surgery[2-4], leading to implant failure and the need for revision arthroplasty, which has a poorer clinical result and a shorter duration of survival, compared to primary TJR[5,6]. As a direct consequence of these failures, many younger people who would otherwise be excellent candidates often postpone surgery. Thus, there is a great demand for a therapeutic solution to this problem, which is long overdue.

Based on a wealth of knowledge of the cellular and molecular events that govern wear debris-induced osteolysis, and the arsenal of anti-resorptive agents (FDA approved and unapproved drugs), we proposed that two fundamental advances are required to develop a therapeutic intervention for aseptic loosening. The first was a quantitative small animal surrogate to formally evaluate the value of molecular targets through genetics, and the efficacy of drugs with various regimens[7]. The second is a quantitative clinical outcome measure that can accurately measure osteolysis in a longitudinal study[8].

To achieve our first goal, we adapted the mouse calvaria model originally developed to study the resorptive effects of cytokines[9], and later modified to study wear debris[10]. The essence of this model is the surgical implantation of wear debris, which induces an inflammatory reaction on the calvaria with subsequent resorption, formation, and remodeling. The central outcome measures used in this model are histomorphometry to quantify the area of osteolysis in the midline suture, the resorption surface and osteoclast numbers[7]. More recently an X-ray method has been developed to quantify osteolysis, which demonstrated a decrease in repair in older mice[11]. Although various wear debris particles have been studied in this model (i.e., PMMA, HA, PE, CoCr), we have found that the most reliable are commercially available titanium (30mg/mouse).

Beyond the tremendous cost advantages of murine models (money, time, labor), we have been able to take advantage of a huge array of genetically defined mice to examine to molecular genetics of wear debris-induced osteolysis *in vivo*. These studies included: TNFR (-/-) and NFκB (-/-)[12], Cox-1 (-/-) and Cox-2 (-/-)[13], TNF-Tg[14,15], RANK (-/-)[16], and IL-6 (-/-) and IL-1R (-/-) mice. In terms of drug and gene therapy screening, we have evaluated: alendronate and pentoxifylline[7], etanercept[14], celecoxib[13], RANK:Fc[16], OPG[17,18], TNFR:Fc[15], vIL-10[19], anti-IL-6 and anti-IL-1R. These studies have elucidated the biological hierarchy in which RANK blockade is clearly the safest and most effective means to prevent and ameliorate wear debris-induced osteolysis.

To achieve our goal of developing a volumetric outcome measure to quantify osteolysis longitudinally in patients with aseptic loosening, we employed VirtualScopics LLC technology to facilitate the analysis of standard computerized tomography (3D-CT)[8,20]. The essence of this technology is artifact suppression to enhance the radiology at the bone implant interface; and density assignment that permits semi-automated quantification of implant, bone and soft-tissue volumes. In our first study to validate 3D-CT as an outcome measure for aseptic loosening, we resolved the correlation between the polyethylene wear rate, using X-rays[21], and periacetabular osteolysis ($R = 0.494$, $p = 0.027$)[8]. In a second study with human cadavers, we determined the reliability and accuracy of the 3D-CT technique by comparing the radiology with histology. These results demonstrated that 3D-CT has a volumetric error of 5.6% for all detected lesions. This error decreased with lesion size, such that for lesion >10ccm

Dr. Schwarz has received grant support from and has consultancies with Immunex Corp., Amgen Inc., and Centocor, Inc. Dr. O'Keefe has no conflict of interest. Dr. Looney has received grant support from and consulted for Centocor, Inc.

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Accepted 4 August 2004

the error was 1.8% [22].

Based on the vast body of information suggesting that tumor necrosis factor-alpha (TNFα) is a strong target for therapeutic intervention[23], the remarkable success of anti-TNFα therapy for erosive arthritis[24], and the development of our 3D-CT outcome measure, we proposed and completed a 20-patient, double-blinded, placebo controlled clinical pilot to evaluate the efficacy of etanercept in patients with established peri-acetabular osteolysis (mean = 29.99 cm^3, range = 2.9-92.7 cm^3) of an uncemented primary THR over one year[20]. 3D-CT data from the 19 patients was used to determine the mean increase in lesion size over 48 weeks, which was 3.19 cm^3 ($p<0.0013$). Analysis of the urine N-telopeptides and functional assessment data failed to identify a significant correlation with wear or osteolysis. In conclusion, 3D-CT was able to measure progression of osteolysis over the course of a year, thus providing a technology that could be used in therapeutic trials.

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