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REVIEW

Local Cellular Responses to Metallic and Ceramic Nanoparticles from Orthopedic Joint Arthroplasty Implants

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Li Zhang
El-Mustapha Haddouti
Kristian Welle
Christof Burger
Koroush Kabir*
Frank A Schildberg*

Clinic for Orthopedics and Trauma Surgery, University Hospital Bonn, Venusberg-Campus 1, Bonn 53127, Germany

*These authors contributed equally to this work

Abstract: Over the last decades, joint arthroplasty has become a successful treatment for joint disease. Nowadays, with a growing demand and increasingly younger and active patients accepting these approaches, orthopedic surgeons are seeking implants with improved mechanical behavior and longer life span. However, aseptic loosening as a result of wear debris from implants is considered to be the main cause of long-term implant failure. Previous studies have neatly illustrated the role of micrometric wear particles in the pathological mechanisms underlying aseptic loosening. Recent osteoimmunologic insights into aseptic loosening highlight the important and heretofore underrepresented contribution of nanometric orthopedic wear particles. The present review updates the characteristics of metallic and ceramic nanoparticles generated after prosthesis implantation and summarizes the current understanding of their hazardous effects on peri-prosthetic cells.

Keywords: nanoparticles, joint arthroplasty, osteoblasts, osteoclasts, macrophages, mesenchymal stem cells

Introduction

Over the last decades, total joint arthroplasty (TJA), such as knee, hip, ankle, elbow and others, has become the most successful procedure in treating joint diseases. Though TJAs provide pain relief and function restoration with minimal impact of activities of daily life, their long-term prosthesis survival still remain a concern. Osteolysis is the most common long-term complication after total joint replacement surgery.[1] Aseptic implant loosening secondary to periprosthetic osteolysis is the leading cause of revision procedures for elbow, hip, knee, or ankle TJA and is the predominant limiting factor of the longevity of current TJAs prosthesis.[2–6] As the only established treatment for peri-prosthetic osteolysis to date, revision surgery is technically complex, and is associated with a high rate of complications, high morbidity rate, poor clinical and functional performance, as well as significant economic impact on the healthcare system.[7]

The particulate wear particles of different material types of prostheses have been recognized as one of the major factors responsible for aseptic implant loosening after joint arthroplasty.[8] Metals, ceramics, and polymers are the commonly used orthopedic biomaterials. After implantation, these prostheses become an internal source of wear particles upon corrosion and abrasion.[9–12] Once released, wear particles can infiltrate into the systemic circulation causing systemic toxicity.[13,14]

Correspondence: Koroush Kabir; Frank A Schildberg
Email koroush.kabir@ukbonn.de; frank.schildberg@ukbonn.de

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They also locally accumulate in adjacent tissue and space, such as bone and bone marrow.[15] Thereafter, these non-degradable particles can represent a long-term hazard and principally interact with the complex peri-implant cell lineages such as bone-forming osteoblasts and their progenitors, bone marrow residing mesenchymal stem cells (MSCs), macrophages, osteoclasts and fibroblasts. This process induces adverse cellular effects and contributes to the pathological mechanisms underlying implant aseptic loosening.

Particulate wear debris range in size from micron to sub-micron. Nanoparticles (NPs) are defined as ultrafine particles with external dimensions with a size of 1–100 nm. Compared to their micro-sized counterparts, nano-sized particles are more biologically active to peri-implant cells. They induce greater cytotoxicity, inflammation, cytokine release, more free radical production and chromosomal damage.[16] However, difficulties in isolating and characterizing nano-scale particles until today suggest that the number and adverse effect of NPs might have been underestimated.[17] Given these challenges, an in-depth understanding of local cellular responses to the released nanoscale wear debris from orthopedic implants will provide a new area in the comprehension of aseptic loosening and offers new scientifically based recommendations to better design suitable prosthetic interfaces and scaffolds. Therefore, in the present review, we provide a general overview of the characteristics of nano-sized metallic and ceramic orthopedic implant wear particles and highlight their biological effect on peri-implant cells. Finally, future challenges in transferring preclinical knowledge to clinical practice are discussed.

Peri-Implant Cell Lineages

After their release, wear particles interact with a complex and diverse collection of cell types in peri-implant tissue adjacent to joint prostheses. Cellular responses to wear particles contribute to pathological mechanisms underlying aseptic loosening because they help determine the rate of occurrence of implant osteolysis at mid-term and long-term implantation time. Here, we mainly focus on 4 cell lineages: macrophages, osteoblasts, osteoclasts, and MSCs.

Macrophages

Macrophages are the key cells in the response to wear particles from joint arthroplasty.[18,19] During the progression of osteolysis, they are systemically recruited to the local site of particle generation. Notably, in osteal tissues also resident osteal tissue macrophages (OsteoMacs) are present,[20] however, their contribution to aseptic loosening has never been studied and needs further exploration. As sentinels of the innate immune system, macrophages are the first cell types involved in this response by recognizing, internalizing, and getting activated upon wear particle exposure. Previous studies reported that nanoscale wear particles induced an increased M1/M2 (pro-inflammatory phenotype/anti-inflammatory phenotype) macrophage ratio in vitro and in vivo.[21] Once activated, macrophages initiate inflammatory cascades characterized by the release of pro-inflammatory cytokines, such as IL-1β, TNFα, and IL-6. These reactions create an inflammatory microenvironment that facilitates osteoclast activation, bone destruction, and eventually aseptic loosening.[19,21]

Osteoblasts

Osteoblasts are the main bone-forming cells responsible for bone deposition and implant osseointegration. They synthesize the components of bone matrix, regulate their mineralization and modulate osteoclasts. Responsible for extracellular matrix expression, their cytoplasm is rich in organelles necessary for protein secretion such as well-developed rough endoplasmic reticulum, large Golgi complex, transfer vesicles, secretory granules, and electron-dense mitochondria. They synthesize the majority of bone matrix constituents including osteocalcin, alkaline phosphatase (ALP) and a large amount of type I collagen and regulate their mineralization. In addition, their cytoskeleton is responsible for cellular structural and mechanical properties such as elasticity and spring constant,[22] which is important to establish successful implant integration.[23] By this, osteoblasts provide a foundation upon which the new bone tissue can grow and thus play a leading role in postoperative implant osseointegration which is crucial for early fixation as well as long-term success of orthopedic implants. Importantly, osteoblasts interact with osteoclasts in a delicate balance via secreted factors such as receptor activator of nuclear factor (NF)-κB ligand (RANKL) and osteoprotegerin (OPG). Binding of RANKL to RANK activates NF-κB signaling pathway that ultimately leads to osteoclastogenesis. OPG is a soluble "decoy receptor" for RANKL and thus a physiological negative regulator of osteoclastogenesis.

Osteoblasts are rather responsible for bone formation. In the context of wear particles, they also indirectly participate in bone degeneration by demonstrating direct

cellular dysfunction (eg, reduced viability, differentiation and mineralization), changing expression of specific inflammatory cytokines (eg, TNFα, IL-1β, IL-6, and M-CSF) as well as directly by the secretion of preosteolytic mediators and specific proteinases.[24,25] These factors not only impair osteoblastic bone formation but also exacerbate osteoclastic bone resorption, which ultimately lead to peri-implant osteolysis.

Osteoclasts

Osteoclasts are the only in vivo cells with bone resorption function. They derive from bone marrow monocyte/macrophage lineage cells. Osteoclastic bone resorption consists of a two-phase process. Bone is acid demineralized, followed by degradation of the demineralized type I collagen-rich matrix by secreted cathepsin K and other acidic proteinases. Osteoclasts maintain bone metabolism homeostasis by acting synergistically with osteoblasts. Numerous hormones, growth factors, and cytokines modulate osteoclast activity by regulating their differentiation, activation, life span, and function. For example, the RANKL/OPG expression ratio determines the degree of osteoclast differentiation and function, and has been shown to be implicated in the process of osteolysis. M-CSF binds to c-FSM and promotes osteoclast proliferation and osteoclast precursor survival. RANKL stimulates RANK on the osteoclast precursor's surface and activates NF-κB signaling pathways. Activated NF-κB favors the survival, differentiation, and activation of osteoclasts through the nuclear factor of activated T cells cytoplasmic 1 (NFATc1).[26]

Unfortunately, to date, only a small number of studies about the direct interaction between osteoclasts and wear particles have been published. Osteoclasts have also been shown to be capable of phagocytosing wear particles in -vitro.[27,28] Nevertheless, after being fully differentiated in vitro, osteoclasts lose the ability to release inflammatory cytokines,[29] indicating a diminished role of osteoclasts in potentiating implant debris-induced inflammation and osteolysis.

MSCs

Multipotent MSCs are residing in bone marrow, trabecular bone, the walls of the microvasculature, and adjacent to implants. By their differentiation into osteoblasts and regulating osteoclast differentiation and activation, MSCs play a critical role in maintaining implants' osseointegration and interface stability, which might determine the rate of occurrence of osteolysis at mid-term and long-term implantation time.

MSCs have been implicated as a target of particles during aseptic loosening.[30] They have been shown to internalize NPs via endocytosis.[31,32] Accumulating evidence indicates that, upon exposure to micron- and submicron-sized particles, MSCs demonstrated ultrastructural changes and compromised cellular functions such as viability, proliferation, migration,[33,34] osteogenic differentiation, and subsequent bone formation as well as disbalanced RANKL/OPG secretion.[30,35–38] These cellular reactions decrease new bone formation, exacerbate osteoclastic bone resorption at the bone-implant interface and contribute to implant loosening.

Metal NPs

Metal implants have been used for biomedical applications since the 19th century. Within the past two decades, they have evolved into the most widely used material in the orthopedic field, eg, fracture repair, joint arthroplasty, due to their high mechanical resistance, excellent molding characteristics and biological compatibility, whereas the long-term effects of wear debris are not known completely. To date, the majority of metal implants are based on titanium (Ti), cobalt (Co) and chromium (Cr).[39,40] Moreover, Tantalum (Ta) components are receiving increasing interest as load-bearing orthopedic biomaterial because of their outstanding biocompatibility, corrosion resistance, and superior strength.[41,42] In order to improve their tribological performance as well as their osseointegration, a number of different surface modification techniques have been recently applied. However, when mechanical stress overwhelms components' protective capacity, corrosive substances such as metallic particles, inorganic metallic salts as well as free metal ions are released.[43] These products, mostly released from metal-on -metal (MOM) and metal-on-polyethylene (MOP) bearings, can accumulate in the surrounding tissues, or even disseminate to distant lymph nodes and organs,[44–46] causing adverse local and/or systemic risk.

Ti- and TiO_2-Based NPs

Ti and Ti-based alloys (eg, Ti-6Al-4V) have evolved to be the most used orthopedic implant materials due to their advantageous bulk mechanical properties and biocompatibility compared to other metallic biomaterials.[47] However, the main limitation of them is their poor tribological behavior.[48] Notably, Ti alloys can naturally form a passive protective

titanium dioxide (TiO_2) layer which provides them with an excellent biocompatibility and corrosion resistance. Therefore, in vivo corrosion and wear of Ti-based implants can produce both Ti and TiO_2 particles (commonly rutile and anatase).[49,50] Interestingly, as TiO_2 NPs have been widely applied in the food industry (packaging and food additives) as well as cosmetic products (eg, toothpaste and sun cream) and are consumed by millions of people on a daily basis,[51] attention has already been drawn due to its potential adverse effects through oral and inhalation exposure.[52–57] Yet, the potential effect of TiO_2 NPs on skeletal system as nano-biomedical applications when exposed internally has not been fully understood.

Effects of Ti NPs on Macrophages

Recent studies showed that Ti NPs (52 nm) drove RAW 264.7 cells to polarize into the M1 phenotype (proinflammatory phenotype) and increased inflammatory cytokine (TNFα, IL-6) production.[58] LiCl promoted M2 macrophage polarization, reduced pro-inflammatory cytokines and enhanced the release of anti-inflammatory and bone-related cytokines, such as IL-4, IL-10 and bone morphogenetic protein 2 (BMP-2) and vascular endothelial growth factor (VEGF). This effect may be attributed to LiCl's attenuation on Ti nanoparticle-induced activation of ERK and p38 phosphorylation in vitro. Further, in vivo results from an experimental air pouch model confirmed LiCl's protective effect on Ti nanoparticle-mediated inflammatory reaction through regulating the ratio of M1/M2 macrophages.[58] Furthermore, recent studies showed that in vitro TiAl6V4 and CoCrMo nanoparticle-induced inflammatory responses in RAW 264.7 cells were mediated by the SIRT1-NF-κB pathway. Moreover, pharmacological activation of SIRT1 by resveratrol attenuated osteolysis and local inflammatory responses in these two metal particle-induced osteolysis (PIO) mouse models.[59] The above-mentioned results indicated that Ti NPs can drive macrophage polarization and induce inflammation both in vitro and in vivo. LiCl and resveratrol can mitigate particle-induced osteolysis through attenuating these effects.

Effects of Ti NPs on Osteoblasts and MSCs

Despite the excellent biocompatibility characteristics of Ti in bulk form, the adverse effects of Ti particles on osteoblast functions have been characterized by a number of researchers.[60–63] Pure Ti particles have been reported to induce apoptosis in osteoblasts.[64,65] In accordance to this, nano-sized Ti NPs (30 nm) dose- and time-dependently induced apoptosis in Saos-2 human osteoblast-like cells. Furthermore, increased elasticity and spring constant and decreased osteoblastic mineralization ability were observed.[66] Notably, Ti NPs induced a less pronounced effect than Co NPs,[66] possibly as a result of Ti NPs' lower uptake rate and better cytocompatibility. The same group also compared Ti with Co NPs on MC3T3E1 cells in vitro. Similarly, although a general decline in viability was found after a Ti (30 nm) NP exposure for 72 hours, there was no significant change in cell elasticity, spring constant, adhesion forces as well as osteoblastic mineralization ability after 21 days,[67] probably due to less particle concentration applied compared to previous studies. Not surprisingly, Ti still induced less increase in spring constant than same sized Co NPs.

Osteogenic inhibition and bone destruction have been observed in Ti particle-induced mouse models. GSK-3β/Wnt/β-catenin signaling pathway has been reported as a key mediator of this process both in vitro and in vivo. Inhibiting GSK-3β activity with drugs such as melatonin, icariin, ghrelin, and LiCl increased downstream β-catenin expression, and mitigated Ti particle-induced suppression of osteogenesis, both in vitro and in vivo.[68–72] Unfortunately, to date, the involvement of GSK-3β/Wnt/β-catenin signaling pathway in nano-sized Ti particle-induced osteolysis has never been studied. More studies are needed to elucidate this aspect.

Nano-sized Ti alloy particles (90% with a diameter of less than 100 nm) caused morphology changes, inhibited rabbit BMSC proliferation, and enhanced the apoptosis rate in vitro in a dose- and time-dependent manner.[37] Moreover, Preedy et al reported rat MSCs exposed to increasing concentrations of Ti NPs (30 nm) resulted in a lower cell elasticity.[38] Notably, Ti NPs induced less effect than Co NPs with similar diameter, supporting the cytocompatibility of the former. Unfortunately, previous studies mainly focused on MSC's physiological function change on Ti implant surface with different nanoparticle coating,[73,74] and no studies are available addressing the effect of nano-sized Ti particles on MSCs. Only one study reported that rat BMSCs demonstrated reduced osteogenic differentiation after incubation with supernatant from Ti NP-stimulated RAW264.7 cells, indicating Ti NP's indirect influence on BMSCs via macrophage-MSC communication. Thus, more studies are needed in the future.[58]

Effects of TiO_2 NPs on Macrophages

Until now, although TiO_2 NPs have been investigated in different cell lines, the underlying mechanisms of how

macrophages internalize TiO_2 NPs have not been fully understood. Recently, Chen et al firstly reported that TiO_2 NPs were probably endocytosed using proteomic analysis in mouse bone marrow-derived macrophages (BMDMs).[75] Also, they found that TiO_2 NPs decreased mitochondrial function, elicited inflammatory responses through activating COX-2 pathways. Notably, an attenuated phagocytic capability of macrophages was observed upon in vitro TiO_2 NP exposure, suggesting potential detrimental effects on immune responses. This result is consistent with results from Huang et al. They found that TiO_2 NPs can prime a specific state of murine macrophages characterized by excessive inflammation (increased pro-inflammatory genes and decreased anti-inflammatory genes) and suppress innate immune function both in vitro and in vivo in a TLR4-dependent manner.[76] These results suggest that TiO_2 NPs drive macrophage polarization and impair macrophage's immune response and may enhance the susceptibility to bacterial infection upon long-time exposure.

ROS-dependent signaling plays a key role in the macrophage-TiO_2 NP interaction. The cytotoxic ability induced by TiO_2 NPs was dependent on ROS.[77] Recently, Dhupal et al reported that TiO_2 NPs (20 nm, negative charge) induced immunotoxicity (apoptosis and toll-like receptor activation) in murine RAW 264.7 cells through ROS-dependent SAPK/JNK and p38 MAPK activation pathway.[78]

TiO_2 NPs have also been reported to activate the NLRP3 inflammasome in macrophages.[57,79] This process, which releases pro-inflammatory IL-1β and IL-18, induces pyroptosis and contributes to its inflammatory and cytotoxic effect. Morishige et al challenged THP-1-derived macrophages with TiO_2 anatase and rutile NPs and found that macrophages recognized and phagocytosed TiO_2. Further, TiO_2 NPs induced NALP3 inflammasome activation and IL-1β release in a ROS- and cathepsin B-dependent manner.[80] Recently, Baron reported that nano-SiO_2 and nano-TiO_2 triggered ATP release, which is a known ROS inducer, and resulted in subsequent NLRP3 inflammasome formation in macrophages through the activation of PLC-InsP3 and inhibition of ADCY-cAMP pathways.[79]

Different TiO_2 NP structures may result in diverse biological reactions in macrophages. Recently, Yu suggested that TiO_2 rutile NPs cause more severe lysosomal membrane permeabilization (LMP) than anatase NPs in RAW264.7 cells. TiO_2 anatase caused less severe necrosis and LMP than rutile NPs, but more severe mitochondrial dysfunction associated with higher levels of apoptosis.[81]

Effects of TiO_2 NPs on Osteoblasts and MSCs

Although they are thought to be nonphagocytic cells, osteoblasts have been shown to engulf and internalize particulate debris within the osteoblast cytoplasm. Cai et al reported that OBs take up TiO_2 NPs mainly via clathrin-mediated and caveolae-mediated pathways.[82] In addition, as recently described, TiO_2 anatase NPs form bio-complexes with proteins and ions from cell culture medium, which act as a kind of "Trojan-horse" internalization by primary human osteoblasts.[83] Nano-TiO_2 particles (4 and 40 nm) disrupt the cytoskeletal networks and impair migration in Saos-2 cells. They also increased FAK phosphorylation and reduced vinculin expression (using 5 nm NPs), resulting in impaired cell adhesion.[84] Interestingly, these cellular reactions were size-dependent, with NPs smaller than 5 nm having a stronger impact than 40 nm NPs. Also, after NP internalization, evidence of extensive DNA fragments, autophagolysosome-like structures, ultrastructure organelle damage (eg, mitochondria swollen), and intensive vacuolization was identified, suggesting cell damage and necrotic lysis.[83,85] Accordingly, a dose- and time-dependent cytotoxicity on human[83–85] and rodent[86–88] osteoblasts was observed. This could be attributed to increased oxidizing stress after NP exposure.[85] Additionally, decreased ALP activity and increased RANKL expression and MMP-9 activity were also observed, suggesting decreased osteogenic differentiation and osteoclastogenesis.[85,86] The inflammatory response of osteoblasts to TiO_2 NPs was evaluated in a 3D Saos-2 spheroid. Cytokines (IL-1β, IL-6, IL-8, IL-12, IL-15, IL-4, IL-10), chemokines (Rantes, MIP-1, IP-10), and VEGF secretion were increased in the supernatant,[89] which is of particular interest as some of these molecules are involved in osteolysis and bone homeostasis. In summary, after internalization by OBs, TiO_2 NPs hamper osteoblastic cellular function (eg, viability, osteogenic differentiation), promote inflammation, and thus contribute to peri-implant osteolysis.

In terms of MSCs, Hou et al reported that, after internalization, TiO_2 NPs of different sizes (14 nm, 108 nm, and 196 nm) had adverse effects on cell viability, proliferation, adhesion and migration on rat bone marrow-derived MSCs, in a dose- and size-dependent manner. Also, osteogenic differentiation was suppressed, characterized by less osteocalcin (OCN) and osteopontin (OPN) expression, weaker ALP activity, and mineralization ability.[82] Interestingly, bigger (196 nm) NPs demonstrated stronger adverse effects than smaller (14 nm and 108 nm) ones, possibly due to higher accumulation of bigger NPs

within MSCs. Similarly, Hackenberg et al also reported a significant reduction in migration of TiO_2 NP-treated human MSCs after 3 weeks without affecting their multi-differentiation capacity.[34]

Co/Cr NPs

Humans are exposed to Co and Cr from industry and surgical devices.[14] MOM replacements were introduced as an alternative bearing surface to MOP in arthroplasty because of their excellent wear and corrosion resistance.[90] The bulk CoCrMo alloys are composed of 58.9–69.5% Co, 27.0–30% Cr, 5.0–7.0% Mo as well as a small amount of elements such as (Mn, Si, Ni, Fe, and C) to improve physical properties.[91] In synovia, they spontaneously form a passive oxide layer which enhances the chemical and mechanical stability. This stable surface layer (up to 85 nm in thickness) is primarily composed of Cr (90%) in the form of oxides, phosphates, and hydroxides as well as minimal Co (5%) in the form of CoO, $Co(OH)_2$, and Co phosphate. However, MOM implants are not immune to corrosion and wear. They have been reported to generate metal particles as well as ions in vivo.[91,92] Wear particles obtained from periprosthetic tissues of MOM patients were reported to be at the nanometer scale (smaller than 50 nm) with morphologies being oval, round, needle-shaped.[93–96] The majority of found wear debris were comprised of oxidized Cr (III) particles with minimal or no Co (IV), which correlate well with the surface composition of CoCr alloy. This can cause adverse reactions, such as the generation of pseudotumors, extensive necrosis, early osteolysis, and implant failure. Though metal ions released from CoCr nanoparticle surfaces can also trigger additional toxicity in cells;[97] however, this is not our focus and will not be discussed here.

Effects of Co/Cr NPs on Macrophages

Similar to histological results from Co nanoparticle-induced lung injury,[98,99] assessments of retrieved tissues from patients with failed CoCr alloy hip prostheses demonstrated necrosis, as well as macrophagic and lymphocytic infiltrates.[95–97] This suggests cytotoxicity of wear products and macrophagic recruitment in periprosthetic tissue.

Kwon reported that Co NPs (30–60 nm) and ions demonstrated dose-dependent cytotoxic effects on the RAW 264.7 murine macrophage cell line in vitro.[100] This is in accordance with the result by Liu et al.[101] Notably, Ti and Cr NPs did not result in a significant viability reduction under the same condition. Wang et al suggest that Co NP's cytotoxicity on RAW 264.7 cell could be attributed to Co ions released due to corrosion in the lysosomes. Interestingly, changing the acidic environment inside the lysosome using Bafilomycin A1 protects the viability of RAW264.7 cells and suppresses Co NP-induced aseptic inflammation by inhibiting intracellular Co NP corrosion and Co ions release.[102] The cytotoxic and inflammatory effects of Co NPs (28 nm) on macrophages were also observed by Nyga et al. This effect is dependent on hypoxia-inducible factor (HIF), a ROS-independent pathway.[103] Notably, it is Co NPs, but not Cr NPs, which inhibit macrophage migration both in vitro and in vivo by promoting adhesion at non-cytotoxic concentrations; this is associated with ROS-RhoA signaling pathway.[104]

Effects of Co/Cr NPs on Osteoblasts and MSCs

Upon Co NP exposure, viability of the cell line MG-63 was reduced in a dose- and time-dependent manner. Also, retraction of cellular pseudopods, pyknosis of the cytoplasm, and cell death was observed. Further, Co NPs inhibited osteoblastic function and differentiation by affecting mRNA and protein expression levels of genes such as *ALP, BGLAP, Col I, OGP,* and *RANKL*.[105] This suggests that Co NPs do not only suppress the osteoblastic growth and differentiation, but also indirectly upregulate osteoclastic function. Similar results have been observed on Saos-2 cells.[106] They showed a reduction in viability after Co NP exposure at 24 hours while Ti NPs had no effect. This indicated that Co NPs were more cytotoxic than Ti NPs.[66] Moreover, decreased mineralization ability, elasticity, spring constant, and increased apoptosis seemed more pronounced by Co NPs than Ti NPs. Similar results have been observed using murine MC3T3-E1 osteoblasts: both Co elemental (30 nm) and Co (II, III) oxide (50 nm) NPs caused a decline in metabolic activity and osteoblast mineralization ability after a 21-day challenge.[67] Same-sized Co NPs had a greater impact than the other NPs. Thus, Co NPs seem to be more detrimental to OB than other NPs.

Preedy et al exposed MSCs to Co NPs and found a lower value of elasticity and spring constant without significant effect on cell metabolic activity and viability. Notably, Co induced greater effects than Ti NPs.[38] Further, independent of impaired proliferation, osteogenic differentiation was strongly impaired by in vivo exposure to MoM-wear NPs, whereas chondrogenesis, adipogenesis, and migration were unaffected.[96]

Ta implants are receiving increasing interest as load-bearing orthopedic biomaterial because of their excellent biocompatibility, superior strength, as well as corrosion resistance properties. In the orthopedic field, this transition metal was primarily applied as void filling implant material for

components in revision hip and knee arthroplasty.[41,42] Porous Ta has been manufactured by coating Ta NPs onto scaffolds. This special component facilitates a high degree of porosity with fully interconnecting pores which results in mechanical properties close to those of human bone and allows for bone ingrowth.[107–110]

During loading wear, nanoscale Ta particles are inevitably released from implant surface. In total hip/knee arthroplasty implant failure cases, analysis revealed the release of Ta-containing particles.[111] Recently, exposure of Ta-containing NPs (median diameter = 14.2 nm) has been identified after implantation failure of Ta hip components in vivo.[112] However, the size, morphology, and composition of Ta particles still warrant further studies, so do their systemic effects and long-term consequences.

Effects of Ta NPs on Peri-Implant Cells

Previous studies focusing on Ta NPs have reported multiple promising functional changes such as enhanced OB adhesion, proliferation,[109,113] MSC differentiation[114,115] as well as inhibited osteoclast differentiation[116] on tantalum substrates. However, the interaction of nanoscale Ta particles with peri-implant cells was seldom investigated. Thus, more studies are needed to fully elucidate these aspects.

To date, only two papers concerning Ta NPs and osteoblasts were published. Ta NPs induced autophagy in MC3T3-E1 cells and promoted cell viability at a low concentration.[117,118] This was indicated by upregulated LC3-II protein expression, autophagic vesicle ultrastructure, and downregulated p62 expression, suggesting an active cytoprotective role through degradation of hazardous substances. The effect was further confirmed using the autophagy inducer rapamycin and the autophagy inhibitor 3-methyladenine (3-MA). However, reduced viability was observed at concentrations ≥25 μg/mL as autophagosome degradation was inhibited and autophagic flux was impaired, as the degradation of p62 was not continuously increased.[118] These results suggest that Ta NPs can promote autophagy activation which could be a potential key factor in osteoblastic reaction to Ta NPs. Such a dose-dependent switch from pro-survival to cytotoxic response has been documented for rare earth oxide NPs.[119,120] The dual role could be attributed to the fact that autophagy plays protective roles within its threshold range, which may be attributed to their role in anti-oxidative stress,[121] clearance of material, and damaged cellular organelles. However, when particle concentration continues to increase, the protective effect may reach its limit, and therefore cell death is inevitable.[122,123]

Ceramic Orthopedic Implant NPs

Ceramic implant materials were firstly introduced in total hip arthroplasty in 1972.[124] Over the past 10 years, they have drawn increasing attention in both orthopedic and dental fields because of their excellent tribology and biocompatibility when applied as articulating surfaces in hip and teeth.[125,126] Current ceramics for orthopedic joint replacement are alumina (Al_2O_3) and zirconia (ZrO_2).[127] Al_2O_3 is the primary or continuous phase (70–95%) and ZrO_2 (known as ZTA) is the secondary phase (5% to 30%) used to toughen the Al_2O_3.[127]

Because of their excellent characteristics of the tribology, ceramic prosthetic implants offer the lowest wear rates among all bearings for THA and are understandably gaining usage in young and active patients.[128] Recent systematic reviews also confirmed the safety use of ceramic bearings in TKA.[129] However, though nanoscale ceramic materials had been identified in failed ceramic joint arthroplasty and were reported to be bioactive, their effects on aseptic loosening remain unclear.

ZrO_2 NPs

Zirconium alloy components with thermally oxidized ceramic ZrO_2 bearing surface (approximately 5 μm in thickness) have been applied as both femoral and knee components.[129,130] They have been reported to be with comparable clinical outcomes, rare implant fractures, and lower wear compared with conventional Co-Cr TJA components.[130,131] However, Zirconium alloy could still undergo rapid accelerated wear if suffering from improper acetabular cup and liner seating or dislocation.[132] Moreover, ZrO_2 NPs are used as bone cement additives (radiopacifier), and nanostructured ZrO_2 are used as surface coating material of orthopedic implants.[133,134] Thus, nano-scaled ZrO_2 particles could be released during in vivo abrasion.

Until now, there have been just a few retrieval studies identifying the characteristics of released ZrO_2 NPs after aseptic loosening of joint arthroplasty implants (plain PMMA cement with ZrO_2 radiopacifier).[135] Also, the foreign body reactions to nanosized ZrO_2 particles have not been fully investigated.

Effects of Zirconia NPs on Macrophages and Osteoclasts

Silge et al reported that ZrO_2 NPs could be internalized by RAW 264.7 cells in vitro.[136] Further, Vennemann et al reported that engulfed ZrO_2 NPs (9–10 nm) can elicit inflammatory and toxic effects on mouse alveolar

macrophages in vitro, but not in vivo.[137] Moreover, after wear particle phagocytosis, macrophages also release pro-inflammatory cytokines (eg, TNFα, IL-1).

Micrometer-sized ZrO_2 particles (1.75 ± 4.66 μm) have been reported to have a direct stimulatory effect on mature human osteoclast function in vitro and thus promote OC-mediated bone resorption.[138] However, little is known about nano-sized wear particles on OCs. Thus, more studies are needed to fully elucidate this aspect.

Effects of Zirconia NPs on Osteoblasts and MSCs

ZrO_2 NPs revealed a significant dose-dependent (from 15 ppm to 150 ppm) decrease in viability of MG-63 cells and L929 cells at 24 hours, while Al_2O_3 NPs had no detectable adverse effect. They also elevated TNFα production of RAW 264.7 cells at 24 hours. Al_2O_3, ZrO_2 and silicon nitride (Si_3N_4) NPs significantly promoted ALP activity in MG-63 cells. Interestingly, Al_2O_3 NPs promoted ALP activity at low concentrations without irritating macrophages in vitro.[139]

ZrO_2 NPs (31.9 ± 1.9 nm) induced MC3T3-E1 cell shrinkage in vitro, with pyknosis-like nuclei, condensed unclear actin filaments as well as more potent cytoskeleton disruption than TiO_2 NPs. At concentrations of 100 μg/mL, ZrO_2 NPs could induce ROS-dependent cytotoxic effects in time- and concentration-dependent manners and showed inhibitory effects on osteogenic differentiation and mineralization of MC3T3-E1 cells in vitro. Further in this study, ZrO_2 NPs induced more potent toxic and oxidative stress effects than TiO_2 NPs (25.4 ± 2.8 nm).[140] These results indicated that both ZrO_2 and TiO_2 NPs are unable to maintain their biocompatibility at higher does. In contrast to this, a different study did not observe reduced viability in osteoblasts and MG-63 after ZrO_2 NPs challenge.[141] This discrepancy may be attributed to the diversity of cell culture protocols, procedures, reagents, and biomaterials used and argues for more standardized studies to compare results on the cell biological effects of NPs.

After exposure to different synthesized yttria-stabilized ZrO_2 NPs (approximately 7 nm in size), rat BMSCs exhibited normal morphology spreading patterns but lower adhesion density in comparison to the control.[142] Also, both ZrO_2 and pure-Ti NPs dose- and time-dependently compromised human BMSC viability through apoptosis induction. Notably, ZrO_2 elicited less cytotoxicity than Ti particles.[143]

Al_2O_3 NPs

Al_2O_3 NPs are important ceramic materials that have been used in a variety of commercial and industrial applications. Based on their applications, the most likely scenario for their exposure is inhalation during bulk manufacturing and handling of freely dispersible NPs at the workplace. With the wide application of ceramic orthopedic implants, ceramic prostheses also have been the internal source of Al_2O_3 NPs. Due to the limitation of the light microscope, previous histological studies of retrieval tissues from uncemented ceramic-on-ceramic prostheses only alumina particles with micrometer-sized particles were described.[144,145] In 2002, Hatton et al firstly identified nanometer-sized Al_2O_3 wear debris in the size range of 5–90 nm (24±19 nm) by transmission electron microscopy (TEM).[146] Yet, very few studies have evaluated the risk associated with these nanomaterials.

Effects of Al_2O_3 NPs on Macrophages

Kim studied the inhalation toxicity of Al_2O_3 NPs in rats with a nose-only inhalation system. Histopathology showed marked alveolar macrophage accumulation in the lungs and revealed that the lung was the primary target organ. Also, significantly increased inflammation was evidenced by elevated TNFα and IL-6 level in bronchoalveolar lavage fluid.[147] In accordance with this in vivo study, Al_2O_3 NPs have been shown to induce acute inflammation in macrophages in vitro. Hashimoto et al exposed RAW 264 macrophages and L929 fibroblasts to Al_2O_3 NPs (13 nm diameter) as well as Al_2O_3 nanowires (2–6×200-400 nm). The Al_2O_3 NPs showed more significant cytotoxicity as well as cell structural and nuclear damage compared to nanowires.[148] Compared to other conditions, only Al_2O_3 (20 nm) NPs at high concentration (1000 μg/mL) could induce a prominent acute ROS release in RAW 264.7 macrophages,[149] suggesting that Al_2O_3 NPs are relatively biocompatible. These results support the inert biological behavior of ceramic biomaterials.

Being used along with vaccines as immune system adjuvants and are known to activate the NLRP3 inflammasome, Al_2O_3 NPs and aluminum-coated nanomaterial treatment upregulated the pro-inflammatory cytokine expression in macrophages.[150,151] In contrast, there were also other studies reporting Al_2O_3 NPs impairing macrophages' natural ability to respond to bacteria and antigen-mediated inflammation. More specifically, even at non-toxic concentrations, both Al_2O_3 NPs and Al NPs could impair the phagocytosis of community-associated methicillin-resistant Staphylococcus aureus (ca-MRSA). They also repressed the secretion of cytokines such as IL-1, IL-6, and TNFα under ca-MRSA stimulation via suppressing the NF-κB pathway.[152] These results suggest that Al_2O_3 NPs change macrophages' natural ability to respond to pathogens.

Effects of Al_2O_3 NPs on Osteoblasts and MSCs

Recent studies showed that Al_2O_3 (50 nm) and TiO_2 (anatase, 15 nm) can be internalized and cause cytotoxicity in rat osteoblast-like UMR 106 cells.[153] In another study conducted by Zhang et al, Al_2O_3 NPs (40–50 nm) induced no detectable adverse effect on MG-63 cells in MTT and total intracellular protein (TCP) assays. Interestingly, Al_2O_3 NPs increased ALP activity at low doses (15 ppm) and decreased it at high doses (500 ppm). This is different from ZrO_2 NPs, which decreased ALP activity at 15 ppm while dramatically increasing it at 500 ppm.[139] Further, Al_2O_3 NPs (<1 μm) dose-dependently increased ALP activity while 1–10 μm particles did not such property. This suggests that both the sizes and composition of the Al_2O_3 NPs might influence their effect on osteoblast function, which is similar to the results in osteoblasts.

MSCs can also take up Al_2O_3 NPs and demonstrated intracellular morphological changes such as cytoplasmic vacuolization, nuclear and DNA fragmentation.[154] In addition, Al_2O_3 NPs could reduce the viability of human MSCs in a dose- and time-dependent manner by arresting cell cycle progression. More specifically, the cell cycle was arrested in the sub-G0/G1 phase, accompanied by a reduced percentage of cells in the G0/G1 phase and G2/M phase.

Interestingly, nanosized Al_2O_3 particles (<50 nm) have been reported to promote fibroblastic autophagy, which negatively regulated RANKL expression and osteolysis, both in vitro and in vivo.[155] Further, Al_2O_3 NPs (<50 nm) could evoke autophagy and even counter Ti particle-induced apoptosis, NF-κB activation, and inflammatory reactions both in MG-63 cells and a mouse calvarial osteolysis model.[156] This suggests that Al_2O_3 NPs play a protective role in Ti particle-induced osteolysis through preventing autophagy, reducing apoptosis, and inflammation. Thus, though ceramic material seems to be biocompatible and has advantageous properties, ceramic NPs' adverse biological effects should not be neglected. Future studies should focus on elucidating the underlying molecular pathogenesis of ceramic NPs on peri-implant cells.

Limitations and Future Perspective

This review updates the characteristics of metallic and ceramic NPs generated after prosthesis implantation and summarizes their biological impact on peri-prosthetic cell lineages. Future studies analyzing other types of nano-scale wear debris, such as polyethylene, PMMA, are necessary, in order to understand the problem of implant loosening as a whole. Also, different implant biomaterials generate wear particles of different types, sizes, shapes, and their impact on peri-implant cells is dependent on the material type. Thus, elucidation of the reasons for these differences would be a starting point for planning material-specific targeting of peri-prosthetic osteolysis.

Second, retrieved particles from loosened implants and primary cells or animal models should be advocated in future studies as they are more relevant to the in vivo conditions found in patients. Nevertheless, because of technical reasons, there are still difficulties associated with the precise and truly qualitative analysis of nanosized particles from clinical samples.[157] Scanning electron microscopy has revealed that particulate materials generated from implant wear vary more greatly in shape than commercially produced particles and are more detrimental or inflammatory to peri-implant tissues. This suggests that the number and biological severity of actually produced NPs may have been underestimated. Thus, current protocols and instruments for effectively isolating and characterizing NPs from clinical samples should be updated in order to accurately define its clinical pathological effects in the future.

Third, with prosthetic biomaterial manufacturing techniques developing, coating novel orthopedic implants with wear-resistant material (such as TiN_3) or including slow-releasing drugs within the prostheses may offer a promising option to mitigate peri-prosthetic osteolysis and extend implant's life span. Moreover, as several pathways or molecular mechanisms (eg, ROS-dependent pathway, SIRT1-NF-κB, autophagy) have been identified during the pathology of wear debris-associated osteolysis (Table 1), further studies are required for developing drugs targeting these pathways and mechanisms to curtail aseptic loosening. However, although some drugs targeting specific cells have demonstrated efficacy in vitro and even in animal models, their translational potential remains to be established. More specifically, many of them are not specific to one cell lineage and may thus cause diverse and systematic adverse effects. Given the fact that multiple peri-implant cells contribute to the development of aseptic loosening, pharmacological blockade of one signaling pathway in one cell type alone is unlikely to successfully alleviate the overall effects of wear particles. Thus, a combination of pharmacologically targeting multiple peri-implant cells as well as their related pathological pathways may be a feasible strategy to curtail wear particle-induced peri-prosthetic osteolysis in the future. However, improvements in the specificity, safety, and manipulability

Table 1 Summary of Pathways of Wear Particle-Associated Osteolysis

NP type	Particle size	Cells/Models	Pathways	Action	Effect	References
Ti alloy	< 100 nm	Primary rabbit BMSCs	Bax/Caspase-3	Activator	MSC apoptosis↑	37
Ti	52.59 ± 20.48 nm	RAW264.7 and mouse air pouch model	MAPK (ERK/P38)	Activator	M1 polarization↑, inflammation↑, indirectly inhibit osteogenic differentiation of rat BMSCs	58
TiAl6V4, CoCrMo	< 180 nm	RAW264.7 and mouse PIO model	SIRT1-NF-κB	Activator	Macrophage inflammatory reaction *in vitro*↑ Inflammatory reaction and osteolysis in PIO animal models↑	59
TiO_2	5 nm and 40 nm	SaOS-2	FAK signaling	Activator	Adhesion↓	84
TiO_2	10 nm	RAW264.7, mouse BMDM	Cox-2	Activator	Inflammatory response↑	75
TiO_2	20 nm	RAW264.7	TLRs-p38MAPK and SAPK/JNK	Activator	Apoptosis↑, inflammatory response↑	78
TiO_2	NA	THP-1-derived macrophages and BMDMs	PLC-β/InsP3-NLRP3 inflammasome	Activator	Inflammatory response↑	79
TiO_2	NA	THP-1-derived macrophages and BMDMs	ADCY-cAMP-NLRP3 inflammasome	Inhibitor	Inflammatory response↑	79
TiO_2	10 nm, 30-40 nm	THP-1-derived macrophages	ROS/Cathepsin B-NLRP3 inflammasome	Activator	Inflammatory response↑	80
Co	28 nm	U937, human macrophages	HIF pathway	Activator	Cytotoxicity↑	103
Co	2-60 nm	Human macrophages and mouse intraperitoneal model	ROS-RhoA	Inhibitor	Macrophage motility↓	104
Ta	41.89 ± 19.58 nm	MC3T3-E1	Autophagy	Activator/Inhibitor	Increase osteoblastic viability during proliferation at low concentration, while inhibit at high concentration	117, 118
ZrO_2	31.9 ± 1.9 nm	MC3T3-E1	ROS	Activator	Cytotoxicity↑	140
TiO_2	25.4 ± 2.8 nm	MC3T3-E1	ROS	Activator	Cytotoxicity↑	140
Al_2O_3	< 50 nm	MG63 and mouse PIO model	Autophagy, NF-κB, Caspase-3	Inhibitor	Apoptosis↓, inflammation↓, osteogenic activity↑, OPG↑, osteolysis in PIO model↓	156

Abbreviations: ADCY, adenylate cyclase; Al_2O_3, aluminum oxide; BMDM, bone marrow-derived macrophages; BMSCs, bone marrow mesenchymal stem cells; Co, cobalt; FAK, focal adhesion kinase; HIF, hypoxia-inducible factor; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; NLRP3, NOD-like receptor pyrin domain-containing-3; OPG, osteoprotegerin; PIO, particle-induced osteolysis; RhoA, ras homolog gene family, member A; ROS, reactive oxygen species; SIRT, sirtuin; Ta, tantalum; Ti, titanium; TLRs, toll-like receptors; TiO_2, titanium dioxide; ZrO_2, zirconium oxide; ↑, upregulated; ↓, downregulated.

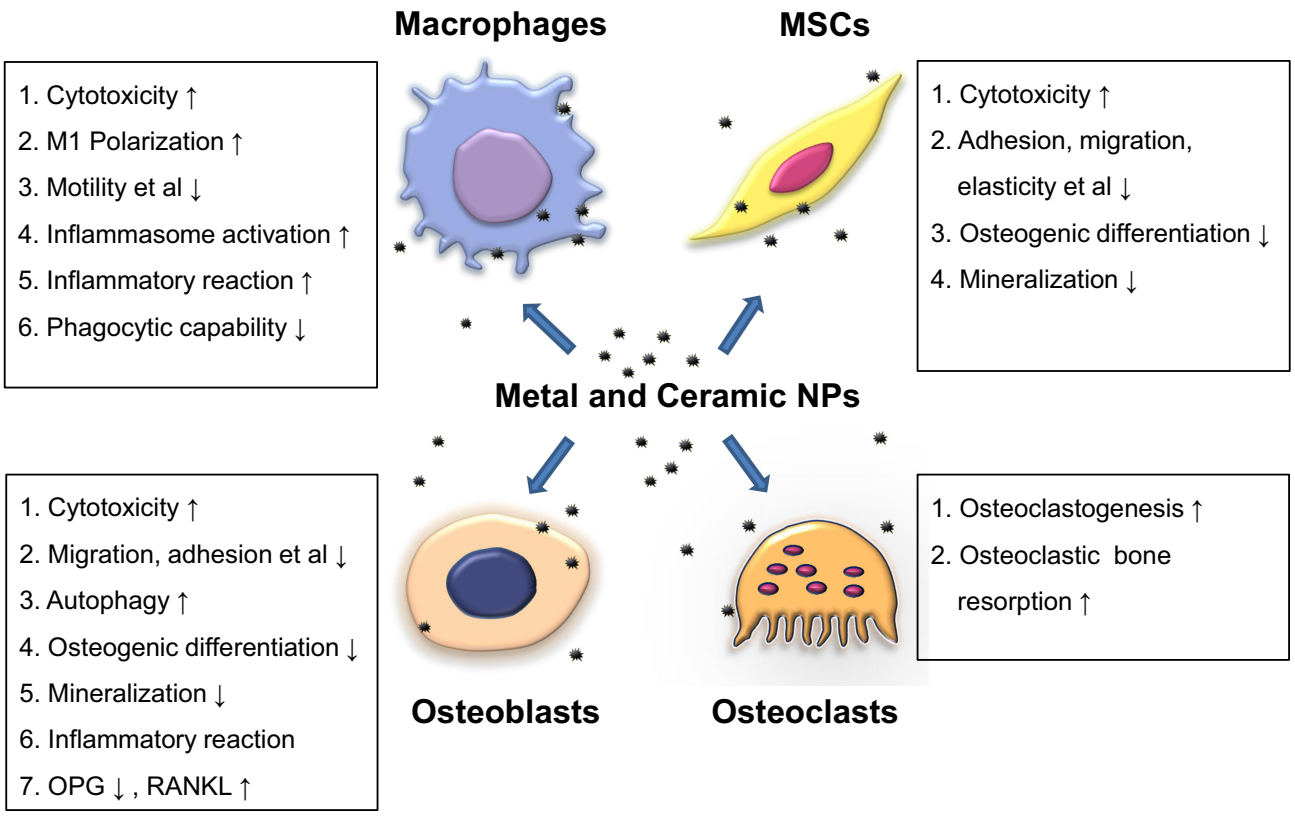

Figure 1 Wear particles pose adverse effects on general cellular functions of peri-implant cells such as viability, adhesion and migration. They also upregulate pro-inflammatory mediators in macrophages and osteoblasts, which contribute to a chronic inflammatory peri-implant environment and osteoclastogenesis. Moreover, they impair osteogenic differentiation and matrix mineralization of osteoblasts and mesenchymal stem cells. These effects not only impede new bone formation but also favor osteoclastic bone resorption. ↑ indicates upregulation, ↓ indicates downregulation.
Abbreviations: MSCs, mesenchymal stem cells; NPs, nanoparticles; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor (NF)-κB ligand.

of these drugs are needed before they can be considered for clinical application.

Conclusion

Wear particles can target peri-prosthetic cells by disrupting multiple cellular functions (eg, cell survival, osteogenic differentiation, mineralization), inducing an inflammatory environment, and activating/inhibiting different pathways. These reactions alter the balance between osteoblastic bone formation and osteoclastic bone resorption, thereby promoting periprosthetic osteolysis and ultimately leading to implant loosening (Figure 1). Future studies are needed to further explore the effect of different nano-sized wear particles on peri-implant cells and their underlying molecular pathogenesis for the development of effective pharmacological interventions.

Abbreviations

Al_2O_3, alumina; ALP, alkaline phosphatase; BMDMs, bone marrow-derived macrophages; BMP-2, bone morphogenetic protein 2; ca-MRSA, community-associated methicillin-resistant Staphylococcus aureus; Co, cobalt; Cr, chromium; HIF, hypoxia-inducible factor; LMP, lysosomal membrane permeabilization; M-CSF, macrophage-colony stimulating factor; MOM, metal-on-metal; MOP, metal-on-polyethylene; MSCs, mesenchymal stem cells; NFATc1, nuclear factor of activated T-cells cytoplasmic 1; NPs, nanoparticles; OCN, osteocalcin; OPG, osteoprotegerin; OPN, osteopontin; OsteoMacs, osteal tissue macrophage; PIO, particle-induced osteolysis; RANKL, receptor activator of nuclear factor (NF)-κB ligand; Si_3N_4: silicon nitride; THA, total hip arthroplasty; TJA, total joint arthroplasty; Ta, tantalum; TEM, transmission electron microscopy; Ti, titanium; TiO_2, titanium dioxide; VEGF, vascular endothelial growth factor; ZrO_2, zirconia; 3-MA, 3-methyladenine.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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