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Joint Replacement Surgery and the Innate Immune System

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Abstract

Total joint replacement is a highly successful, cost-effective surgical procedure that relieves pain and improves function for patients with end-stage arthritis. The most commonly used materials for modern joint replacements include metal alloys such as cobalt chrome and titanium alloys, polymers including polymethylmethacrylate and polyethylene, and ceramics. Implantation of a joint prosthesis incites an acute inflammatory reaction that is regulated by the innate immune system, a preprogrammed non-antigen specific biological response composed of cells, proteins, and other factors. This “frontline” immune mechanism was originally designed to combat invading microorganisms, but now responds to both pathogen-associated molecular patterns or PAMPs (by-products from microorganisms), and damage associated molecular patterns or DAMPs (molecular by-products from cells), via pattern recognition receptors (PRRs). In this way, potentially injurious stimuli that might disrupt the normal homeostatic regulatory mechanisms of the organism are efficiently dealt with, ensuring the survival of the host. Initial surgical implantation of the joint replacement, as well as ongoing generation of wear debris and byproducts during usage of the joint, activates the innate immune system. Understanding and potentially modulating these events may lead to improved function and increased longevity of joint replacements in the future.

Keywords

joint replacement; innate immune system; biomaterials; wear; pathogen-associated molecular patterns; damage associated molecular patterns; pattern recognition receptors; toll-like receptors

I. TOTAL JOINT REPLACEMENT: THE PRESENT

Total joint replacement surgery is unarguably one of the greatest advances in medicine over the last 50 years. The longevity of a technically sound hip or knee reconstructive operation in an elderly patient exceeds 15–20 years with a probability of >90%. Whereas previously

many hip and knee revision surgeries were performed for wear-related complications, issues related to infection, suboptimal implant position, instability, stiffness, and chronic pain now predominate. Furthermore, the numbers of joint replacements of the lower extremity have increased dramatically over the last decade, and both younger and elderly more infirm patients are now requesting these procedures.^{1,2} Enhanced, more wear-resistant metal-on-polyethylene and ceramic-on-polyethylene bearings have proven to be even more successful than conventional polyethylene for hip replacement, but whether these materials will withstand the increased demands of younger, more active patients in the long term is unknown.³⁻⁵ Whereas an elderly patient may perform 500,000 to 1 million gait cycles (steps) per year, these may be four to five times greater in a younger, healthy, active person.⁶ Thus, implant durability is an important issue.

At present, the use of highly cross-linked polyethylene (XLPE) dominates the choice of bearing surfaces for total hip replacement. This is due in part to the potential for adverse tissue reactions for metal-on-metal (MOM) articulations, and issues related to edge loading, striped wear, breakage and chipping, squeaking, and difficulties in assembly of ceramic-on-ceramic (COC) articulations.⁷⁻¹¹ The use of larger femoral heads to decrease the dislocation rate and improve range of motion has also emerged, with the concomitant use of newer, more wear resistant polyethylene articulations. Concerns involving decreased mechanical properties of the HXLPEs have become evident.^{12,13} Acetabular polyethylene liner fractures have been reported, especially in thin liners articulating with large femoral heads; breakage occurs at the location of the peripheral locking mechanism.^{14,15} The recent introduction of new polyethylene types, such as those incorporating vitamin E free radical scavengers, repeated cycles of heating below the melting point and annealing, and others, attempt to maintain the enhanced wear characteristics of XLPE without compromising the fatigue and crack initiation/propagation properties.¹⁶

For total knee replacement, cemented components incorporating metal articulating with conventional polyethylene remains the gold standard. HXLPE appears to function well in limited short-term series. Further long-term follow-up is necessary before definitive statements can be made. It must be noted that the biomechanics and kinematics of the knee and hip joints are vastly different; thus, material performance may be different for the same type of polyethylene in different anatomical locations. As knee replacements are currently being performed in younger, more active patients, and the use of conventional polyethylene continues to predominate, one might expect increased numbers of revision knee replacements to be performed in the future, due to wear and periprosthetic osteolysis.

Because of the success of joint replacement surgery, and the aging of our population who maintain as active a lifestyle as possible, wear-related issues continue to persist, and will probably increase (at least with knee replacements) with time. Thus, it is imperative to understand the biological aspects concerning prosthesis wear and periprosthetic osteolysis in order to develop viable strategies for prevention and treatment. In this respect, the innate immune system plays a pivotal role. In addition, because of the ongoing (but declining) use of MOM implants, certain aspects of the adaptive T cell-mediated immune system become relevant. Indeed, metal particulates and ions have taken on new significance given recent

findings of increased corrosion with the use of large metallic heads and modular femoral necks.^{17–20}

II. THE INNATE IMMUNE SYSTEM

The innate immune system is a preprogrammed non-antigen specific series of events that are triggered by any potentially injurious stimulus. These stimuli may take many forms, such as invasion of microorganisms, adverse physical/mechanical, chemical, thermal, and electrical stimuli, interruption of nutrient supply, and others. These events disrupt the normal homeostatic regulatory mechanisms that help ensure survival of the host.

Innate immunity first developed for combatting the external threat of pathogens at the front line of host defense. However, these events are constrained by relying on a limited and invariant repertoire of receptors to recognize many different microorganisms. The innate immune system incorporates a mechanism whereby the offending microbial stimulus is sensed by local and circulating surveillance cells via surface and intracytoplasmic receptors that recognize simple molecules and regular patterns of molecular structure known as pathogen-associated molecular patterns (PAMPs), which are present on many microorganisms but not on the host cells.²¹ The receptors are known as pattern recognition receptors (PRRs), and can perceive dangerous molecular structures such as mannose-rich oligosaccharides, peptidoglycans, and lipopolysaccharides in bacterial cell walls, and unmethylated CpG DNA, which are common to many pathogens and have been conserved during evolution. The PRRs of the innate immune system evolved earlier than the highly diverse receptors of the adaptive immune system equipped in vertebrates. The main cell types expressing PRRs are macrophages, neutrophils, and dendritic cells. For example, macrophages express a number of cell surface receptors that allow them to recognize different pathogens. Some, like the mannose and glucan receptors and the scavenger receptors, bind cell wall carbohydrates of bacteria, yeast, and fungi. Toll-like receptors (TLRs) are an important family of PRRs present on the macrophages and other immune cells. The innate immune system is thus able to broadly distinguish self from non-self, and to mount an attack against invaders.²²

Immune responses are induced not only by microbial infection, but also by sterile tissue damage and degeneration. This paradox was first explained by Matzinger, who proposed that the immune system is designed to fight both external and internal dangers, rather than mediate recognition of non-self over self.²³ Thus, the innate immune system has further developed as a preprogrammed non-antigen specific series of events that are triggered not only by external threats of microorganisms, but also by similar molecular patterns induced by occurrences of tissue degeneration and inflammation occurring as internal matters within cells/tissues. These internal events include adverse physical-chemical-thermal and other stimuli that liberate cellular by-products that contain certain molecular structures. These are termed damage-associated molecular patterns (DAMPs), or “alarmins.”^{24,25} Internal and external threats may occur separately or together. Thus, both PAMPs and DAMPs are sensed by the immune cells via PPRs, and local and/or systemic host responses are evoked for self-defense. Excessive injurious stimuli often disrupt the normal homeostatic regulatory mechanisms that help ensure survival of the host.

Intensive research of the innate immune system has elucidated signaling type sensors equipped on the cell surface and in the cytoplasmic structures, which include TLRs, nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and retinoid acid inducible gene (RIG)-I-like receptors (RLRs).^{26,27} Based on current research, it is evident that at least TLRs and NLRs are involved in the pathogenesis of joint diseases such as osteoarthritis and rheumatoid arthritis.²⁸ TLRs are located on the cell surfaces and endosomes. They can sense exogenous PAMPs and endogenous DAMPs. There are at least 10 TLRs with different roles in human immunity; these are located on the cell surface or endosomes. NLRs include NOD-1, NOD-2, and NLRP3, which are in the cytoplasm. The evoked signaling by these sensors can promote the activation and nuclear translocation of transcription factors (IRFs, NF- κ B, and AP-1) that regulate expression of cytokines, such as IFN α/β , TNF- α , and pro-IL-1 β . These cells facilitate cross talk among different cell types, and promote assembly of the caspase-1 inflammasome and subsequent release of IL-1 β from pro-IL-1 β .^{22,28}

III. JOINT REPLACEMENT AND THE INNATE IMMUNE SYSTEM

With regard to total joint replacement, events such as acute or indolent infection and ongoing production of wear particles, metal ions, and other material byproducts can stimulate the innate immune system, potentially leading to an adverse clinical outcome. Tissue retrieval studies, as well as *in vitro* and *in vivo* models, have shown that the above pathways of the innate immune system are activated by these stimuli.^{29–39} Indeed, it has recently been shown that metal ions and polymeric byproducts can stimulate TLRs.^{40–42}

Although joint replacement surgery is a highly efficacious, cost-effective procedure that alleviates pain and improves function, complications such as microbial infection, aseptic loosening and osteolysis, and metal-induced adverse periprosthetic inflammation have been reported as examples of adverse local tissue responses. There are increasing concerns regarding the role of the innate immune system (and more recently, with metal by-products, the adaptive immune system) in the pathogenesis of postsurgical adverse events that compromise joint replacement surgery.^{43,44} In this respect, further research on issues related to orthopaedic implants and the immune system is highly warranted, so that implants could someday function exceptionally for the duration of the patient's lifetime.

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