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.

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Abbreviations: AAV, adeno-associated virus; ASO, antisense oligonucleotide; COX, cyclooxygenase; Dex, dexamethasone; 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, IκB 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; PGE2, prostaglandin E2; 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, vacular 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. 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. Other causes include infection (7%), recurrent dislocation (6%), periprosthetic fracture (5%), and surgical error (3%).

2. Wear debris and osteolysis

Wear debris, primarily generated from the prosthetic joint articulating surfaces, is widely recognized as the major cause of aseptic loosening. Wear debris can be generated from all the components of the prosthesis (including polyethylene, ceramic and metal) as well as bone cement. The accumulation of wear particles over time leads to inflammatory reactions and subsequent osteolysis around the implant surface. 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 E2 (PGE2). 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 manners, leading to the differentiation, maturation and activation of osteoclasts from the precursor cells of hematopoietic lineage. They also inhibit osteoprogenitor cells, thereby inhibiting/suppressing proliferation, differentiation and function of osteoclasts, as well as inducing apoptosis of osteoblast. 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. 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. 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. 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. 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. 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. 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. 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,
these limitations would preclude the applications of these models in the study of biomechanical properties of implant and the evaluations of long-term effectiveness/safety of novel therapeutic interventions.

3.2.3. Murine prosthesis failure model
Researchers have tried to implant polymer or metal rods on mouse distal femur or proximal tibia to evaluate wear debris induced periprosthetic inflammation and osteolysis with a non-weight bearing characteristics. Yang et al. developed a mouse model with stainless steel or titanium-alloy pin implanted into the proximal tibia of mice followed by monthly intra-articular particles injection. At 12 weeks post-surgery, they showed a significant decrease in periprosthetic bone mineral density and pull-out force for particle challenged groups. In this model, particles were introduced at the time of surgery and periodically thereafter via intra-articular injections. While it is a significant improvement from the calvaria model, the model does not precisely simulate the clinical situation where wear particles are generated continuously by constant wear and tear due to joint movement. To address this challenge, Goodman's group further improved this model by subcutaneously implanting an osmotic pump. A hollow rod was press fit into the distal femur and connected to the particle suspension-loaded pump, which can continuously deliver particles at a constant rate to the intramedullary cavity. Clearly, this model simulates the clinical scenario than all the other models. The cost of the model development (including the surgery implantation and the cost of the osmotic pump), however, is prohibitive.

3.2.4. Rat models
The rat version of the subcutaneous air-pouch model has also been developed. Due to the relatively bigger body size, however, most of the rat studies have focused on incorporation of prosthesis. Similar to mouse situation, there are also two versions of the rat models with prosthesis: (1) A pin was implanted to the distal femur or proximal tibia with periodic particle injection; (2) A pin was inserted into the femur with continuous intramedullary infusion of particles using an osmotic pump.

4. Treatment options
To date, there is no drug specifically approved for prevention or inhibition of periprosthetic osteolysis. The improved understanding of the biological cascade of wear particle-induced aseptic implant loosening has suggested two potential therapeutic targets: modulate osteoclast formation/function and inhibit periprosthetic inflammation. The established aseptic implant loosening animal models provide in vivo tools for evaluation of these treatment options.

4.1. Modulate osteoclast formation and function

4.1.1. Bisphosphonates
For wear particle-induced osteolysis, the effector cell type for bone destruction is osteoclasts. Therefore, effective inhibition of osteoclast function becomes a natural target for therapeutic intervention. Bisphosphonates have been shown to inhibit mature osteoclast function and induce apoptosis. They are commonly used for treatment of metabolic bone diseases such as osteoporosis, hypercalcemia and Paget’s disease. Numerous experiments have proved the significant decrease in osteolysis after treatment with bisphosphonate. For example, Horowitz et al. demonstrated pamidronate was effective in reducing particle mediated osteolysis in vitro. Alendronate inhibited wear particle-induced osteolysis in murine calvarial model as well as both canine and rat models with tibial implants. Despite the promising positive data for treating particle-induced osteolysis in cell culture and animal studies, there is no significant powered, randomized, controlled clinical trial that could prove this type of drug can effectively treat aseptic loosening in patients/clinical settings. Therefore, clinical evaluation of bisphosphonates for treatment/prevention of particle-induced osteolysis in patients represents an area for future/further studies.

4.1.2. Statin
Another class of osteoclast inhibitor is statins. As 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, statins target the mevalonate pathway of osteoclast, which is of the same inhibition mechanism as bisphosphonates. von Knoch et al. showed simvastatin treatment markedly decreased ultra-high-molecular-weight polyethylene (UHMWPE) debris-induced osteolysis in murine calvarial model. They also did a comparison between statin and bisphosphonate. A single dose of the zoleodronate decreased UHMWPE particle-induced osteolysis in murine calvarial model as effectively as daily treatment with simvastatin.

4.1.3. RANK/RANKL signaling blockade
The central role of receptor activator of nuclear factor kappa B ligand (RANKL) in osteoclastogenesis makes it an attractive therapeutic target. The inflammation induced by wear debris leads to an increased expression of RANKL, an essential osteoclast differentiation factor. It stimulates osteoclastogenesis and bone resorption by binding to RANK on osteoclast precursors and mature osteoclasts. Osteoprotegerin (OPG) is a naturally occurring decoy receptor for RANKL, which could inhibit RANK/RANKL binding. OPG gene therapy has successfully proved reduced wear-debris-induced osteolysis in murine calvarial model. In addition, AMG-162, a human immunoglobulin monoclonal antibody with high affinity for human RANKL, showed an anti-resorptive effect for osteoporosis in postmenopausal women in clinical trials. It remains to be seen whether this agent will be effective in the treatment of osteolysis patients.

4.1.4. NF-κB signal pathway inhibitor
Because RANK signaling is transduced via NF-κB, inhibitors of this signaling pathway are effective in treating osteolysis. A NF-κB essential modulator (NEMO)-binding domain peptide has been found to block the binding of IKK2 and IKK1 to IKKγ/NEMO, inhibit NF-κB activation and alleviate poly (methyl methacrylate) (PMMA)-induced inflammatory and osteolytic responses in murine calvaria model. Meanwhile, bortezomib (a proteasome inhibitor) and pyrrolidine dithiocarbamate (an IκBα stabilizer) were proved to be effective in inhibiting titanium particle-induced inflammation in vitro and in vivo. In addition, Ren et al. demonstrated erythromycin (EM) treatment inhibited wear debris induced inflammation, osteoclastogenesis and bone degradation in mouse.
osteolysis model. More importantly, they also proved oral EM could reduce the inflammation of periprosthetic tissues and aseptic loosening in patients. The mechanism study suggested that EM inhibited wear debris-induced osteoclastogenesis by modulation of murine macrophage NF-κB activity.

4.2. Inhibition of periprosthetic inflammation

4.2.1. Anti-tumor necrosis factor alpha (TNF-α) therapy

As mentioned before, inflammatory cytokines play a vital role in the development of osteolysis. Modulation of inflammatory cytokines has been explored as a potential treatment for wear-debris induced osteolysis. Etanercept, a decoy receptor of TNF-α, inhibits cytokine production from particle stimulated macrophages and bone resorption in a bone wafer pit assay. For in vivo evaluation, etanercept reduced bone resorption and osteoclastogenesis in a murine model of titanium particle-induced osteolysis. TNF-α gene delivery also demonstrated its anti-resorptive effect in murine calvarial model. For clinical evaluation of etanercept, a pilot study of 20 patients with established periprosthetic osteolysis was reported. However, the data showed no significant difference in the progression of osteolysis between the etanercept and placebo-treated groups using a volumetric three-dimensional computed tomography as an outcome measurement technique. The reasons might be etanercept itself, insufficient sample size or due to non-sensitive evaluation method, thus further studies are needed. Another anti-TNF-α drug, which has been investigated, is pentoxifylline, a potent TNF-α secretion inhibitor. Orally administered pentoxifylline reduced the inflammatory response of isolated monocytes to wear debris in healthy subjects, but has not been tested in osteolysis patients.

4.2.2. COX-2 inhibitor

PGE2 is a well-known pro-inflammatory mediator of aseptic loosening. COX-2 is the principal cyclooxygenase (COX) responsible for the production of PGE2. As anti-inflammatory agents, COX-2 inhibitors are clinically used in the treatment of arthritis. Studies showed celecoxib, a COX-2 inhibitor, suppressed wear-debris induced osteolysis in both murine calvaria and rabbit prosthesis model. Oral administration of celecoxib resulted in a significant decrease in bone resorption. In addition, celecoxib treatment was also effective in reducing the in vivo bone resorption induced by wear debris in a murine model.

4.2.3. Anti-inflammatory cytokines (IL-10 and IL-4)

Unlike pro-inflammatory cytokines, there are some anti-inflammatory cytokines which possess immuno-regulatory and inhibitory properties. Two of such anti-inflammatory cytokines that have been widely studied as options for the treatment of osteolysis are IL-4 and IL-10. In vitro data showed IL-4 or IL-10 could inhibit expression of TNF-α and IL-6 by monocyte/macrophage in response to titanium or PMMA particles. Another approach is gene delivery. Researches showed gene delivery of IL-10 inhibited TNF-α and IL-1β production and inhibited wear debris-induced osteolysis in both murine calvaria and air pouch model.

4.3. Miscellaneous

4.3.1. Bone formation promoter

Both bone formation by osteoblasts and bone resorption by osteoclasts are responsible for bone homeostasis. Agents that promote bone formation could also be used for treating aseptic implant loosening. Transforming growth factor beta (TGF-β) stimulates osteoblast-like cell proliferation and also regulates osteoclast migration and differentiation. Local administration of TGF-β increased bone ingrowth in a rabbit model. Fibroblast growth factor-2 (FGF-2), a protein produced by osteoblasts, modulates osteoblastic proliferation/differentiation, stimulates endosteal bone formation and induces neovascularization. Local infusion of FGF-2 increased net bone formation in the presence of polyethylene particles in the rabbit tibia. In addition, besides inhibiting osteoclasts, statins markedly promoted bone formation and net bone growth in UHMWPE particle-induced osteolysis in murine calvarial model.

4.3.2. Other factors responsible for bone resorption

Besides osteoclast itself, other factors are also required for bone resorption. For example, V-ATPases are proton pumps playing a vital role in bone resorption by mediating extracellular acidification of the resorption lacuna between bone surface and osteoclast ruffled border plasma membrane. Qin et al. proved saliphenylhalamide, a new V-ATPase inhibitor, attenuated wear particle-induced osteolysis in murine calvarial model. There are also reports about anti-resorptive effects of cathepsin K inhibitors, vitronectin receptor antagonists, and src tyrosine kinase inhibitors, but with no publication reporting their direct use in treatment of wear-debris induced osteolysis. These drugs may be explored in the future as therapeutic or preventative agents for the treatment of wear particle-induced osteolysis.

5. Drug delivery system for implant loosening

The systemic anti-inflammation or anti-osteolysis therapies discussed in the last section have several limitations, which include the necessity of high-dose, lack of efficacy, systemic side effects, and consequently poor patient compliance. Apparently, these limitations can be partially attributed to the lack of tissue specificity of these medications to the wear-particle induced osteolysis sites. To address this issue, a few drug delivery systems have been explored to provide the drug candidates with tissue specificity to osteolysis lesion.

5.1. Polymer drug conjugate

As discussed above, EM represented an interesting drug candidate for the prevention and treatment of periprosthetic membrane inflammation. In order to deliver adequate levels of EM to the periprosthetic inflammation site with sustained pharmacological activity, Admira et al. developed a poly(amidoamine) dendrimer (PAMAM)-EM conjugate. PAMAM G4-OH was partially functionalized with amine groups on the surface using amino-valeric acid and conjugated to EM prodrug (EM-2-glutarate) through an ester bond. In vitro macrophage culture data suggested that the dendrimer enabled more drugs to be transported into cells, and the conjugate released the drug at a reasonable time frame. However, there is no in vivo evaluation for this PAMAM-EM conjugate.

Besides dendrimer, N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer has been used as a carrier for anti-inflammatory drug dexamethasone (Dex). The linker between...
the HPMA copolymer and Dex is a hydrazone bond, which is acid cleavable. The in vitro drug-release studies showed that the release of Dex is almost linear with a sustained release rate of about 1% of the loaded drug per day at pH 5.86. By using murine calvaria model, a single tail vein injection of P-Dex attenuated osteolysis with the same therapeutic effect as daily Dex treatment85. In addition, P-Dex was proved to be primarily localized at the particle-induced inflammation site. Therefore, the conjugation resulted in a sustained and targeted therapeutic effect with potentially reduced systemic adverse effects.

5.2. Polymer matrix based drug delivery system

Different from the prodrug approach described in Section 5.1, controlled drug release at the osteolysis lesion can also be realized by physically entrapping therapeutic agents in polymeric matrix materials. For example, fluvastatin poly(lactic-co-glycolic acid) (PLGA) microspheres were prepared using an in-water drying method. In vitro study showed a gradual release of fluvastatin for more than 1 month. In vivo study demonstrated a significant amount of new bone formation around the titanium implant in rat tibia and an increase in bone strength, 4 weeks after transdermal injection to the dorsum of rats87.

The reported PLGA microsphere is the only publication using polymer matrix based drug delivery system for treating aseptic implant loosening. Others have used polymer matrix system to establish lipopolysaccharide (LPS)-induced implant loosening model or treat LPS induced implant loosening. For example, an injectable hyaluronan gel has been developed as a LPS delivery vector to establish murine calvarial model88. The gel could maintain fluidity for up to 30 min after cross-linker was added, and the injection was performed within this window to the calvaria site. Compared with pure LPS, the gel-delivery system produced a dramatic increase in inflammatory soft tissue deep to the calvarial bone due to the controlled release and localization of LPS to the injection site. If the same gel system is developed loading with drug, it might have a great potential for application to intra-articular injection against inflammation or osteolysis. In addition, a biodegradable gelatin-chitosan cationic hydrogel loading an antisense oligonucleotide (ASO) targeting murine TNF-α was developed to treat LPS induced osteolysis89. The transfection efficiency of the hydrogel was much higher than lipofectamine 2000 and chitosan. In vivo data showed the hydrogel was digested and absorbed 2 months after implantation. Hydrogel delivered ASO could effectively suppress TNF-α, M-CSF, RANKL, and notably decreased osteoclastogenesis, thus inhibiting osteolysis. In contrast, naked ASO itself had little suppression effects. Since TNF-α also played a very important role in aseptic implant loosening, the hydrogel might also be effective in treating this disease.

5.3. Implant coating

Coating bisphosphonates to the surface of implant is a widely used method to increase osseo-integration80,81. Besides systemic/local administration or directly coating drugs to the implant, there is also ongoing research using polymer coating with sustained release effect. Schmidmaier et al. developed a biodegradable poly(d,l-lactide) coating of implants for continuous release of growth factors for simulating fracture healing82. The coating was 14.8 μm on titanium wire surface with a reduction of about 8% within 6 weeks in vitro. The same group also developed a implant coating using poly(d,l-lactide) incorporated with bisphosphonates to inhibit osteoclasts. There was a significant decrease in osteoclast formation and activity in the coated group93. The data also showed an increased OPG concentration and a beneficial effect on osteoblast differentiation and protein synthesis84.

5.4. Gene therapy

Zhang et al.95 developed a cell-based OPG gene therapy. They transduced mouse fibroblast-like synoviocytes (FLS) with AAV-OPG or AAV-LacZ in vitro, and then transfused the cells into the failing knee prosthesis. The FLS localized in the knee joint periprosthetic tissue and expressed target protein, resulted in a successful therapeutic influence by decreasing TRAP+ and CD68+ cells, inflammatory cytokines, as well as reversing bone resorption. Compared with the in vivo local gene transfer, the cell-based technique had a comparable OPG level, but with decreased potential side effects such as vector-mediated cytotoxicity and adverse immunological reactions.

6. Challenges and prospective

6.1. The lack of early detection method and therapeutic outcome evaluation criteria

For orthopedic implant loosening, the most difficult challenge is early diagnosis. Currently, physical examination and periodically radiographic evaluation are the only clinically used methodology in identifying implant loosening96,97. However, implant loosening is a silent disease with no clinical symptoms and anatomical change at the early stage. Present radiographic evaluation standards provide very limited information and normally underestimate the degree of bone loss98. Although three dimensional computed tomography, magnetic resonance and positron emission tomography (PET) imaging have been developed for measuring osteolysis99,101, there is still no sensitive detection and clearly quantitative measurement criteria of periprosthetic osteolysis at very early stage of the disease development102. Therefore, the development of novel early detection methodologies and the establishment of therapeutic outcome evaluation criteria should be the main focus of the field.

Based on one of the pathological feature of inflammation (leaky vasculature), a HPMA copolymer based early detection system has been developed. The HPMA copolymer-IRDye conjugate could identify sites of inflammation induced by the wear debris at the early stage of implant loosening in murine calvaria model103. Adaptation of this system for the use of high-energy radioisotopes instead of optical imaging probes might permit the development of imaging tools for human application. To further increase the sensitivity of the detection probe, active targeting moieties for inflammation could be used. Because activated macrophages express folate receptors103, folate-targeted imaging agents has been developed for diagnose of adjuvant-induced arthritis in rats104,105. Because of the important role of activated macrophages in the
6.2. The lack of development in drug delivery system

Due to the well-established biology of wear-particle-induced osteolysis, many therapeutic strategies have been explored as treatment for implant loosening. Though no drug has been specifically approved for the treatment of the disease, many anti-inflammatory agents have been used off-label in clinical management. As discussed in Section 5, most of these medications do not have tissue specificity to the osteolysis lesion. Therefore, after systemic administration of anti-inflammatory or anti-osteolysis drugs, their accessibility to the osteolysis lesion relies solely upon vascular perfusion. Because of the overall limited blood supply at the bone–implant interface, high systemic drug dose is required to achieve effective drug concentration at the site of loosening, which often induces systemic adverse side effects. Meanwhile, poor patient compliance is also a problem, considering the development of implant loosening is a long and slow process, which requires regular/frequent drug administration (e.g., daily). To overcome these limitations, there is a clear need of developing better drug delivery system for the treatment of this disease. As summarized in Section 5, however, the work in this area was very limited.

As a chronic inflammatory skeletal disorder, aseptic implant loosening shares many pathological similarities with arthritis, including inflammation induced osteolysis, formation of periprosthetic membrane/osteolysis synovial membrane, activated monocytes/macrophages/fibroblasts and elevated inflammatory cytokines. Many treatment therapies and nanotechnologies that have been developed for treating arthritis may also be applicable for aseptic implant loosening as well.

6.2.1. ELVIS mechanism and systemic delivery

The inflammation process is characterized by a sequence of pathophysiological events, including vascular restructurating, inflammatory cell recruitment, destruction of the initiating stimulus, removal and repair. The enhanced vascular fenestration allows small, colloidal drug delivery systems to extravasate at the inflammation site and then be sequestered by local inflammatory cells. This novel passive-targeting mechanism has been validated in the treatment of several inflammatory disease models and was coined as ELVIS (extravasation through leaky vasculature and inflammatory cell-mediated sequestration) mechanism. The fields of drug delivery and nanomedicine have matured over the years with many delivery tools developed to accommodate a wide range of therapeutic agents and to increase their therapeutic index. Long circulating liposomes, macromolecular prodrugs, nanoparticles, and micelles can all be explored to target the osteo-inflammation site via ELVIS mechanism. Furthermore, targeting ligands can also be introduced to the delivery system to enable active targeting. Folate targeted therapies has been developed for treatment of rheumatoid arthritis, allowing decreased toxicity to normal tissues. Other targeting ligands may also be used, such as the E-selectin ligand overexpressed on the surface of leukocytes and alpha v beta 3 integrins expressed on angiogenic vascular endothelial cells.

6.2.2. Local delivery

Aseptic implant loosening is a local inflammatory disease. This provides an opportunity for local treatment via intra-articular route, resulting in a high local concentration with decreased systemic exposure. However, rapid clearance from the joint cavity could impair the effectiveness of this strategy and require frequent administration. Furthermore, the technical difficulty in intra-articular injection, the potential safety concern and poor patient compliance limit its application. Therefore, there is a need for the development of effective local delivery systems with sustained therapeutic effect. For such approach, delivery systems such as nanoparticles, liposomes, microspheres or hydrogels may be considered for intra-articular or transdermal delivery.

6.2.3. Delivery systems for combination therapy

Periprosthetic osteolysis involves a cascade of proinflammatory mediators, cell-signaling mechanisms and cellular elements. They are complex and interrelated. Therefore, concerns have been raised for the attempt of blocking only one therapeutic target. For example, OPG treatment could decrease bone loss, but not reduce inflammation. Elevated levels of IL-1β and TNF-α are able to promote osteoclastogenesis even in the presence of very low RANKL levels. Based on this assessment, we believe the administration of combination therapy, which would block multiple pathological pathways, would be efficacious in term of clinical management of peri-implant osteolysis. Apparently, such therapeutic strategy would necessitate the development of formulations that would delivery multiple therapeutic agents simultaneously.

7. Conclusion

Aseptic implant loosening is a major complication in total joint replacement. Considerable effort has been invested in understanding the biology and identification of therapeutic interventions for the disease. A thorough research of literature has revealed, however, that the development of early diagnostic tools and drug delivery systems for the disease has been very limited. Given the projected significant increase of total joint replacement procedure in the coming years and the fact that wear particle-induced osteolysis is unavoidable; we believe this is a field of opportunity for pharmaceutical scientists. As a vast arsenal of nanotechnology tools has been developed during the last decade, we believe there is a lot that we can contribute to improve the current clinical diagnosis and therapeutic intervention of aseptic implant loosening.

References


