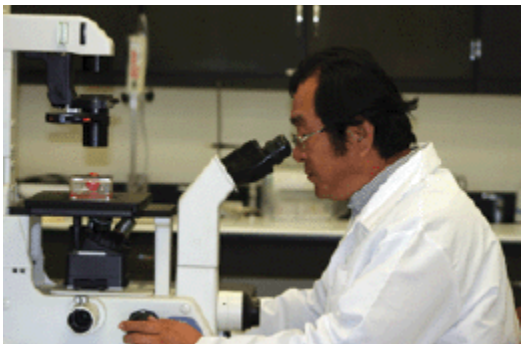
Narrowing the Focus on Aseptic Loosening

By Jay D. Lenn

OREF Grant Recipient Examines Role of Mononuclear Cells

Aseptic loosening, the most common cause of long-term failure in hip and knee replacements, occurs when normal wear on a prosthetic joint produces microscopic debris particles that trigger an immune system response. This immunologic activity mediates osteolysis, which loosens the bond between the implant and bone.



Using an inverted microscope, Dr. Yang examines human monocyte behaviors.

The molecular and cellular mechanisms of aseptic loosening have not been thoroughly identified, and current research models provide limited insight into this common complication. In 2008, Shang-You Yang, MD, PhD, a research scientist at Orthopaedic Research Institute, Via Christi Wichita Hospitals and associate professor at Wichita State University, Wichita, Kan., received a research grant from the Orthopaedic Research and Education Foundation (OREF) to investigate the mediators of aseptic loosening in a novel approach that transplants the human microenvironment of a failed prosthetic joint into a mouse model. Dr. Yang's co-principal investigator, **David McQueen, MD,** is a clinical professor of orthopaedic surgery at Orthopaedic Research Institute, Via Christi Health.

A miniature lab for joint failure
Dr. Yang's research builds on a basic understanding of aseptic loosening. "When we do a revision surgery, we find a layer of soft, periprosthetic tissue at the interface of the joint and bone. Previous studies have shown that this tissue exhibits a varied cellular composition, including lymphocytes, macrophages, monocytes, and foreign-body giant cells," he explained.

Studies have also demonstrated that some of these immune system cells produce proteins that mediate the production of osteoclasts.

Dr. Yang is using periprosthetic tissue and tiny bone fragments donated from patients who have undergone revision surgery due to aseptic loosening of the prosthesis. The donor tissues and bone are implanted into back and thigh muscles of mice. Half of the mice also receive injections of donor peripheral blood mononuclear cells (PBMCs)—lymphocytes,

macrophages, and monocytes—labeled with fluorescent tags that can be tracked with fluoroscopic analysis up to 30 days.

With this model, Dr. Yang and his research team can identify in situ the recruitment of PBMCs to the periprosthetic site. They also can correlate the infiltration of cells at the site with levels of osteoclast-promoting proteins, the growth of periprosthetic tissue, changes in bone density, and erosion. The data can be used to address the following questions:

- Does the periprosthetic tissue influence the growth or degeneration of transplanted bone?
- Does the transfusion of PBMCs influence inflammation in the periprosthetic tissues?
- Does the transfusion of PBMCs influence patterns of osteoclast development and bone resorption?
- Does the quantity of the wear debris present in the periprosthetic tissue influence the activation and migration patterns of PBMCs?

Does the type of debris matter?
The second aim of Dr. Yang's research is to examine the differences among common prosthetic materials in debris-related PBMC trafficking, inflammation, and osteoclast development, using the same mouse model.

Labeled PBMCs are cultured for 3 days with particles of cobalt-chromium alloy, titanium alloy, polymethyl methacrylate, or ultra-high molecular weight polyethy-lene. The models receive the same human tissue transplants and injections with the cultured PBMCs.

Dr. Yang and his research team are examining the immunologic protein profile in the cultured PBMCs prior to injections and the profile of the transplanted periprosthetic tissue. Dr. Yang's team is using the data to address the following questions:

- Does preincubation of debris particles with PBMCs influence cell trafficking to the periprosthetic tissue?
- Which types of debris significantly influence PBMCs in the formation of periprosthetic tissue and bone resorption?
- What are the primary mediators promoting the osteoclastogenesis and osteolysis in response to the trafficking of systemic PBMCs to the periprosthetic site?
- Are specific lymphocyte antigens involved in driving circulating cells to debris-associated inflammation?

Solutions for joint survival
A more solid understanding of the cellular and molecular mediators of aseptic loosening could lead to better-informed surgical decisions. Dr. Yang noted, "It would be a significant advantage if the outcome of a joint prosthesis could be predicted in advance. For example, in the future we may be able to use immunologic screening to determine whether an individual would be more sensitive to titanium particles rather than cobalt-chromium particles."

He added that the results of his work could also lead to the development of novel biologic response modifiers designed to prolong the life of a prosthetic joint.

Dr. Yang credits OREF for making this work possible. He stated, “OREF was the first foundation I turned to for research support. Without the OREF grant, I couldn’t perform the experiment and get the preliminary data I need for funding from the National Institutes of Health.”

Dr. Yang’s research has led to published manuscripts in Inflammation Research and the Journal of Orthopaedic Research.

Jay D. Lenn is a contributing writer for OREF. He can be reached at communications@oref.org

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