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MEETING REPORT

Biological control of peri-implant bone remodeling and implant loosening (Sun Valley 2012)

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Research pertaining to the induction of osteolysis and subsequent loosening of orthopedic implants was the subject of a session at the IBMS Sun Valley workshop in the August of 2012. The session was organized by D Rick Sumner, PhD, and included talks by Stuart Goodman, MD, PhD, Nadim Hallab, PhD, Per Aspenberg, MD, PhD, and Rick Sumner, PhD. Considerable attention was paid to two candidate mechanisms of implant loosening—particle-induced osteolysis and fluid pressure-induced osteolysis.

Aseptic loosening and mechanical instability, which are often closely linked, are the two primary mechanisms of failure in primary total joint replacement (TJR).[1] Current clinical management protocols are largely based on surgical intervention, which are inherently costly.[1] The number of TJR revisions performed annually in the United States is well over 70 000 and the annual incidence is expected to increase to more than 350 000 by 2030.[2] These statistics are particularly worrisome because of the relatively high failure rates of revision TJR, ranging from 10 to 25%.[3,4]

Particle-induced osteolysis is widely accepted as a key factor in aseptic loosening,[5–10] although lack of initial mechanical stability and other factors may also play a role.[11–13] Wear debris and other particles and ions released from implants are thought to invoke the innate immune system through Toll-like receptors 2 and 4 and the NALP3 (NACHT, LRR and PYD domains containing protein) inflammasome.[10,14,15] It is becoming clear that endotoxins such as lipopolysaccharides can potentiate the ability of particles to induce an inflammatory response.[16] The potential role of adaptive immunity is not clear.[17,18] Collectively, the inflammatory responses increase osteoclastogenesis and bone resorption and may also induce osteoblast apoptosis.[10] In addition to these inflammatory pathways, particles can directly downregulate collagen type I production by osteoblasts,[19] negatively affect osteogenic lineage cell proliferation and differentiation[20] and can induce a catabolic phenotype in osteoblasts and osteocytes.[21]

Dr Goodman provided an excellent history of study into the problem, highlighting the work of Hans Willert[22] and James M Anderson.[23] The relatively novel concept of trafficking of endogenous cells was discussed. In particular, it is now clear that most macrophages at the implant site come from remote sites and that mesenchymal stem cells also traffic to the implant site.[24–26] Having recognized this, it may be possible to develop novel treatment strategies.

Dr Hallab reviewed work on particles and noted that it is clear that most debris comes from the articular surfaces[27] and that polyethylene particles are the culprit, although other particles elicit significant reactivity *in vitro*. The potential role of the inflammasome danger signaling pathway in particle-induced osteolysis is now gaining interest.[14] It is now becoming clear that adaptive immunity in addition to innate immunity may play a role in the biological reaction to orthopedic biomaterials.

Dr Aspenberg raised the possibility that relative motion between the bone and implant may be a precondition for particle-induced loosening and not merely the end-stage result of a largely biological process. This possibility is based in part on the observation that 'late' loosening of prostheses has not been observed in the absence of early implant migration. These studies rely on the use of very sensitive radiographic techniques.[11] Implant motion relative to bone can induce high-velocity fluid flow, which in turn may directly cause bone resorption.[28]

Dr Sumner reviewed a new rat model of particle-induced implant loosening[29] and prevention of depressed implant fixation strength by co-administration of the bone anabolic agent, sclerostin antibody.[30] It is now well documented that particle administration stimulates bone resorption and suppresses bone formation in the peri-implant trabecular bone. Sclerostin antibody mitigates these negative effects, thereby preserving or even increasing the local bone stock and increasing the mechanical attachment of the implant to the bone.

It is clear that the overall pathogenesis may include many causes and there may be a complex interaction between particles derived from the implant and the initial stability of the implant. It is even possible that peri-implant osteolysis and implant loosening have multiple causes, implying that this is not simply one disease. Nevertheless, the importance of particles to the process of peri-implant osteolysis and loosening is nearly universally accepted. Consideration of other factors such as fluid pressure emphasizes that alternative mechanisms may be important. With the improved understanding of pathogenesis,

it is likely that new prevention and treatment strategies that are being investigated in pre-clinical models may be ready for clinical testing in the relatively near future.

Note: Abstracts from the 42nd International Sun Valley Workshop: Musculoskeletal Biology can be accessed at: http://www.ibmsonline.org/p/cm/ld/fid=156.

Conflict of Interest

The author declares no conflict of interest.

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