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Wear Particles, Periprosthetic Osteolysis and the Immune System

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Abstract

The immune system modulates many key biological processes in humans. However, the exact role of the immune system in particle-associated periprosthetic osteolysis is controversial. Human tissue retrieval studies, in vivo and in vitro experiments suggest that the immune response to polymer particles is nonspecific and macrophage mediated. Lymphocytes may modulate this response however direct lymphocyte activation by polymer particle-protein complexes seems unlikely. However, metallic byproducts may complex with serum proteins and lead to a Type IV, lymphocyte mediated immune reaction. In predisposed individuals, this reaction may rarely lead to persistent painful joint effusions, necessitating debridement and excision of the bearing surfaces of the prosthesis. In these patients, retrieved periprosthetic tissues exhibit histological evidence of perivascular lymphocytic cuffing. These findings are worrisome, given the fact that increasing numbers of metal-on-metal joint implants are being implanted in younger more active individuals worldwide.

Keywords

total joint replacement; immune system; particles; osteolysis

Introduction

The exact role of the immune system in periprosthetic osteolysis of joint replacements is controversial. In general, several types of immune processes appear to be relevant to this debate. A foreign body, granulomatous response to material byproducts denotes a chronic inflammatory reaction that is non-specific (that is, not specific for a particular antigenic stimulus), and is composed mainly of activated macrophages and fibroblasts, but few T lymphocytes. There is generally no capacity for memory of these events when the inciting agent is presented to the body during future exposures. For this reason, this more primitive response is also called the innate or native immune response. For example, this type of reaction is seen in response to fragments of most suture materials. In contrast, adaptive immune responses are antigen specific and can be one of four types. The type most relevant to the current discussion is the Type IV hypersensitivity reaction, which involves a specific antigen, co-stimulatory molecules, an antigen presenting cell and T lymphocytes. In hypersensitivity reactions, T lymphocytes play a prominent role in sustaining the chronic inflammatory response, and providing a mechanism for memory of the characteristics of the specific antigenic stimulus. Diseases such as rheumatoid arthritis and lupus erythematosis are thought to be due

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to adverse T cell mediated immune reactions against specific body proteins (so called auto-immune reactions).

Whereas few would dispute an important role for the innate or native immune system, i.e. the non-specific macrophage-mediated cellular response to particles, recent evidence suggests that there may be a role for the acquired or specific immune system that is lymphocyte driven, at least in response to metallic debris. This debate is of more than academic interest for three reasons. First, there are increasing numbers of metal-on-metal prostheses being implanted in younger patients, who are more active and will live many decades longer than elderly patients who traditionally received joint replacements. Thus the "particle burden" is different (primarily metallic rather than polymeric) and of potentially much longer duration. Second, methods to mitigate adverse cellular responses may have to be directed against different cell populations with different cytokine profiles. Third, removal of implant bearing surfaces or the entire prosthesis may be necessary if adverse clinical and immunological events occur. Options for materials used in subsequent revision surgery would be limited. Revision surgery increases morbidity and cost to the patient and the health care system.

Is the foreign body reaction to particulate debris non-specific?

Debris from joint replacements, whether polymeric, metallic or ceramic, stimulates the ingress of polymorphonuclear leukocytes and macrophages into the local site. This non-specific cellular reaction may lead to an extensive foreign body and chronic inflammatory reaction simulating infection. Professor Hans-Jorg Willert and colleagues first described this reaction in relation to degrading orthopaedic implants and put forth the hypothesis that periprosthetic osteolysis will occur if the generation of particles and local mechanisms to handle the debris were in a state of decompensation or disequilibrium [1,2]. Indeed, his early drawings of the reaction espoused the concept that debris and inflammatory cells and factors could circulate more widely around the prosthesis and surrounding soft tissues. This concept, later coined "the effective joint space" explains the appearance of osteolytic lesions at distant points around well-fixed and loose implants [3].

The non-specific foreign body reaction is primarily composed of macrophages, foreign body giant cells, fibroblasts, and occasional lymphocytes and small caliber blood vessels. Osteoclasts may line the bone-implant interface, however reactive bone formation is also an important finding [4]. The periprosthetic tissues may produce high levels of pro-inflammatory cytokines (such as tumor necrosis factor alpha, interleukines-1 and -6 etc), chemokines for macrophages, polymorphonuclear leukocytes and lymphocytes, prostanoids, nitric and superoxide metabolites etc [5,6]. The cytokine profile does not appear to be indicative of a specific immune response. Santavirta et al showed that in cases of cemented arthroplasty with progressive osteolysis, the periprosthetic tissues constituted a more aggressive granulomatous reaction containing multinucleated giant cells and C3bi-receptor and nonspecific esterase-positive monocyte-macrophages [7]. This reaction was different from tissues surrounding loose implants without osteolysis which were composed primarily of fibrous tissue. The Finnish group (as did Willert) suggested that aggressive granulomatosis involved an uncoupling of the normal sequence of monocyte-macrophage-mediated clearance of debris that is normally followed by resolution of the reaction via a fibroblast-mediated synthesis and remodeling of the extracellular matrix.

T lymphocytes are not uncommon and may constitute up to approximately 10% of cells at the interface of loose implants [8]. These cells may have an immuno-modulatory effect on the foreign body reaction. Hercus and Revell noted T cell infiltration with occasional perivascular clustering in retrieved periprosthetic tissues [9]. Multiplex PCR (MPCR) testing of tissues did not show a predominance of Th1/Th2 cytokines. The major cytokines expressed included IL-2,

IL-4, IL-13, and IFN-gamma. Farber et al. found that antigen presenting cells (primarily macrophages) from tissues surrounding loose cemented acetabular components expressed B7-1 and B7-2, key molecules of the B7-CD28 co-stimulatory pathway, indicating activation of the immune response [10]. Bainbridge, Revell and Al-Saffar found that CD86 was the predominant costimulatory molecule ligating to the complementary CD28 molecule at the bone-prosthesis interface of revised implants [11]. They proposed that the intracellular indigestible particles from the prosthesis together with elevated costimulatory molecule expression, may promote T-cell inflammatory reactions in the prosthetic tissues.

With respect to the reaction to polymer particles, macrophage ingress has been noted in nude mice without functional lymphocytes [12]. Santavirta et al found no evidence of an immune response to polymethylmethacrylate particles when cultured with lymphocytes [13]. Wooley et al found that immunoglobulin complexed with polyethylene from failed retrieved plastic acetabular components could fix complement, which could then attract inflammatory cells to the polyethylene surface [14]. Li et al found that the few T lymphocytes found in retrieved periprosthetic tissues were not activated, as the interleukin-2 receptor (IL-2R), interleukin-2 (IL-2), interferon-gamma (IFN-gamma), and tumor necrosis factor-beta (TNF-beta) were not expressed [15]. Baldwin et al. found no evidence of a classic immune response to revised Accord knee prostheses (Depuy International Ltd., Leeds, UK) using immunohistochemistry [16]. However, Wooley et al found significantly higher in vitro proliferative cellular responses to PMMA and cobalt-chromium alloy particles in patients with osteoarthritis at revision surgery for aseptic loosening than in patients with osteoarthritis at either primary surgery or surgical revision for mechanical failure or infection [17]. Furthermore, patients demonstrated elevated proliferative responses and cytokine production in vitro in response to PMMA and cobalt-chromium alloy particle challenge postoperatively after THR, compared to preoperatively.

Whether T lymphocytes are innocent bystanders or active participants in the reaction to loose implants containing polymers is still unresolved. It would appear that the innate immune system is activated by polymeric wear debris; when there is a state of disequilibrium in which particle production overwhelms local mechanisms to deal with these events, progressive periprosthetic osteolysis occurs.

Metallic wear particles- ? A specific T lymphocyte immune trigger

With the recent revival in the use of metal-on-metal bearing surfaces, metal particles have attained a higher profile with regards to a possible association with the immune system. Lalor and Revell have shown that in some cases, a cell-mediated type IV immunological reaction to metallic particles is likely [18,19]. Periprosthetic tissues harvested from failed implants containing titanium screws and a cobalt chrome or titanium alloy femoral head articulating with a high density polyethylene socket demonstrated abundant macrophages containing titanium particles, numerous T lymphocytes but few B lymphocytes [18]. Two of the patients exposed to titanium containing skin ointment had a positive skin reaction. Lalor and Revell also performed immunohistochemical studies of tissues from 10 patients undergoing revision hip replacement from a previous failed cobalt chrome alloy or titanium alloy implant [19]. A comprehensive panel of monoclonal antibodies was applied including CD25 (the T lymphocyte IL-2 receptor, a sign of lymphocyte activation), HLA-DR (activated lymphocytes and macrophages), CD11c (activated macrophages that are antigen presenting cells), CD35 and CD36 (markers for macrophages), CD2 (T lymphocytes) and CD 22 (B lymphocyte). Metal particles and abundant T lymphocytes were readily seen in all sections and in some, the IL-2 receptor was expressed. Many of the macrophages surrounding the T lymphocytes expressed HLA-DR and the macrophages expressed CD11c, indicating that they were antigen presenting cells. Positive controls (rheumatoid synovium) demonstrated similar findings. The authors concluded that expression of the IL-2 receptor is a marker of early activation of T lymphocytes,

and may not occur later on, when a condition is more advanced. These findings suggest that in cases of excessive metal particle production, a cell-mediated Type IV immune reaction may occur.

Metal allergy to orthopaedic implants is a rare phenomenon. In a study of 22 patients undergoing primary total joint replacement who had no known prior metal allergies, 32% developed a positive leukocyte migration inhibition test to titanium, cobalt, chromium, or nickel ion solutions 3 months to 1 year after surgery. One patient developed a severe reaction [20]. Hallab et al recognized that hypersensitivity and an excessive eczematous immune reaction to implanted metallic biomaterials probably exists in less than 1% of those undergoing total joint replacement [21]. The etiology of these immune reactions is probably metal degradation products complexed with serum proteins to form haptens. Implant-related hypersensitivity reactions are thought to be T lymphocyte cell-mediated, type-IV delayed-type hypersensitivity immune reactions. However, the exact role of T lymphocytes is still unclear. In one study, peripheral blood was taken from sixteen patients with a loose cobalt-alloy hip prosthesis. CD4+ T helper cells and CD8+ T killer lymphocytes were decreased, suggesting a generalized lymphosuppressive effect of prosthetic loosening or sequestration of lymphocytes away from the systemic circulation [22]. In another study, patients with metal-on-metal or metal-on-polyethylene implants showed a significant decrease in the number of T lymphocytes and a significant increase in the serum level of chromium and cobalt after total hip arthroplasty [23].

Metal-on-metal hip replacements generate greater numbers of particles of smaller diameter than metal on polyethylene implants. In one retrieval study, metal-on-polyethylene bearings were estimated to generate about 5×10^{11} particles per year, whereas metal-on-metal implants produced about 6.7×10^{12} to 2.5×10^{14} particles per year [24]. Most of the metal particles generated were less than 50 nm in diameter, much smaller by a factor of 10 compared to the polyethylene particles [24].

Although intermediate results from metal-on-metal articulations have been encouraging, there have been some worrisome reports implicating a cell-mediated Type IV immune reaction. Willert and colleagues reported a series of 19 revisions of metal-on-metal implants, revised because of pain and effusion [25]. The components were all well fixed. Seven of the 19 cases demonstrated periprosthetic osteolysis. Histologic examination demonstrated perivascular lymphocytic cuffing. In a companion article by Davies et al, the periprosthetic tissues were shown to be more ulcerated and contain more lymphocytes and plasma cells and less macrophages than metal-on-polyethylene implants [26]. Another study found a 6% (10/169) incidence of osteolysis at 27.2 months post metal-on-metal THR. The patients with early periprosthetic osteolysis had a significantly higher rate of hypersensitivity reactions to cobalt chloride patch testing compared with controls without osteolysis, suggesting a delayed-type hypersensitivity reaction [27].

The adverse effects of different types of metallic particles on cells relevant to bone have been thoroughly investigated [28]. The effects of metallic particles on hematopoetic cells is more controversial. Peripheral blood monocytes and lymphocytes were cultured with/without titanium particles in the presence of the nonspecific immune activator pokeweed mitogen (PWM). Titanium particles induced monocyte production of IL-1beta at levels similar to that induced by PWM alone. Titanium particles and PWM stimulated even higher levels than either stimulus alone. However, titanium particles did not activate lymphocytes (DNA synthesis and IL-2 secretion were unchanged), nor did it suppress the PWM-induced stimulation of lymphocytes [29]. Titanium and cobalt-chromium alloy particles and ions have been shown to affect the immune system in mice when injected into the peritoneal cavity [30]. The release of interleukin-2 and interleukin-4 by lymphocytes, proliferation of T and B cells, and

immunoglobulin production by B cells were significantly inhibited by titanium and cobalt-chromium particles, as well as by titanium, cobalt, and chromium ions in vitro, however these metals were not cytotoxic to murine lymphocytes in vitro. Au et al found that nickel and vanadium metal ions decreased cell viability and proliferation, and induced apoptosis in Jurkat T lymphocyte cells in a dose-dependent manner [31].

Granchi et al cultured peripheral blood mononuclear cells from healthy donors, patient candidates for primary total joint replacement, patients with well-fixed implants and patients with aseptic loosening of a hip prosthesis [32]. When cultured with metal ions used in the implant manufacturing process, the cells from patients with loose and well-fixed prostheses had a higher cobalt-induced “activation index” compared to healthy donors. The chromium-induced “activation index” was higher in patients with a loose prosthesis compared to healthy donors and candidates for joint replacement. In all patient groups, exposure to chromium extract increased the expression of CD69 activation antigen on CD3/T lymphocytes using flow cytometry; this difference was statistically significant when cells from patients with loose implants were compared to those from unexposed patients.

Hallab and colleagues measured lymphocyte responses (lymphocyte proliferation using Lymphocyte Transformation Testing (LTT), and cytokine release) to implant metals (Cr(+3), Co(+2), Ni(+2) at 0.1mM, and Ti(+4) at 0.001 mM) in six patient groups [33]: Group 1a=young controls, Group 1b=age matched controls, Group 2a=subjects with osteoarthritis (OA) and no history of metal sensitivity, Group 2b=OA subjects with history of metal sensitivity, Group 3a=total hip arthroplasty (THA) subjects with no to mild radiographic osteolysis, and Group 3b=THA subjects with moderate osteolysis. Patients with a THA (Groups 3a and b) were more than 3 fold more reactive to Cr ($p<0.04$), than were controls (Groups 1a & b) or OA subjects (Groups 2a & b). THA subjects with moderate osteolysis (Group 3b) were more reactive to Co than patients with mild osteolysis (Group 3a, 43% vs 0% incidence). Patients with periprosthetic osteolysis showed increased interferon-gamma (IFN-gamma) and interleukin-2 (IL-2) levels in response to Cr challenge. These findings suggest the presence of a metal-specific adaptive immune response and a relationship with osteolysis. A limitation of this study is the fact that patients who had a hip replacement did not undergo LTT and cytokine release testing prior to receiving a hip implant.

Discussion

A nonspecific macrophage-mediated foreign body immune reaction to wear particles from joint replacements has been clearly established, especially for polymeric materials. This reaction may be modulated by lymphocytes but it does not appear that immune complexes involving orthopaedic polymers activate specific T lymphocytes. Although the issue is still unresolved, at least in some patients, there appears to be activation of the specific T lymphocyte immune system to metal particles, probably complexed with specific serum proteins. This metal-protein complex can probably serve as a hapten. The observation of perivascular lymphocytic cuffing around in tissues from revised painful metal-on-metal implants is a highly suggestive finding of T cell mediated processes. However, this hypothesis is not straightforward. Immunosuppression (decreased numbers of T lymphocytes) has also been documented with excessive metallic wear particles.

The clinical implications of these findings are as follows: In specific patients, the generation of excessive metallic debris may be associated with an adverse T cell mediated Type IV immune reaction which may lead to pain and clinical failure. Exchange of the bearing surfaces or excision of the prosthesis may be necessary to alleviate the symptoms. This complication of metal-on-metal bearing implants is potentially more important in younger, more active patients in whom the prosthesis will be in situ for longer periods of time. In addition, factors

such as prosthesis size, design, anatomic orientation, patient characteristics and other factors may be relevant to the production of metallic byproducts [34].

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