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REVIEW

Therapeutic intervention for wear debris-induced aseptic implant loosening

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Abstract Wear debris-induced aseptic loosening is an inflammatory bone disorder, which compromises the long-term success of total joint replacement. Despite the extensive research and great progress in treating inflammation-induced osteolysis for inflammatory arthritis, no drug has been proven for treatment/prevention of aseptic implant loosening. Also, there is very limited research on developing effective drug delivery systems for this pathological condition. In this review, we will discuss different therapeutic interventions and various delivery systems that have been developed for aseptic implant loosening. To provide the prospective for the future research in this area, the biology of wear particles-induced osteolysis, animal models developed for aseptic implant loosening and the potential challenges the field is facing are also presented in the discussion.

Abbreviations: AAV, adeno-associated virus; ASO, antisense oligonucleotide; COX, cyclooxygenase; Dex, dexmethasone; ELVIS, extravasation through leaky vasculature and inflammatory cell-mediated sequestration; EM, erythromycin; FGF-2, fibroblast growth factor-2; FLS, fibroblast-like synoviocytes; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; HPMA, *N*-(2-hydroxypropyl) methacrylamide; IKK, IκBα kinase; IL, interleukin; IRDye, infrared dye; IκBα, inhibitor of nuclear factor kappa B alpha; LacZ, *β*-galactosidase; LPS, lipopolysaccharide; M-CSF, macrophage colony-stimulating factor; NEMO, NF-κB essential modulator; NF-κB, nuclear factor kappa B; OPG, osteoprotegerin; PAMAM, poly(amidoamine) dendrimer; P-Dex, HPMA copolymer–dexamethasone conjugate; PET, positron emission tomography; PGE_2, prostaglandin E_2; PLGA, poly(lactic-*co*-glycolic acid); PMMA, poly(methyl methacrylate); RANK(L), receptor activator of nuclear factor kappa B (ligand); TGF-*β*, transforming growth factor beta; TNF, tumor necrosis factor; TRAP, tartrate-resistant acid phosphatase; UHMWPE, ultra-high-molecular-weight polyethylene; V-ATPases, vacuolar adenosine triphosphatase

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1. Introduction

Despite the great progress in treating rheumatoid arthritis and osteoarthritis, total joint replacement surgery still remains the final treatment option in many cases to relieve pain and restore joint function. There are almost 1.5 million total joint replacement surgeries performed annually worldwide and the number is expected to increase to 4 million annually by 2030[1,2]. Although total joint replacement provides great success, the prosthetic implants are not built to last forever. The overall 10-year success rate for total joint replacement is 90% with close to 10% of patients requiring revision surgery, which is more challenging and associated with a shorter duration of implant survival as well as posing higher risks for the patients. Aseptic loosening is the predominant factor limiting the longevity of the prosthesis, accounting for over 75% of joint replacement failure[3]. Other causes include infection (7%), recurrent dislocation (6%), periprosthetic fracture (5%), and surgical error (3%)[3,4].

2. Wear debris and osteolysis

Wear debris, primarily generated from the prosthetic joint articular surface, is widely recognized as the major cause of aseptic loosening[5]. Wear debris can be generated from all the components of the prosthesis (including polyethylene, ceramic and metal) as well as bone cement[6]. The accumulation of wear particles over time leads to inflammatory reactions and subsequent osteolysis around the implant surface[7]. Wear debris are primarily phagocytosed by macrophages, resulting in the secretion of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8) and prostaglandin E_2 (PGE_2). These cytokines upregulate nuclear transcription factor nuclear factor kappa B (NF-κB) and further ensues the proinflammatory cascade. The cellular mediators act in autocrine and paracrine fashions, leading to the differentiation, maturation and activation of osteoclasts from the precursor cells of hemopoietic lineage[8,9]. They also inhibit osteoprogenitor cells, thereby inhibiting/suppressing proliferation, differentiation and function of osteoblasts, as well as inducing apoptosis of osteoblast[10–13]. In addition to inflammatory mediators, lysosomal enzymes and matrix metalloproteinases (*e.g.*, stromelysins, gelatinase and collagenase) are released, and directly act on bone, causing further resorption[14]. These factors act in concert, eventually disturbing the normal homeostatic balance between bone degradation and formation, resulting in periprosthetic osteolysis. Several excellent reviews have been published detailing the biology of wear particles induced aseptic implant loosening[3,4,15].

3. Aseptic implant loosening animal model

In order to study the etiology, prevention and treatment of aseptic implant loosening, several animal models have been developed. It would take a significant amount of time to actually simulate/mimic the clinical scenario and establish an animal model with gradual debris production. Even for modified rat model which had a running wheel for 2 h/day for 5 days a week, it took 6 months to generate cement debris particles and synovial-like interface membrane with areas of bone resorption[16]. Due to the prohibitive natural wear particle generation time frame, many research groups have chosen to artificially introducing wear particles, in order to focus on the biology of wear debris-induced osteolysis.

3.1. Large animal models

Several large animal prosthetic implant models using rabbits, sheep and dogs have been developed to mimic the clinical condition of interaction between implant–bone interface and long term studies of aseptic loosening[17–20]. For these models, stable intramedullary prosthesis was implanted and particles were administrated at the implantation site. Due to the large size of the bones and joints, they have advantages of using clinically relevant implants, which can be subjected to appropriate physiological loads. The cost and management issues, however, prevent the wide use of large animals, especially for screening studies to explore novel therapeutic interventions.

3.2. Small animal models

Developing small animal models is of particular interest, owing to cost effectiveness and easy handling. Furthermore, the mouse genome is known. The availability of genetically manipulated variants and molecular methods makes murine models advantageous in identifying underlying biological mechanisms. Currently, there are three commonly used mouse models for studying implant loosening.

3.2.1. Murine air pouch model

This model was established on the back of a mouse by subcutaneously injecting sterilized air, followed by surgical introduction of a section of calvaria from a syngeneic mouse donor[21,22]. Polyethylene, poly(methyl methacrylate) or metal particles were then injected into the pouch. Osteolysis was shown in the calvaria within 10 days. The soft tissue reactions can be easily captured using this model. Due to the lack of blood supply, however, the implanted bone is necrotic, which ignores the self-healing (bone formation) process.

3.2.2. Murine calvaria model

To overcome the aforementioned problem in the air pouch model, murine calvaria model was developed. In this model, particles can be applied directly to the top of the calvaria after a midline sagittal incision[23,24]. A minimum invasive method was recently developed to introduce the particles by direct injection of the suspension of the particles to the top of the calvaria[25]. The particles deposited would lead to profound inflammation, osteoclast formation and bone resorption within 1 week.

The murine air pouch and calvaria models represent many biological features of the wear debris-associated osteolysis. Because of the short duration of model induction, they are the most frequently used animal models in implant loosening research. Their limitations, however, are also obvious. The models do not have a prosthetic implant and the prosthesis/medullar canal interaction is absent. Furthermore, the time needed to develop the models is very short, which does not reflect the chronic nature of the clinical condition. Evidently,