



Revision joint replacement, wear particles, and macrophage polarization

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ABSTRACT

Currently, younger, more active patients are being offered total joint replacement (TJR) for end-stage arthritic disorders. Despite improved durability of TJRs, particle-associated wear of the bearing surfaces continues to be associated with particulate debris, which can activate monocyte/macrophages. Activated macrophages then produce pro-inflammatory factors and cytokines that induce an inflammatory reaction that activates osteoclasts leading to bone breakdown and aseptic loosening. We hypothesized that activated macrophages in tissues harvested from revised joint replacements predominantly express an M1 pro-inflammatory phenotype due to wear-particle-associated cell activation, rather than an M2 anti-inflammatory phenotype. We further questioned whether it is possible to convert uncommitted monocyte/macrophages to an M2 phenotype by the addition of interleukin-4 (IL-4), or whether it is necessary to first pass through an M1 intermediate stage. Retrieved periprosthetic tissues demonstrated increased M1/M2 macrophage ratios compared to non-operated osteoarthritic synovial tissues, using immunohistochemical staining and Western blotting. Uncommitted monocyte/macrophages with/without polymethyl-methacrylate particles were transformed to an M2 phenotype by IL-4 more efficiently when the cells were first passed through an M1 phenotype by exposure to endotoxin. Wear particles induce a pro-inflammatory microenvironment that facilitates osteolysis; these events may potentially be modulated favorably by exposure to IL-4.

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1. Introduction

Total joint replacement (TJR) is a successful operation for patients suffering from disabling arthritis and other degenerative conditions. However, wear of artificial joints occurs in association with the level of activity and duration of implantation. TJR failure is often associated with osteolysis and is a long-term complication that may require revision surgery [1–5]. Production of wear particles which are biologically active and indigestible incites an innate inflammatory reaction that may lead to periprosthetic bone loss, implant loosening and pathological fracture through osteolytic bone [4–8]. Particles are phagocytosed by monocyte/macrophage lineage cells, leading to their proliferation, differentiation, and activation [1,9,10]. These events lead to intracellular signal transduction involving activation of transcription factor NFκB and nuclear translocation, which up-regulate gene expression mechanisms for pro-inflammatory cytokines, chemokines, and other substances [5,11,12]. The end result is the disruption of the homeostatic balance between bone formation and resorption [5,11,12].

A current hypothesis suggests that macrophage activation in osteolysis may culminate in a specific phenotype, with polarization to either M1 or M2 profile, due to the undifferentiated nature of

monocyte/macrophage precursors, and the microenvironment of cell activation [9,13]. Studies also suggest that there may be epigenetic control of macrophage polarization, suggesting a possible genetic predisposition for osteolysis [14–16]. Specifically, this hypothesis suggests that wear particles initiate the migration of monocyte/macrophage precursors to the local site of particle production, and subsequent differentiation and activation to a classical M1 phenotype that initially promotes acute inflammation. This acute inflammatory state overcomes the anti-inflammatory environment supported by alternatively activated M2 macrophages that normally promotes bone healing, debris scavenging, wound healing, and angiogenesis [11,12].

The cytokine production profiles of M1 and M2 macrophages differ significantly and can be used to identify different predominant populations in a specific clinical situation. M1 macrophages produce primarily pro-inflammatory mediators, including TNF- α , IL-1, IL-6, and type 1 interferon, as well as IL-12 and IL-23, with the expression of inducible nitric oxide synthase (iNOS) and HLA-DR [17–19]. In contrast, M2 macrophages produce low levels of IL-12 and pro-inflammatory cytokines. The M2 profile is characterized by increased IL-4, IL-10, and IL-13 production, and expression of CCL1, CCL18, FIZZ1, mammalian chitinase Ym1, Arginase 1, CD163, and chitotriosidase [11,12,20,21]. This differential cytokine production and receptor expression can be used to characterize which macrophages are present in a clinical situation. Once

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