Proceedings of Anticancer Research, 2026, Volume 10, Issue 2
http://ojs.bbwpublisher.com/index.php/PAR
ISSN Online: 2208-3553
ISSN Print: 2208-3545

Does Pyroptosis, Apoptosis, and Necroptosis (PANoptosis) Exist in Particle-induced Periprosthetic Osteolysis? Evidence from Cell, Rodent and Patient Studies

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Abstract: *Background*: Periprosthetic osteolysis (PPO) is the main cause of aseptic loosening after total joint replacement, which is caused by chronic inflammation induced by wear particles. Apoptosis, pyroptosis, and necroptosis have been studied respectively, but the mechanism of PANoptosis (synergistic inflammatory cell death) integrated by them has not been studied in PPO. *Methods*: A total of 43 studies that met strict cell death criteria were screened through systematic reviews (PubMed/Web of Sci, 2020–2025). RAW264.7 macrophages were placed under endotoxin-free TC4 titanium particles (100/400 μg/mL, for 24 hours). A rat femoral implant model was established, and Ti particles were injected locally (with a concentration of 5 mg/mL and a volume of 100 μL; there were 8 rats in each group). Analyze the periprosthetic interface membrane tissues of 12 patients with aseptic loosening revision surgery and the control synovial tissues of 8 patients with primary total hip replacement surgery. Detect PANoptosis markers using Western blot and immunohistochemistry (IHC). *Results*: Through systematic analysis, it can be seen that in all cell types and models, there is consistency in the co-activation of pyroptosis (involving GSDMD, CASP1), apoptosis (involving CASP3, CASP8) and necroptosis (involving p-MLKL, p-RIPK1). *In vitro* experiments, Ti particles upregulated the three pathway effector molecules in a dose-dependent manner. Exposure to intra-body particles can cause significant periprosthetic bone loss and is accompanied by the expression of PANoptosis markers. In the human interface membrane of failed implants, the level of its effector molecules is higher than that of the control group. *Conclusion*: This study provides integrated evidence that PANoptosis is activated in wear particle–induced PPO in both experimental and clinical settings. Targeting PANoptosis may become a new method to inhibit inflammation-induced osteolysis and improve the long-term survival rate of implants.

Keywords: Periprosthetic osteolysis; PANoptosis; Wear particles; Macrophage cell death; Osteoblast dysfunction; Aseptic loosening; Inflammatory bone loss; Orthopedic implant failure

Online publication: April 14, 2026

1. Introduction

The total joint arthroplasty (TJA) continues to be the most commonly used treatment for patients suffering from osteoarthritis, osteonecrosis of the femoral head, and advanced rheumatoid arthritis [1]. The largest challenge to the long-term success of TJA arises from nanoscale wear debris generated via the interaction of prosthetic bearing surfaces during normal activity [2,3]. Research supports the notion that these same particles are responsible for stimulating periprosthetic osteolysis, damaging the interface between the prosthesis and bone, leading to loss of the attachment of the two, requiring complicated revisions and far-reaching clinical and economic consequences [4]. Although there is a need for therapeutic approaches to avert or postpone the development of periprosthetic osteolysis, continued in-depth studies are needed to fully understand the precise cellular and molecular mechanisms of this process [5].

Apoptosis, necroptosis and pyroptosis, collectively referred to as regulated cell death (RCD), represent three of the best-characterized RCD pathways. All three pathways have distinct molecular cascades that are involved in development, homeostasis, host defense and inflammatory diseases [6]. The initiator caspase-8/9/10 (CASP8/9/10) activates the effector caspases-3/7 (CASP3/7), resulting in the orderly disassembly of the cell [7–9]. Pyroptosis is a lytic and inflammatory event mediated by the formation of pores in the membrane, and results from the cleavage of gasdermin D (GSDMD) by inflammatory caspases (CASP1/4/5 in humans). The cleavage causes the N-terminal portion of GSDMD to oligomerize into pore-like structures on the plasma membrane, leading to cell swelling and rupture [10–12]. Necroptosis, a lytic pathway, occurs upon activation of the RIPK1-RIPK3 complex, which results in the phosphorylation, oligomerization and translocation of mixed lineage kinase domain-like protein (MLKL) to the plasma membrane. This ultimately results in a breakdown of the integrity of the plasma membrane [13,14]. Although RCD networks were thought to be distinct and linear, research has shown that there are many interactions between RCD networks and that they have many common regulatory factors [15].

This molecular interaction has occurred in many settings, including sterile inflammatory responses and infections [15], and is responsible for the multifactorial activation of several essential features of a wide range of regulated cell death (RCD) pathways. From these observations, we can articulate the new idea of PANoptosis [16], defined as a unique mode of RCD driven by inflammatory stimuli through the formation of the PANoptosome, a multi-component protein assembly [17]. The PANoptosome serves as a central hub for all of the key molecular elements associated with pyroptosis, apoptosis, and necroptosis. However, while the PANoptosome facilitates the coordination of these pathways, it possesses attributes that deviate from merely being an aggregation of the elements of its associated pathways [18]. Further evidence indicates that PANoptosis plays a critical role in additional infectious processes and malignancies, and that its impact on sterile disease-derived inflammatory illnesses has now become clear [19,20]. Evidence does exist to show that PANoptosis rapidly accelerates and enhances pro-inflammatory processes and is implicated in individuals with cytokine storm syndromes [20]. Due to its role as a significant source of pro-inflammatory signals. PANoptosis has also been implicated in synovial inflammation, including cases of rheumatoid arthritis, and represents a link between inflammatory diseases of the joints and PANoptosis [21].

PPO is characterized by an inflammatory environment with activated macrophages and the release of IL-1β, IL-6, TNF-α, and other pro-inflammatory cytokines [22–27]. Yet, we don't know how RCD activities interact and what pathways are activated under these conditions. Because wear particles may activate ALL of the pathways for pyroptosis, apoptosis, and necroptosis via a single signal, we hypothesized that there was not simply a single or dual activation of these RCD pathways, but rather a PANoptotic process where ALL these pathways are simultaneously activated. To confirm our hypothesis, we established a protocol using bioinformatic analyses to identify which RCD pathways have been activated in PPO. Next, we validated this protocol through in vitro, in

vivo, and analyses of human tissues to determine whether PANoptosis occurs in particle-induced osteolysis. Our first step in determining if PANoptosis occurs in particle-induced osteolysis has now been done, expanding the understanding of the pathophysiological effects of this process on both the failure of orthopedic implants and their long-term viability. Our work provides the structure necessary for simultaneous analyses of the 'crosstalk' between RCD pathways, allowing us to understand their roles as a unit and giving direction to future research into finding prognostic biomarkers and target therapies to prevent osteolysis and improve long-term stability of implants.

2. Method

2.1. Data source

PubMed and the Web of Science databases were systematically searched using criteria developed by combining the two main components of our research: The PANoptosis family (pyroptosis, apoptosis, and necrosis) and how either periprosthetic osteolysis or wear particle-derived conditions have been associated with PANoptosis. Both mechanisms for identifying publication dates were done between 2020 and 2025, with the final searches performed on June 1, 2025. Each database's search queries were devised to have appropriate terminology, along with specific database-based search operators. The initial search was conducted to identify those databases that contained duplicate articles. Subsequently, the remaining articles were screened based on the criteria established for the screening of records containing information on all three methods of cell death. The workflow for this screening process is illustrated in **Figure 1**.

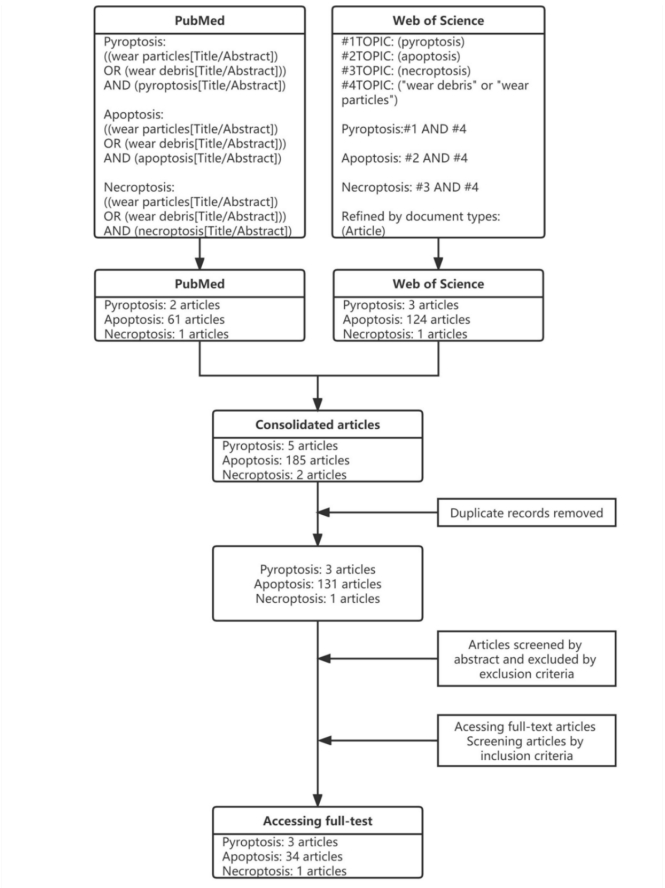

Figure 1. Flow chart of literature screening.

3. Inclusion/exclusion criteria

To meet the inclusion criteria, the studies needed to include the following: (1) Studies whose primary focus was either the pathophysiology of osteolysis induced by wear particles or studies of animal/cellular models that had been validated as capable of inducing bone resorption by particulate means; (2) Studies conducted using rodents (including primary or established cell lines) as experimental material; (3) Tissue and/or cell-type-specific analysis based upon established painstaking osteoblasts or macrophages; (4) Experimental testing provided that at least 2 independent techniques were employed to demonstrate the occurrence of pyroptosis, apoptosis or necroptosis, with one assay having focused on a specific protein that is involved in all 3 forms of cell death and (5) Experiments Designs with a random comparative focus between experimental groups and untreated control groups.

The exclusion criteria were: (1) Non-osteogenic/bone-related cellular models other than macrophages, osteoblasts, or osteoclasts; (2) Particulate exposure protocols with undefined dosage or exposure duration; (3) Studies with insufficient molecular evidence for verifying the cell death modality using established biomarkers.

4. Data mining and sorting analysis

The study obtained information regarding cell types, animal species, modeling techniques, cell death measures and associated assay outcomes for representative proteins for each cell death classification from the literature provided to us as citations derived from our database search. Citations generated by the citation databases were then transferred into a citation management system for ease of reference. Two medical/biological oncologists independently reviewed all of the articles resulting from our search, conducted data collection/extraction of applicable articles and gathered relevant data from those sources and produced a table of the results achieved by both oncologists for all data collected by them individually. In cases of discrepancy, a third investigator participated in the discussion to reach a final decision on inclusion.

For in vitro experiments, cluster analysis was performed based on cell type, including only those cell types used to study pyroptosis, apoptosis, and necroptosis. For in vivo animal experiments, cluster analysis was based on the classification of common rodents, ensuring that animals treated with wear particles were of the same category. In summary, the core data were organized and analyzed using Microsoft Excel (version 2024) and EndNote X9.

5. Experimental methods

5.1. Preparation of TC4 alloy particles and implants

The TC4 alloy particles (TiPs) had a mean diameter of 60 nm as measured by scanning electron microscopy. After sterilization (180℃ autoclave, 3 h), the endotoxin levels were verified via limulus amebocyte lysate assay (< 0.01 EU/mL), confirming that the TiPs were endotoxin-free. A 5 mg/mL TiPs stock suspension was prepared by ultrasonic homogenization in phosphate-buffered saline. Surgical-grade TC4 alloy implants (10.0 mm length, 1.5 mm shaft diameter) were sterilized by ultraviolet irradiation prior to *in vivo* application.

5.2. Cell culture

An immortalized rat bone marrow mesenchymal stem cell (BMSC) line and RAW264.7 macrophages (Bio-Channel, Nanjing, China) were cultured. Both cell types were grown in complete Dulbecco's Modified Eagle

Medium (DMEM), containing 10% fetal bovine serum (FBS), 100 U/mL penicillin, 100 μg/mL streptomycin, 2 mM L-glutamine, and 1 mM sodium pyruvate, and kept at 37°C with 5% CO_2. Specific to BMSCs, osteogenic differentiation was initiated during the late-log phase by adding 10 mM β-glycerophosphate and 50 μg/mL ascorbic acid to the culture medium.

5.3. Implantation model

Male Sprague-Dawley rats (12 weeks old, 220–250 g; Guangzhou Ruige Biotech, China) were acclimatized under controlled conditions (25°C, 12 h light/dark cycle) with *ad libitum* access to food and water. Following a 12 h preoperative fast, the rats were positioned supine on an operating table, and local anesthesia was induced using a combination of isoflurane gas and lidocaine. The surgical procedure involved: (1) preparation of the right hindlimb (supine positioning, hair removal, and disinfection with iodophor); (2) a medial parapatellar arthrotomy to expose the femoral intercondylar fossa; (3) debridement of the articular cartilage using a #11 scalpel blade; (4) preparation of the medullary cavity by drilling with a 0.7 mm bit to a depth of 5 mm; and (5) implantation of a sterile titanium rod (10.0 mm length × 1.5 mm diameter). Concurrently, the experimental group received an injection of 100 μL TC4 particle suspension (5 mg/mL) into the surgical site, while the control group underwent a sham procedure (injection of vehicle alone). Post-implantation, the wound was irrigated with phosphate-buffered saline (PBS) containing 100 U/mL penicillin and 100 μg/mL streptomycin, followed by layered closure. Animals were housed individually postoperatively under standard conditions (18–22°C, standard diet). Terminal tissue sampling was performed at the 2-week endpoint.

5.4. Collection of patient samples and clinical information

This study was designed with two patient cohorts. Interface membranes were obtained from patients undergoing revision total hip arthroplasty (THA) for aseptic loosening (with periprosthetic joint infection excluded). For comparison, synovial tissues were collected from patients receiving primary THA due to femoral neck fractures. All specimens were sourced from the Department of Orthopedics, Nanfang Hospital, Southern Medical University, between 2016 and 2019. The study protocol was approved by the hospital's Ethics Committee (Approval No.: Nanfang Hospital Ethics Committee-2019-087).

5.5. Western blotting

Interface membranes were harvested from patients undergoing revision total hip arthroplasty (THA) for aseptic prosthetic loosening (cases with periprosthetic joint infection were excluded). For comparison, synovial tissues were obtained from patients with femoral neck fractures undergoing primary THA. All specimens were collected at the Department of Orthopedics, Nanfang Hospital, Southern Medical University, between 2016 and 2019. This study protocol was approved by the Ethics Committee of Nanfang Hospital (Approval No. NFH-EC-2019-087).

5.6. Immunohistochemistry

Tibial specimens were processed through fixation in 4% paraformaldehyde (Servicebio, China) for 24 hours, followed by decalcification in a 10% ethylenediaminetetraacetic acid (EDTA, Servicebio) solution for 3 weeks. Following standard dehydration (graded ethanol series) and paraffin embedding, the tissue was sectioned at 4 μm. The cutting direction was set perpendicular to the long axis of the implant. To retrieve antigens, sections underwent

a two-step procedure: treatment with 3% hydrogen peroxide for 10 minutes, followed by autoclave-mediated heat-induced epitope retrieval in sodium citrate buffer (pH 6.0) at 121°C for 15 minutes. We used immunostaining techniques to identify the expression of proteins associated with the processes of PANoptosis and osteogenic differentiation. We then conducted a quantitative analysis by examining 5 randomly selected microscopic fields for each of the samples.

6. Result

6.1. Literature data

6.1.1. Summary and analysis of literature data

A total of forty-three studies looking at the three cell death types of apoptosis, pyroptosis, and necroptosis were used in this systematic review. The studies include four mouse in vitro models, twenty-four cell studies, fifteen combined mouse in vitro and in vivo experiments, and three clinical studies. The forty-three studies evaluated the three different types of cell death using thirty-six of the cell experiments. To validate wear particle-induced cell death, studies had to meet two criteria: (1) functional assessment of cell viability using assays such as terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL), propidium iodide (PI) staining, flow cytometry (FC), Cell Counting Kit-8 (CCK-8), MTT, or lactate dehydrogenase (LDH) release; and (2) molecular confirmation of at least one canonical pathway-specific biomarker (Table 1). Both required demonstrating statistic ally significant differences versus controls, as explicitly documented in the original studies [28–33].

In the 36 cell-based experiments, cobalt-chromium (CoCr), titanium (Ti), and ultra-high molecular weight polyethylene (UHMWPE) particles were the most commonly used stimuli. The primary cell types used were macrophages, osteoblasts, and osteoclasts. The results are summarized according to cell type in Tables 2, 3 and 4. Of these experiments, 15 were conducted on macrophages, 17 on osteoblasts, and 5 on osteoclasts. Most studies detected one of the PANoptosis-related cell death modes. Specifically, pyroptosis and apoptosis have been studied in macrophages; all three death modalities have been explored in osteoblasts; and osteoclast differentiation is often promoted by macrophages following apoptosis or pyroptosis, contributing to osteolysis.

Among the included animal studies, most utilized the mouse calvarial or tibial osteolysis model to simulate aseptic loosening. The predominant mouse strains were C57BL/6 and BALB/c. Animal model tabulates results in Table 5.

Regarding clinical samples, three of the included studies involved human tissues, all of which used the periprosthetic interface membrane. These results are summarized in Table 6.

Table 1. The key proteins of three forms of cell death in PANoptosis

Cell death type	Key proteins
Pyroptosis	NLRP1, NLRP3, ASC, CASP-1, 4, 5, 11, C-CASP-1, GSDMD, IL-1β, IL-18.
Apoptosis	CASP-3, 7,8, 9, C-CASP-3, Bcl-2, Bax
Necroptosis	RIP1, p-RIP1, RIP3, p-RIP3, MLKL, p-MLKL

Abbreviations: ASC, Apoptosis-associated speck-like protein containing a caspase recruit domain; Bax, B-cell lymphoma 2-associated X; Bcl-2, B-cell lymphoma 2; CASP, cysteinyl aspartate-specific protease; C-CASP, cleaved CASP; GSDMD, gasdermin D; IL, interleukin; MLKL, mixed lineage kinase domain-like pseudokinase; NLRP, nucleotide-binding domain and leucine-rich repeat pyrin-domain containing protein; p-MLKL, phosphorylation of MLKL; p-RIP, phosphorylation of RIP; RIP, receptor-interacting protein kinase.

Table 2. Summary of wear particles induced cell death pathways of macrophages

Wear particle types		Cell death type	Cell type	Cytokine	DOI
CoPs	CoCr	apoptosis	J7742	TNF-α , IL-1β , IL-6	10.1002/(sici)1097-4636(19981215)42,4<655,,aid-jbm23>3.0.co;2-b
	Cr2O3	apoptosis	J7742	TNF-α	10.1002/jbm.b.32991
	CoCl2, CrCl3	apoptosis	J7742	NA	10.1016/j.biomaterials.2004.08.004
	Co	apoptosis	RAW264.7	TNF-α, IL-1β, IL-6, IL-10	10.1007/s12011-015-0381-9
	CoCrMo	pyroptosis	RAW264.7	IL-1β, IL-18, RANKL, NLRP3, CASPASE-1, GSDMD	10.1016/j.cej.2022.135115
Ti	Ti	apoptosis	RAW264.7	NA	10.3892/ijmm.2018.3698
	Ti	apoptosis	RAW264.7	CASPASE-3, BAX, FAS	10.1002/jbm.a.36938
	TiAl6V4 particles	apoptosis	RAW264.7	NA	10.3892/mmr.2015.3529
	Ti	Pyroptosis	RAW264.7	Ang-1, AIM2	10.1007/s12010-024-04961-z
UHMWPE	UHMWPE	apoptosis	J7742	TNF-α	10.1016/S0736-0266(02)00099-2
	UHMWPE	apoptosis	RAW264.7	TNF-α	10.1016/j.biomaterials.2017.07.028
	Alumina particles and Polystyrene (PS) beads	apoptosis	J7742	CASPASE-3, IL-6	10.1023/A,1024723326036
	Alumina ceramic and UHMWPE	apoptosis	J7742	CASPASE-3	10.1016/S0736-0266(01)00077-8
	Alumina ceramic and UHMWPE	apoptosis	J7742	TNF-α	10.1007/s10856-006-9230-x
Other	mHAp	apoptosis	RAW264.7	NA	10.1039/c4ra02995j

Abbreviations: CoPs, Cobalt wear particles; UHWPE, ultra-high molecular weight polyethylene; TNF, tumor necrosis factor; IL, interleukin; RANKL, nuclear factor κB receptor activating factor ligand; NLRP, nucleotide-binding domain and leucine-rich repeat pyrin-domain containing protein; Capspase, cysteinyl aspartate specific proteinase; GSDMD, gasdermin D; BAX, B-cell lymphoma 2-associated X; FAS, Factor Related Apoptosis; PARP, poly ADP-ribose polymerase; IκB, inhibitor of NF-κB; IKK, inhibitor of kappa B kinase.

Table 3. Summary of wear particles induced cell death pathways of osteoblasts

Wear particle		Cell death	Cell type	Cytokine	DOI
Cops	Co	Necroptosis	C2C12	TNFα,CASP3, CASP8	10.1016/j.ta>>2013.05.005
	CoCrMo	Apoptosis	MLO-Y4	IL-6, TNFα	10.1016/j.bone.2009.05.020
	CoCrMo	Apoptosis	MC3T3-E1	LC3,ERN1, MAPKs, BAX, BCL2, CASP3	10.1080/15548627.2015.1106779
	CoCrMo TIA1674	Apoptosis	MC3T3-E1	IKBa, NFKB, SIRT1	10.1016/j.actbio.2016.11.051
Ti	TiO_2	Apoptosis	MC3T3-E1	G-CSF,M-CSF, TNFα	10.1007/s10856-011-4375-7
	Ti	Apoptosis	MC3T3-E1	TNTA,CASP3, RUNX2, ALP	10.1111/nyas.14774
	Ti	Apoptosis	MC3T3-E1	BMP2,OCN, RUNX2	10.1002/cbin.10957
	Ti	Apoptosis	MLO & MC3T3-E1	cecamexin, CASP3, Bax, Bel2, IL6, TNFα, RUNX2, OCN	10.1111/jcmm.17460
	Ti	Apoptosis	MC3T3-E1 & L929	IL-6, TNFα	10.1016/j.cdsurb.2011.09.044

Table 3 (Continued)

Wear particle		Cell death	Cell type	Cytokine	DOI
	Ti	Apoptosis	MC3T3-E1	CASP3	10.1007/s11010-014-2240-y
	Ti	Apoptosis	MC3T3-E1	RANKL, OPG, sclerostin, β-catenin	10.1042/BSR20203003
	Ti	Pyroptosis	rMSC	SIRT3, RUNX2, CASP1, GSDMD, IL1β, IL18, OCN, OSX	10.1016/j.bioactmat.2021.02.039
UHMWPE		Apoptosis	BMSC	TGFβ, RANKL, OPG	10.1089/ten.tea.2014.0144
Pyroptosis		MLO-Y4	CASP1, IL1β, GSDMD	10.1186/s13036-022-00314-8	
Other	PMMA	Apoptosis	MC3T3-E1	RUNX2, OSX	10.1002/jor.21035
	TCP	Necroptosis	MLO-Y4	RIP1, MLKL, LC3, PINK	10.1016/j.tox.2023.153627
	BHA	Apoptosis	MC3T3-E1	CASP3, BCL2, BAX	10.1007/s11427-017-9258-3

Abbreviations: CoCrMo, cobalt-chromium-molybdenum alloy; PMMA, polymethyl methacrylate; TCP, tricalcium phosphate; BHA, bovine hydroxyapatite; TiO_2, titanium dioxide; rMSC, rat mesenchymal stem cells; BMSC, bone marrow stromal cells; MLO-Y4, murine osteocyte-like cell line; MC3T3-E1, murine pre-osteoblast cell line; C2C12, murine myoblast cell line; L929, murine fibroblast cell line; RUNX2, runt-related transcription factor 2; OCN, osteocalcin; OSX, osterix; ALP, alkaline phosphatase; OPG, osteoprotegerin; SIRT, sirtuin; LC3, microtubule-associated protein 1A/1B-light chain 3; ERN1, endoplasmic reticulum to nucleus signaling 1; MAPKs, mitogen-activated protein kinases; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; TGFβ, transforming growth factor beta; β-catenin, beta-catenin.

Table 4. Summary of wear particles induced cell death pathways of osteoclasts

Wear particle types		Cell death type	Cell type	Cytokine	Assement	DOI
CoPs	CoCrMo	pyroptosis	BMDMs	GSDMD, IL-1β, CASPASE-1	ELISA, WB, HE, IH, IF	10.1186/s40779-022-00404-0
Ti	Ti	apoptosis	BMDMs	NA	CCK8, WB	10.1002/jbm.a.36972
	Ti	apoptosis	BMDMs	NLRP3, GSDMD, IL-1β, TNF-α	ELISA, LDH, WB	10.1002/jor.24826
Other	PMMA	apoptosis	M-CSF-dependent osteoclast	NA	NA	10.1002/jor.20184
Multiple	UHMWPE, CoCr, Ti, PMMA	apoptosis	MMCs	NA	ELISA, TUNEL	10.1002/jbm.b.20031

Abbreviations: BMDMs, bone marrow-derived macrophages; M-CSF, macrophage colony-stimulating factor; HE, hematoxylin and eosin staining; IF, immunofluorescence; CCK-8, Cell Counting Kit-8; LDH, lactate dehydrogenase; TUNEL, terminal deoxynucleotyl transferase dUTP nick end labeling; WB, Western blot.

Table 5. Summary of particle-induced periprosthetic osteolysis in mouse model

Mice type	Wear particles	Injure duration	Death type	DOI
C57BL/6J male mice	CoCrMo	14days	pyroptosis	10.1186/s40779-022-00404-0
C57BL/J6 mice	CoCrMo	14days	apoptosis	10.1080/15548627.2015.1106779
C57BL/J6 mice	CoCrMo	14days	apoptosis	10.3791/56276
C57BL/J6 mice	CoCrMo	2, 4, 6, 8, 10, 12, 14days	apoptosis	10.1002/jor.22128
C57BL/J6 mice	CoCrMo	14days	pyroptosis	10.1016/j.cej.2022.135115
C57BL/J6 mice	UHMWPE	12days	apoptosis	10.1016/j.actbio.2013.08.031

Abbreviations: C57BL/6J, a commonly used inbred mouse strain; CoCrMo, cobalt-chromium-molybdenum alloy; UHMWPE, ultra-high-molecular-weight polyethylene.

Table 6. Summary of tissue samples from patients with particle-induced periprosthetic osteolysis

Sample Type	Wear particles	Tissue type	Death type	Assessment	DOI
AL/PPI	Ti	Periprosthetic interface membranes	apoptosis	IHC(LC3) and TUNEL	10.1002/jbm.a.36938
AL/DDH	Ti	Periprosthetic interface membranes	apoptosis	IHC(CST) and qPCR(CST)	10.1111/nyas.14774
AL/HD	CoCrMo	Periprosthetic interface membranes	pyroptosis	WB(NLRP3, CASP1, GSDMD)	10.1016/ j.cej.2022.135115

Abbreviations: AL/PPI, aseptic loosening due to primary prosthetic implantation; AL/DDH, aseptic loosening in patients with developmental dysplasia of the hip; AL/HD, aseptic loosening associated with hip dysplasia; IHC, immunohistochemistry; qPCR, quantitative polymerase chain reaction; WB, Western blot.

6.1.2. Synthesis analysis

In vitro modeling of osteolysis primarily employs three types of wear particles: cobalt alloy, titanium alloy, and ultra-high molecular weight polyethylene. *In vivo*, rodent studies primarily involve implanting wear particles onto the calvarial surface to induce osteolysis. Other methods described in the literature include the tibial implant model and the bone graft balloon model. These models effectively replicate prosthetic aseptic loosening in animals, providing validated experimental platforms. Beyond these established systems, investigations have extended to examining programmed cell death in periprosthetic interface membranes from patients with clinically confirmed prosthetic loosening.

The analysis incorporated 24 *in vitro* studies using macrophages, osteoblasts, and osteoclasts. These studies demonstrated a time-dependent upregulation (peaking 24–48 h after stimulation) of pyroptosis, apoptosis, and necroptosis markers following wear particle exposure, along with the frequent detection of key PANoptosome components (**Tables 2, 3 and 4**). A consistent pattern was observed in 14 rodent osteolysis models and 3 clinical studies (**Tables 5 and 6**), with PANoptosome components detected across all experimental paradigms. This co-occurrence of multiple cell death modalities supports the activation of PANoptosis in PPO.

6.2. In vitro and in vivo experimental data

6.2.1. Wear particles induce macrophage PANoptosis

Given the limited evidence on macrophage necroptosis in PPO from our literature search, we performed experimental validation. RAW264.7 cells were stimulated with TC4 particles at concentrations of 100 μg/mL and 400 μg/mL for 24 hours and compared to an unstimulated control. Western blot analysis revealed a concentration-dependent upregulation of proteins associated with PANoptosis-related genes (**Figure 2**). Specifically, markers of pyroptosis (CASP1, GSDMD), apoptosis (CASP3, CASP8), and necroptosis (phosphorylated MLKL and RIPK1) showed dose-responsive activation. These findings indicate that wear particles trigger the coordinated activation of PANoptosis in macrophages, suggesting an integrated cell death mechanism in particle-induced osteolysis.

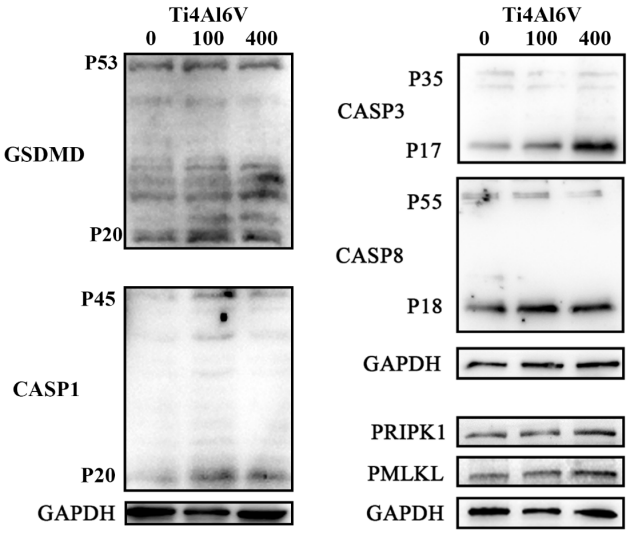

Figure 2. Wear particles contribute to macrophage PANoptosis. PANoptosis-related markers (GSDMD, CASP1, CASP 3, CASP8, pRIPK3, pMLKL).

6.2.2. Wear particles promote periprosthetic osteolysis and inhibit bone regeneration

Having validated the effects of TiPs on PANoptosis *in vitro*, we then established a murine model of particle-induced femoral osteolysis. We also collected periprosthetic interface membrane tissues from patients with aseptic loosening (AL) and synovial tissues from healthy donors (HD) to systematically evaluate the expression of PANoptosis pathway components. Using standardized immunohistochemistry, we analyzed the expression of PANoptosis markers (CASP3, CASP8, GSDME, GSDMD, pMLKL, pRIPK1) in the osteolytic regions of murine femurs (Figure 3A) and in the clinical samples (**Figure 3B**). The analysis revealed a significant upregulation of these effector molecules in the osteolytic bone of particle-treated mice and in the interface membranes of AL patients, compared to their respective controls.

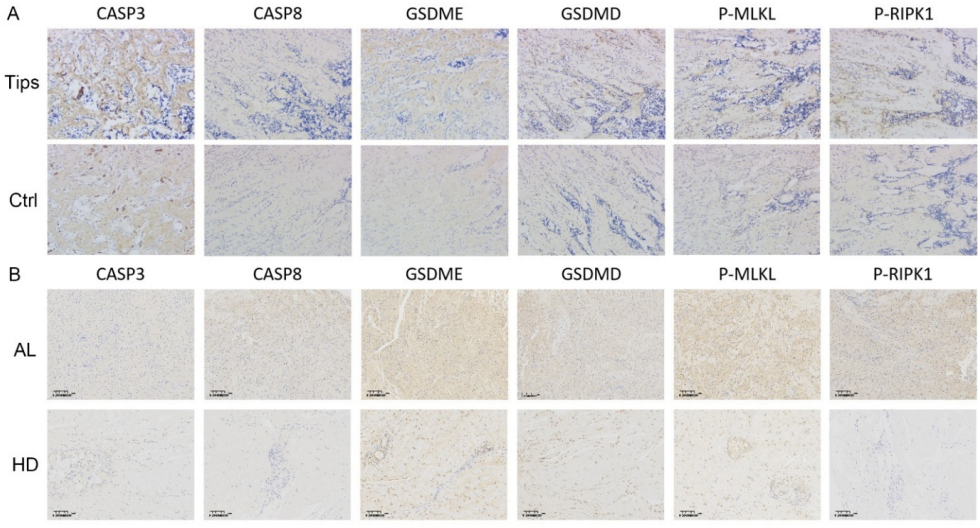

Figure 3. (A) Immunohistochemical staining of key PANoptosis markers (CASP3, CASP8, GSDME, GSDMD, p-MLKL, p-RIPK1) in mouse tissues exposed to Ti particles. (B) Representative immunohistochemical images from clinical tissue samples: AL (aseptic loosening) and HD (hip dysplasia), showing upregulation of these markers in pathological conditions.

7. Discussion

7.1. Periprosthetic osteolysis (PPO): A paradigm of sterile inflammatory bone loss

Implant failure due to periprosthetic osteolysis (PPO) caused by a chronic inflammatory response to wear particles released from the prosthetic implant is the primary cause of aseptic loosening and frequently requires implant revision [1,3,34]. A chronic pro-inflammatory response to wear particles leads to the breakdown of bone homeostasis and increased osteoclast formation and activation, resulting in increased bone resorption and ultimately implant failure (Osteolysis). PANoptosis has recently been characterized as a pro-inflammatory programmed cell death (PCD) pathway and a mechanism through which multiple diseases converge [35,36]. PANoptosis is unique in that it is characterized by the simultaneous activation of the principal mediators of pyroptosis, apoptosis and necroptosis; the PANoptosome, a multimolecular complex, is responsible for the coordination of this cascade of events. This represents a paradigm shift in our understanding of how PCD pathways function, as they are no longer viewed as isolated, linear processes, but as the basis of a dynamic and powerful synergy through the concerted efforts of inflammatory pathways. The findings of this multi-dimensional study demonstrate that PANoptosis induced by wear particles plays a critical role in the pathogenesis of PPO and serves as a molecular link between the initial particle challenge and the subsequent inflammatory cascade/master loop of bone homeostasis disruption (**Figure 4**).

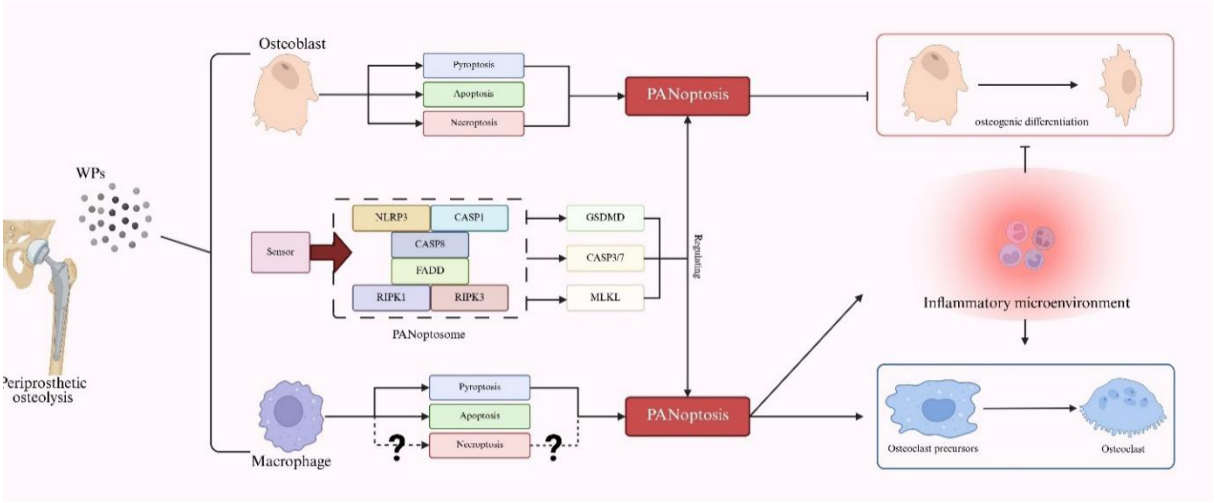

Figure 4. Mechanism of PANoptosis in PPO.

Wear particles (WPs) activate a common sensor complex, leading to the formation of the PANoptosome, which integrates pyroptosis, apoptosis, and necroptosis pathways via NLRP3, CASP1, FADD, RIPK1, and RIPK3. This results in the release of pro-inflammatory cytokines (e.g., IL-1β, GSDMD) and DAMPs, promoting an inflammatory microenvironment. In osteoblasts, PANoptosis impairs osteogenic differentiation and bone regeneration. In macrophages, it drives sustained inflammation and may contribute to osteoclastogenesis through the recruitment and activation of osteoclast precursors. The question marks indicate that the specific triggers and signaling molecules involved in macrophage PANoptosis remain incompletely defined.

7.2. Wear particles induce macrophage PANoptosis, amplifying the inflammatory microenvironment

There is a great deal of evidence that when macrophages ingest wear particles, this releases a series of chemicals into the body that activate the immune system, resulting in an inflammatory response. According to this evidence,

the exposure of macrophages to wear particles leads to two events: death of the macrophage and a significant increase in inflammatory chemicals (such as IL-1β, IL-6 and TNF-α) that continues the inflammatory response in the body (**Figure 5**) [22–24]. The understanding of apoptosis caused by wear particles (due mostly to NLRP3-inflammasome-triggered GSDMD cleavage) and pyroptosis in macrophages has been established fairly well [7–12], fits into this picture. Our studies have contributed data to fill this gap. Our data show that wear particles stimulate the expression of multiple proapoptotic, propyroptotic, and pro-necroptotic genes; however, more importantly, they induce co-activation of the active forms of pyroptotic (cleaved GSDMD), apoptotic (cleaved CASP3), and necroptotic (phosphorylated MLKL) effector proteins within the same populations of cells. This supports the conclusion that macrophages do not die by a single mechanism but rather by a novel form of cell death termed PANoptosis, which is characterized by the synergistic activation of multiple cell death pathways. This PANoptotic response may play an important role in amplifying the inflammatory process leading to osteoclast activation and subsequent bone loss.

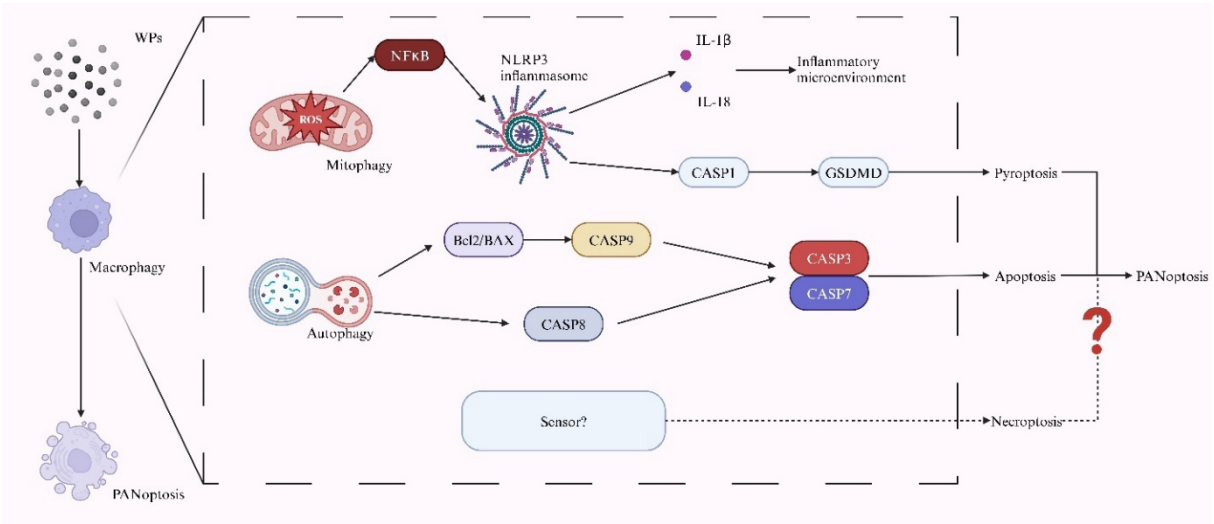

Figure 5. Wear particles stimulate PCD in macrophages: WPs trigger mitochondrial damage and ROS accumulation, leading to mitophagy and activation of the NLRP3 inflammasome. This results in caspase-1-mediated pyroptosis via GSDMD cleavage and IL-1β/IL-18 release. Concurrently, autophagy and Bcl-2/BAX signaling promote apoptosis through CASP9 and CASP3/CASP7 activation. The integration of these pathways may lead to PANoptosis, although the specific sensor and necroptosis components remain unclear.

7.3. Wear particles trigger osteoblast PANoptosis, compromising bone formation

In terms of pathology, the disorder of PPO is defined as having cumulative bone loss through fragmented bones, and additionally, bone formation processes are impeded by the chemicals released from artificially altered surfaces that cannot be reformed when introduced to the human body. The results of our study supported previous research demonstrating that polyethylene wear particles cause pyroptotic, apoptotic, and necroptotic cell death of osteoblasts [37–39]. Previous research has demonstrated the pathway for pyroptosis via NLRP3 inflammasome activity and via autophagic apoptosis. Interestingly, the results of the present synthesis suggest a potential dose-dependent response, with less than 50 mg/mL polyethylene particle concentration producing isolated apoptotic cell death and concentrations over 50 mg/mL resulting in a more lytic method of cell death (**Figure 6**). Of major significance is that this activation of multiple cell death pathways coincides with decreased osteogenic differentiation and function [25–27]. Therefore, from the viewpoint of osteoblasts, the two primary forms of trauma

are the direct killing of osteoblasts through PANoptosis and the significant inhibition of the bone-forming potential of osteoblasts that survived the PANoptosis pathway. Collectively, these two processes create a severe deficit in the amount of new bone being produced, and thus create a shift in the skeletal balance towards continued and progressive destruction of bone by osteolysis.

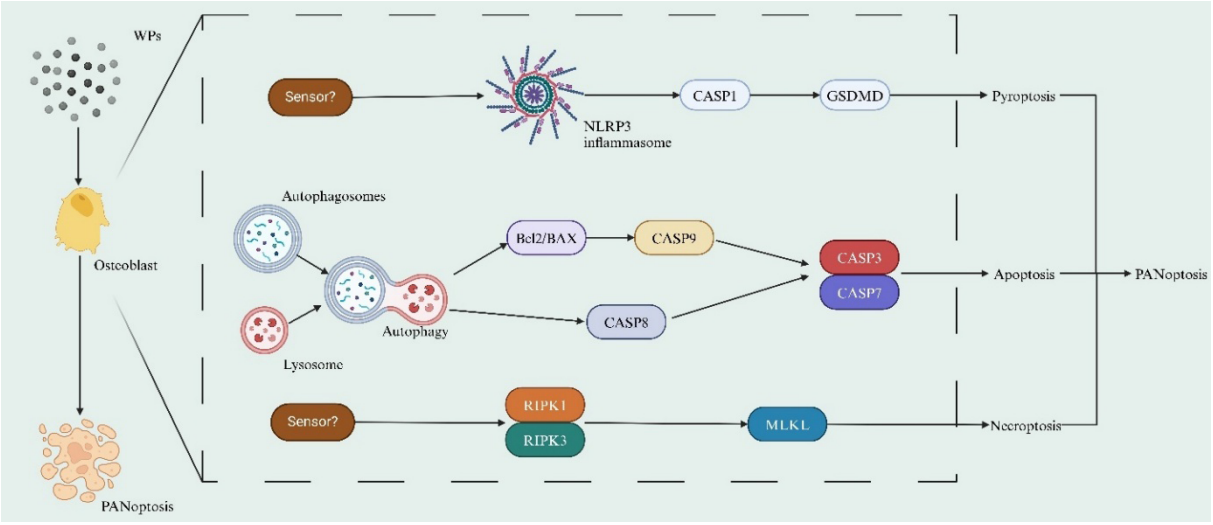

Figure 6. Wear particles stimulate PCD in osteoblasts: Wear particles (WPs) trigger multiple PCD pathways: pyroptosis via NLRP3 inflammasome activation and GSDMD cleavage; apoptosis through autophagy-mediated Bcl-2/BAX signaling and caspase cascade (CASP9 → CASP3/7); and necroptosis via RIPK1/RIPK3/MLKL axis. The integration of these pathways may lead to PANoptosis, although the specific sensor molecules remain undefined.

7.4. Wear particles promote osteoclastogenesis through direct and indirect mechanisms, driving osteolysis

Osteoclast activity is important when it comes to understanding bone resorption; osteoclasts are widely accepted as the primary cells in bone loss. Traditionally, it has been reported that osteoclastogenesis (the formation of new osteoclasts) results from exposure to wear particles, causing a pro-inflammatory environment. The process begins with oxidative stress caused by the generation of wear particles, followed by the pyroptotic death of macrophages, and the subsequent release of osteoclastogenic cytokines, such as IL-1β and IL-18. Mutually exclusive from each of these events is the induction of cytokines, which signal both differentiation and activation of osteoclasts from myeloid precursors (**Figure 7**) [40]. Our findings advance this paradigm to include additional aspects of how wear particle exposure contributes to the promotion of osteolysis by fossil fuels. The involvement of the broader PANoptosis response of macrophages, which includes not only pyroptosis but also all three pathways of cell death, results in a more diversified and powerful combination of DAMPs and cytokines. The influence of this combined exocytotic and pro-inflammatory secretion (the PANoptotic secretome), has the potential to augment the ongoing stimulation of osteoclast formation and activation. Ultimately, wear particles promote osteolysis through two modes: by directly stimulating the formation of osteoclast precursors and by more effectively generating a shift toward greater osteoclast potential with the amplification of the inflammatory environment caused by events of PANoptosis.

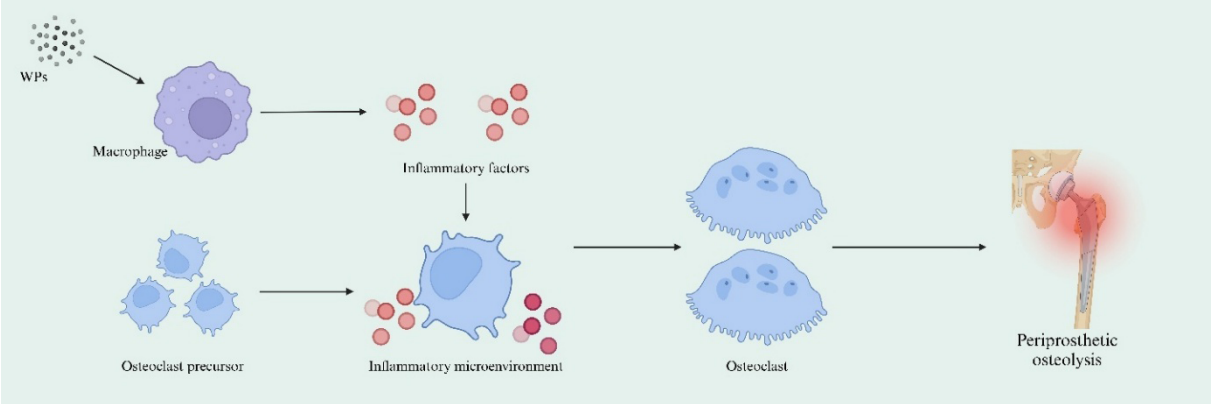

Figure 7. Schematic of wear particle-induced periprosthetic osteolysis via macrophage-mediated inflammation and osteoclastogenesis. Wear particles (WPs) activate macrophages to release inflammatory factors, which create a pro-inflammatory microenvironment. This environment promotes the differentiation of osteoclast precursors into mature osteoclasts, leading to bone resorption and periprosthetic osteolysis.

7.5. Convergent evidence from in vivo and clinical studies

Clinical and preclinical studies demonstrate a strong correlation with our findings at the cellular level. Studies utilizing rodent in vivo models of particle-induced osteolysis have repeatedly shown that multiple clinically relevant wear particles (CoCrMo, Ti, and UHMWPE) can induce substantial loss of bone surrounding prostheses; histopathology often showing positive histological evidence for cell death in these models [41]. The strongest evidence supporting translatability to the clinic comes from the direct study of human tissues by utilizing synovial interface membranes derived from patients undergoing revision surgery due to aseptic loosening. We were able to show that these membranes had co-localized and spatially juxtaposed molecularly characterized markers of pyroptosis, apoptosis and necroptosis located within osteolytic areas. Furthermore, we found that levels of RANKL, a key factor for osteoclast development, were elevated in those areas of the membranes with multi-modal PCD markers (**Figure 8**) [4,5]. These associations provide convincing support for our hypothesis that PANoptosis represents an in vitro "artifact" but rather represents a unique characteristic of human disease.

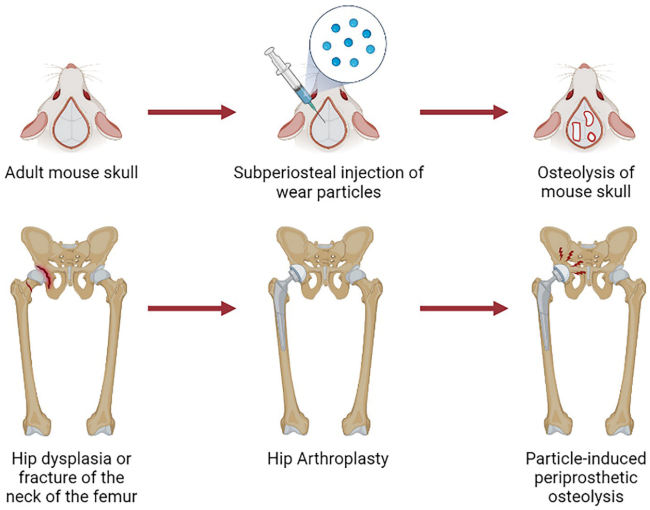

Figure 8. Two animal models for studying particle-induced periprosthetic osteolysis: cranial injection and hip arthroplasty with hip dysplasia.

7.6. Molecular basis for PANoptosome assembly in PPO

The PANoptosis process is mediated by the structure of a supramolecular complex called the PANoptosome, which integrates sensors, adaptors, and effectors from three cell death pathways: pyroptosis, apoptosis, and necroptosis [17,42]. Although PANoptosome components, such as the sensor ZBP1, adaptors ASC and FADD, and the catalytic proteins RIPK1, RIPK3, and caspase-8, are well-documented during viral infections and cancer [43]. The role of the PANoptosome in sterile (non-infectious) inflammatory conditions, such as particle-related occupational disease (PPO), has not previously been explored. Our findings support the viability of investigating the potential for particle-induced PANoptosome assembly in PPO. In a series of cellular models exposed to particles, we have observed that the core components involved in PANoptosome assembly were co-regulated in all three types of cell death: NLRP3, ASC and CASP1 (pyroptosis), FADD and CASP8 (apoptosis), and RIPK1 and RIPK3 (necroptosis). Therefore, the co-presence of these essential components establishes a solid platform for further studies to assess whether a PANoptosome assembles in PPO in response to wear particle signals.

8. Limitations

There were only three major databases used for the literature analysis, which limited the amount of literature available for review; also, the search terms were only applied to titles, abstracts and keywords. Therefore, it is probable that relevant literature articles that were published in other locations or that utilised different terminology or definitions are missing. Another limitation of this study is that while findings from our experiments showed that translational evidence existed and confirmed our findings through experimental models, the number of human samples available to be tested for translational purposes remains limited, and therefore will require further testing in larger study populations to confirm our findings. A third limitation of this study is that there is not yet any biochemical evidence available demonstrating that wear particles can induce the formation of a PANoptosome in terms of its functional assembly, despite the fact that we have observed concomitantly that the PANoptosome and components were activated/overexpressed simultaneously with the presence of wear particles.

9. Conclusion

This study demonstrates that PANoptosis plays an important role in the development of periprosthetic osteolysis (PPO) in a way that is more accurate than previously described. Findings support this hypothesis by integrating data from in vitro -based assays and animal-based work to create a more complete understanding of PPO due to PANoptosis. Important areas for future research include: validation of PANoptosome formation in response to the presence of wear particles; a detailed understanding of the functional relationship between PANoptosis and the regulatory mechanisms surrounding PANoptosis within an osteolytic microenvironment; and the discovery of potential targets within the molecular framework of PANoptosis for the development of new treatment options for PPO.

Ethical Approval

The collection of human specimens was approved by the local ethics committee (NanFang Hospital of Southern Medical University, NFEC- 2019-087). The animal use protocol listed below has been reviewed and approved by the Institutional Animal Care and Use Committee (ACUC) of Ruige Biotechnology (20240710–002)

Disclosure statement

The authors declare no conflict of interest.

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