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PERSPECTIVES

Black Phosphorus Nanomaterials and the Senescent Osteoimmune Microenvironment: Mechanisms, Opportunities, Challenges, and Future Outlook

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Abstract: The pathogenesis of senile osteoporosis involves immune cell imbalance, inflammaging, and dysregulation of the RANKL/OPG bone–immune axis, collectively defining the concept of immunoporosis. These interrelated processes mutually reinforce one another, leading to a 2–3-fold prolongation of bone healing time, while conventional single-target therapies fail to achieve coordinated regulation of bone regeneration and the immune microenvironment. Black phosphorus (BP) nanomaterials, as an emerging class of biomaterials, represent a paradigm shift from "passive scaffolds" to "active immuno–bone synergistic regulators." BP exerts multifunctional effects by restoring macrophage M1/M2 polarization balance, scavenging reactive oxygen species (ROS) to disrupt inflammatory feedback loops, and modulating the RANKL/OPG axis, thereby promoting a transition from a pro-inflammatory, destructive state to an anti-inflammatory, reparative phenotype. Experimental evidence indicates that BP can reduce pro-inflammatory cytokine expression by approximately 60% and achieve bone defect bridging rates of up to 93%. However, the clinical translation of BP remains challenged by the complexity of aging-related immune mechanisms, insufficient long-term safety data, and unclear translational pathways. This Perspective systematically discusses the regulatory mechanisms of BP in the aged osteoimmune microenvironment, the current limitations, and future research directions.

Keywords: black phosphorus nanomaterials, immunoporosis, inflammaging, RANKL/OPG axis, osteoimmune regulation

Introduction

With the rapid progression of global population aging, senile osteoporosis has emerged as a major cause of fractures, disability, and mortality in older adults.[1,2] Among individuals aged 65 years and older, the lifetime risk of osteoporotic fractures is estimated at 40–50% in women and 13–22% in men,[3] with fracture incidence continuing to rise with advancing age.[4] This condition imposes substantial medical, economic, and societal burdens.[5] Beyond traditional paradigms of bone mass loss and microarchitectural deterioration, the pathogenesis of senile osteoporosis is increasingly recognized as an osteoimmune disorder characterized by immune cell imbalance, inflammaging, and dysregulation of the RANKL/OPG bone–immune axis. These interconnected mechanisms synergistically disrupt osteoblast–osteoclast homeostasis and impair bone remodeling, rendering fracture-induced bone defects particularly difficult to heal in elderly individuals.[6–12]

Currently available anti-osteoporotic agents, including bisphosphonates, denosumab, and teriparatide, predominantly act on single molecular targets and lack interventions tailored to aging-specific osteoimmune mechanisms. As a result, they are insufficient to modulate the complex immune–bone crosstalk required for effective bone regeneration and immune microenvironment remodeling in older populations.[13–16] Moreover, anabolic parathyroid hormone analogs such as teriparatide and abaloparatide are restricted to treatment durations of less than two years and carry potential

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tumorigenic risks.[17] These limitations underscore the urgent need for therapeutic strategies capable of simultaneously improving bone quantity, microstructural integrity, and aging-associated osteoimmune dysfunction to address refractory bone defects in senile osteoporosis.

To overcome the shortcomings of conventional therapies and achieve coordinated regulation of the immune–bone system, recent research has explored various bone repair nanomaterials, including MXenes, bioactive glass, and cerium oxide nanozymes. MXenes exhibit favorable electrical conductivity and hydrophilicity and can modulate immune responses by regulating T-cell N-glycosylation and reducing ROS levels; however, their application in tissue regeneration remains in its infancy.[18–20] Bioactive glass demonstrates good osteoconductivity and can promote macrophage polarization toward the M2 phenotype through the release of ions such as Se, Sr, and Zn, yet its dense pore architecture and low specific surface area limit both mechanical performance and bioactivity.[21–23] Cerium oxide nanozymes possess strong antioxidant capacity and can enhance osteogenic differentiation,[24,25] but their long-term in vivo metabolism remains insufficiently characterized, and they lack direct bone mineralization-promoting effects.[26] These constraints highlight the need to identify more effective and versatile nanomaterials.

In this context, black phosphorus nanomaterials have attracted increasing attention. Since their initial report in 2014,[27] BP-based materials have been rapidly translated into biomedical applications,[28] evolving from photothermal osteogenic scaffolds[29–31] to active osteoimmune immunomodulatory regulators.[32,33] Compared with other nanomaterials, BP not only promotes osteogenic differentiation and bone regeneration but also exerts immunomodulatory effects by regulating macrophage polarization, suppressing excessive inflammation, and improving the osteoimmune microenvironment through multi-target synergistic mechanisms. These properties enable BP to address aging-specific pathophysiological and immunological alterations in a coordinated manner, thereby enhancing bone repair and overall skeletal health.[32–34] Nevertheless, challenges such as poor environmental stability, difficulty in precisely controlling degradation kinetics, and limited long-term safety data continue to impede its clinical translation.

This Perspective highlights BP as a representative paradigm shift from “passive scaffolds” to “active immuno–bone synergistic regulation” and focuses on the following key issues (Figure 1):

(1) How do immunosenescence, inflammaging, and dysregulation of the bone–immune axis mutually reinforce each other in the aged osteoimmune microenvironment to form a difficult-to-reverse pathological cycle? What other mechanisms are involved, and what are their specific roles?
(2) How do black phosphorus nanomaterials reverse pathological alterations in the aged bone microenvironment through immune remodeling, antioxidant effects, and osteoimmune crosstalk?
(3) What are the key bottlenecks in immune mechanism elucidation, long-term safety, and clinical translation when applying black phosphorus nanomaterials in elderly patients?
(4) How can AI-assisted design, aged animal models, and long-term safety evaluation facilitate the clinical translation of black phosphorus nanomaterials in the future?

Pathological Basis of the Aged Osteo-Immune Microenvironment

Osteoporosis is highly prevalent in older adults (≥65 years), and bone regenerative capacity is markedly compromised. This phenomenon is primarily driven by immune cell imbalance, inflammaging, and dysregulation of the bone–immune axis within the osteo-immune microenvironment. These factors interact synergistically, forming a complex pathological network. As a consequence, bone healing time in elderly patients is prolonged by approximately 2–3 fold compared with younger individuals, accompanied by a significantly increased incidence of nonunion and pronounced reductions in bone volume fraction (BV/TV) and bone mineral density (BMD).[35–37]

At the cellular level, profound immune dysregulation characterizes the aged bone microenvironment. Macrophage polarization is severely disrupted, with the bone marrow M1/M2 macrophage ratio markedly elevated, reaching an average of 22.1 ± 16.0.[38] Pro-inflammatory M1 macrophages continuously secrete TNF-α and IL-6, which directly suppress osteoblast function[39] and upregulate RANKL expression, thereby promoting osteoclastogenesis and exacerbating osteoporosis.[7] In parallel, neutrophils in aged individuals exhibit enhanced formation of neutrophil extracellular traps

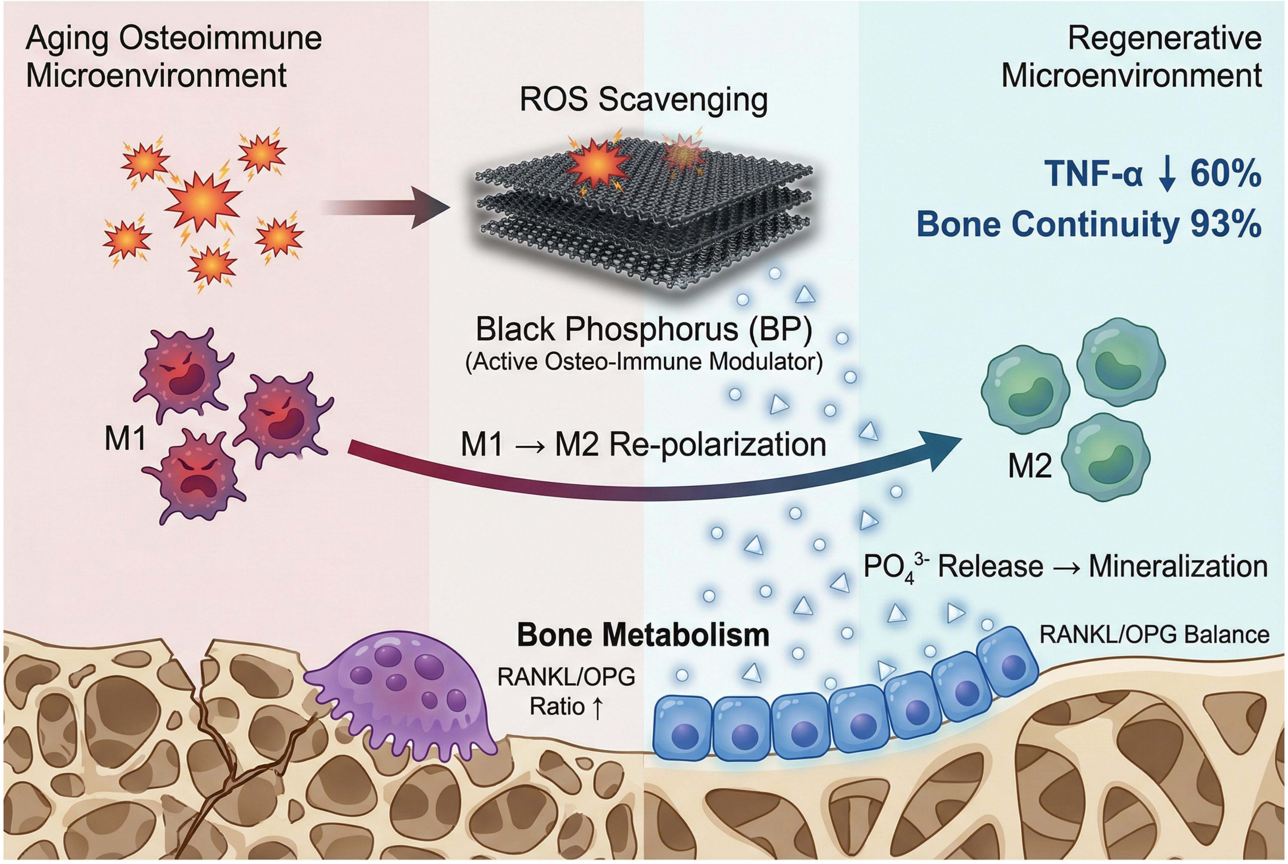

Figure 1 Mechanistic overview of black phosphorus nanomaterials in remodeling the aged osteo-immune microenvironment.

Notes: The left panel illustrates the pathological features of the aged osteo-immune microenvironment, including excessive reactive oxygen species (ROS) accumulation, predominance of M1 macrophages, and an increased RANKL/OPG ratio that drives osteoclast hyperactivity. The central panel highlights black phosphorus (BP) nanomaterials as an active immuno-osteogenic modulator, exerting therapeutic effects through three coordinated mechanisms: ROS scavenging, induction of macrophage polarization from the pro-inflammatory M1 phenotype toward the reparative M2 phenotype, and restoration of RANKL/OPG axis homeostasis. Concurrently, BP releases PO_4^{3-} ions to directly support bone mineralization. The right panel depicts the reprogrammed regenerative microenvironment following BP intervention, characterized by M2 macrophage dominance, enhanced osteoblast activity, and dense trabecular architecture. Notably, BP treatment reduces TNF-α expression by approximately 60% and achieves a bone continuity formation rate of up to 93%.Symbol legend: ↑, upregulation/increase; ↓, downregulation/decrease; →, transition or causative relationship.

Abbreviations: ROS, reactive oxygen species; BP, black phosphorus; RANKL, receptor activator of nuclear factor-κB ligand; OPG, osteoprotegerin; TNF-α, tumor necrosis factor-α; PO_4^{3-}, phosphate ion.

(NETs). Excessive NET accumulation intensifies local inflammation and tissue damage, further accelerating bone destruction.[11,40] The balance between regulatory T cells (Treg) and T helper 17 (Th17) cells is also disrupted, with reduced Treg numbers or impaired function, decreased Foxp3 expression, and a relative expansion of Th17 cells. This shift results in elevated IL-17 levels,[41,42] which contribute to bone mineral density loss and inflammatory bone damage.[43] Aberrant activation of the PI3K/Akt and STAT3 signaling pathways, commonly observed in aging, further skews T-cell differentiation toward Th17 dominance and amplifies bone-destructive processes.[44,45]

Inflammaging represents another central pathological feature, with excessive reactive oxygen species (ROS) accumulation as a key driver. Aging is associated with mitochondrial dysfunction, diminished activity of antioxidant defense systems (SOD, CAT, and GPx), and progressive ROS accumulation.[46] These alterations lead to sustained NF-κB activation[47] and facilitate TXNIP–NLRP3 interaction, triggering caspase-1 activation and promoting the maturation and release of IL-1β and IL-18.[48–52] Together, these events establish a self-amplifying inflammatory cascade—"ROS → NF-κB → TXNIP/NLRP3 → IL-1β/IL-18 → further ROS generation"—which exacerbates oxidative stress and tissue injury.[53,54] Aging also enhances expression of the senescence-associated secretory phenotype (SASP), comprising pro-inflammatory cytokines, chemokines, growth factors, and matrix-remodeling enzymes,[55,56] thereby inducing a "senescence contagion" effect.[57] Immune cells recruited by SASP are functionally compromised and fail to efficiently clear senescent cells; instead, they aggravate local inflammation, suppress osteogenic differentiation of mesenchymal

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stem cells (MSCs), and promote osteoclastogenesis.[58–60] Moreover, aging-induced mitochondrial damage, genomic instability, and impaired autophagy result in cytoplasmic DNA accumulation,[61] activating the cGAS–STING pathway and driving type I interferon production, NF-κB–dependent inflammation,[62] and SASP amplification.[63] Importantly, cGAS–STING signaling interacts with the NLRP3 inflammasome, forming a positive feedback loop that further enhances ROS production.[64] This pathway also increases Toll-like receptor sensitivity to damage-associated molecular patterns (DAMPs) while attenuating responses to pathogen-associated molecular patterns (PAMPs),[54] leading to persistent expression of inflammatory mediators such as IL-6, IL-1β, and IL-23. In concert with TGF-β, these factors promote differentiation of $CD4^+$ precursor cells into Th17 cells, thereby aggravating immune dysregulation.[42]

The RANKL/OPG bone–immune axis is likewise disrupted in aging. The balance between RANKL and its endogenous antagonist osteoprotegerin (OPG) critically determines osteoclast differentiation and bone resorption intensity.[39] Pro-inflammatory cytokines, including TNF-α, IL-6, and IL-17, strongly induce RANKL expression while suppressing OPG production.[65,66] Under aging or chronic inflammatory conditions, sustained elevation of these cytokines significantly increases the RANKL/OPG ratio, intensifying bone resorption.[67] TNF-α further amplifies this effect by promoting TRAF3 degradation and enhancing RANKL-induced osteoclastogenesis.[68] This imbalance is reinforced by bidirectional interactions between immune and bone cells: M1 macrophage–derived TNF-α and IL-6 persistently inhibit osteoblast activity,[39,69] whereas increased Th17 cells and IL-17 levels drive inflammatory bone destruction and immunosenescence-associated degenerative changes.[70,71] Concurrently, aging-associated decline in MSC immunosuppressive capacity leads to excessive IL-6 production,[72] positioning senescent MSCs as potent amplifiers of inflammation. Through paracrine signaling, aged MSCs suppress osteogenic differentiation of neighboring MSCs and exacerbate bone marrow inflammation.[59,60] They may also activate pro-inflammatory programs that impair hematopoietic stem and progenitor cell clonogenicity,[73] collectively contributing to compromised bone homeostasis and potentially insufficient bone perfusion.

In addition to these core mechanisms, the aged bone microenvironment exhibits other notable pathological features. Mechanotransduction is impaired by age-related alterations in lacunar morphology and degeneration of the lacunar–canalicular network,[74,75] leading to reduced YAP/TAZ activity and Piezo1 channel dysfunction, and ultimately diminishing osteocyte mechanosensitivity and skeletal responsiveness to mechanical loading.[76,77] Epigenetically, aged MSCs display global DNA hypomethylation alongside increased promoter-specific methylation[78] and abnormal histone modifications, including altered SETD2/H3K36me3 levels,[79,80] which collectively compromise osteogenic potential. From a proteostatic perspective, aging is associated with autophagic dysfunction and markedly reduced autophagy in bone tissue,[81,82] disrupting proteostasis networks[83] and resulting in impaired osteoblast mineralization and delayed bone regeneration.[84] Collectively, these alterations define the distinctive features of the aged osteo-immune microenvironment, with immune imbalance, inflammaging, and bone–immune axis dysregulation remaining the dominant pathological drivers.

Table 1 provides a systematic overview of the pathological basis of the aged bone–immune microenvironment.

Mechanisms and Experimental Evidence Underlying the Regulation of the Aged Osteo-Immune Microenvironment by Black Phosphorus Nanomaterials

Targeting the three major pathological features of the aged osteo-immune microenvironment, black phosphorus (BP) nanomaterials demonstrate multifaceted and highly specific regulatory effects.

At the level of immune cell imbalance, BP effectively reverses macrophage polarization dysregulation in aged bone marrow. Both in vitro and in vivo studies show that PLGA/BP scaffolds significantly downregulate M1-associated markers, including TNF-α, IL-6, and IL-1β, while upregulating M2-associated markers such as IL-10, TGF-β, and CD206, resulting in a marked reduction in the M1/M2 ratio.[32,33,39] By lowering oxidative stress, BP attenuates M1-polarizing signals, whereas its degradation products further promote M2-related gene expression through pathways such as STAT6, reinforcing this shift in macrophage phenotype.[33] Moreover, BP indirectly restores Treg/Th17 balance by enhancing M2 polarization and suppressing inflammatory signaling, thereby reducing IL-17 and other pro-inflammatory mediators and inhibiting osteoclast activity.[32,33,56,88,89] Collectively, these actions reprogram the bone microenvironment from a pro-inflammatory, destructive state toward an anti-inflammatory, reparative phenotype.

Table 1 Pathological Foundations of the Aged Osteo-Immune Microenvironment

Type	Mechanism	Key Molecules/Cells	Specific Details	Impact	Ref.
Immune cell composition and functional dysregulation	Predominance of M1 macrophages with reduced M2 proportion	M1/M2 macrophages, TNF-α, IL-6	Clinical bone marrow M1/M2 ratio = 22.1 ± 16.0; M1/M2 ratio ↑ in OVX mice	Persistent pro-inflammatory milieu, inhibition of osteoblast function, upregulation of RANKL and enhanced osteoclastogenesis	[7,38,85]
	Increased formation of neutrophil extracellular traps (NETs)	NETs, proteases, oxidases	NET formation capacity ↑ in aged individuals	Exacerbation of local inflammation and tissue damage, interference with bone repair	[11,40]
	Decreased Treg and increased Th17 populations	Treg ($CD4^+Foxp3^+$), Th17 ($CD4^+IL\text{-}17A^+$), IL-17	Th17/Treg ratio higher in SLE patients than controls (SMD = 0.80, $p < 0.001$)	Treg/Th17 imbalance aggravates inflammation and promotes bone resorption	[41–43]
Molecular drivers of inflammaging	ROS accumulation activates inflammatory signaling cascades	ROS, NF-κB, NLRP3, IL-1β	Mitochondrial dysfunction → decreased SOD/CAT/GPx activity	Formation of a positive feedback loop: "ROS → NF-κB → NLRP3 → IL-1β → ROS"	[46,53,54]
	Intervention with ROS scavengers	ROS scavengers	Reduced ROS levels accompanied by attenuation of NLRP3 inflammasome components and caspase-1 activation	Suppression of NLRP3 activation and IL-1β secretion, partially reversible inflammation	[86]
	Paracrine effects of SASP	IL-6, IL-8, TNF-α, MMPs, VEGF	Senescent MSCs → increased IL-6 and MMPs	"Senescence contagion" effect → inhibition of osteogenesis and promotion of osteoclastogenesis	[55,59,60]
	Regulatory pathways of SASP	p16/p21, mTOR, NF-κB	Sustained upregulation of p16/p21 in senescent cells; mTOR and NF-κB signaling maintains stable SASP gene expression	Senescent cells act as persistent sources of chronic inflammation	[57,63]
Aberrant innate immune pathways	Persistent activation of cGAS–STING signaling	Cytosolic DNA, cGAS, STING, IFN-I	DNA damage and mitochondrial stress lead to cytosolic accumulation of nDNA/mtDNA and activation of the cGAS–STING axis	Type I interferons interact with NLRP3/TLR pathways, amplifying inflammatory responses	[61,62,64]
	Dysregulated TLR signaling	TLRs, DAMPs, PAMPs	Enhanced sensitivity of TLRs to DAMPs (eg, HMGB1, mtDNA, oxidized lipids) with sustained downstream activation	Increased responsiveness to DAMPs → exacerbation of sterile inflammation	[54]

(*Continued*)

Table 1 (Continued).

Type	Mechanism	Key Molecules/Cells	Specific Details	Impact	Ref.
Age-related imbalance of the bone–immune axis	RANKL/OPG axis imbalance	RANKL, OPG, TNF-α, IL-6	Increased RANKL/OPG ratio; degradation of TRAF3	Excessive osteoclast activation leading to bone loss	[65,66,68]
	Th17/IL-17–mediated osteoclastogenesis	Th17, IL-17, RANKL	Elevated Th17 cells and IL-17 levels associated with low BMD	Accelerated bone resorption and skeletal deterioration	[85,87]
	Functional decline of MSCs	IL-10, TGF-β, IL-6, SASP	Aged MSCs → increased IL-6 secretion	Phenotypic shift from "immunoregulatory cells" to "inflammatory amplifiers"	[59,72,73]
	Impaired immune–bone cell interactions	TNF-α, IL-6, M1 macrophages	Sustained high expression of pro-inflammatory cytokines (TNF-α, IL-6) with concomitant alterations in osteogenic signaling	Suppression of osteoblast activity and bone matrix formation	[69]
	Th17-driven bone destruction	Th17, IL-17	Increased Th17 proportion and IL-17 expression correlated with activation of RANKL-related pathways	IL-17-induced immunosenescence → bone degeneration	[70,71]
Clinical outcomes	Delayed bone regeneration and increased nonunion rates	M1 macrophages, NLRP3–IL-1β, TNF-α/IL-6, Th17/IL-17, RANKL/OPG, MSCs, osteoblasts/osteoclasts	Bone healing delayed by 2–3-fold in aged populations; BV/TV and BMD significantly decreased	Synergistic effects of immunosenescence and inflammaging result in impaired bone regeneration	[35–37]

Abbreviations: SMD, standardized mean difference; BMD, bone mineral density; BV/TV, bone volume fraction; OVX, ovariectomy; SLE, systemic lupus erythematosus; NETs, neutrophil extracellular traps; SASP, senescence-associated secretory phenotype; RANKL, receptor activator of nuclear factor-κB ligand; OPG, osteoprotegerin; MSCs, bone marrow mesenchymal stem cells.

Beyond immune cell imbalance, BP plays a pivotal role in mitigating inflammaging. Through efficient scavenging of reactive oxygen species (ROS), improvement of mitochondrial function, and attenuation of inflammatory injury, BP counteracts age-related chronic inflammation.[47,90] Mechanistically, BP interrupts the ROS–TXNIP–NLRP3 signaling cascade, suppressing NLRP3 activation,[48,91] inflammasome-related cytokine release,[49,92,93] and pathways associated with the senescence-associated secretory phenotype (SASP). Consequently, the secretion of pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α, as well as matrix metalloproteinases (MMPs), is markedly reduced, leading to an overall improvement in the inflammatory milieu.[56,94–98] In parallel, BP-mediated modulation of the immune microenvironment indirectly restrains excessive activation of the cGAS–STING pathway, further alleviating chronic inflammation associated with immunosenescence.[99–102]

Within the RANKL/OPG osteo-immune axis, BP exerts dual immunomodulatory and osteogenic effects. By downregulating pro-inflammatory cytokines such as TNF-α and IL-6 and promoting M2 macrophage polarization, BP indirectly reduces RANKL expression and suppresses osteoclast differentiation, thereby correcting osteo-immune imbalance.[32,33] Concurrently, BP facilitates osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs), activates key osteogenic pathways including PI3K–AKT,[32,33] and induces immunoreparative factors such as IL-10 and TGF-β,[103] enabling a critical transition from tissue destruction to regeneration. Additionally, the controlled degradation of BP results in sustained release of phosphate ions (PO_4^{3-}), which directly enhances bone matrix mineralization[29] and activates osteogenic regulators such as Runx2 and BMP-2, thereby driving BMSC differentiation toward osteoblast lineages and achieving comprehensive modulation of the osteo-immune axis.[104,105]

Consistent with these mechanistic insights, BP has shown compelling therapeutic efficacy in experimental models. In an aged rat vascularized bone regeneration model, Wu et al reported that BP–GelMA hydrogel scaffolds reduced TNF-α expression by 60%.[56] In a titanium implant study, Ma et al demonstrated that BP–HA-coated implants increased the bone formation area by 47% compared with pure hydroxyapatite coatings.[106] From an immunomodulatory perspective, Jing et al summarized evidence that BP-based strategies increased bone mineral density by 32% while restoring the macrophage M2/M1 polarization ratio.[107] In a mouse model of osteoarthritis, Lu et al observed a reduction exceeding 70% in IL-17A expression.[47] Notably, Wu et al further demonstrated in an aged rat nonunion model that a BP–IL-4 co-delivery system, employing an "immunomodulation-first, osteogenesis-later" strategy, achieved a bone continuity formation rate of 93%, compared with 40% in controls.[108] Given that the degradation kinetics of BP are tunable,[109] Cai et al reported that AI-assisted, personalized 3D-printed BP scaffolds shortened the healing duration of aged bone nonunion by 35% in vivo,[110,111] highlighting a promising translational avenue for improving bone injury and fracture repair in elderly populations.

Table 2 provides a comprehensive overview of the key regulatory mechanisms and representative experimental data supporting the role of black phosphorus nanomaterials in the immunosenescent bone microenvironment.

Challenges and Limitations

Despite its promising potential, the clinical application of black phosphorus (BP) remains constrained by three major challenges: the complexity of immune mechanisms within the aged osteoimmune microenvironment, the lack of long-term safety data, and unclear pathways for clinical translation (Table 3).

Complexity of Immune Mechanisms in the Elderly

Current evidence is largely derived from animal models, with a notable absence of human studies. In particular, the regulatory effects of BP on immune cells such as macrophages and T cells within the aged osteoimmune microenvironment have not been systematically elucidated.[33,124,125] Moreover, aging is associated with a reduced number of bone marrow mesenchymal stem cells (BMSCs), diminished proliferative capacity, and a pronounced tendency toward adipogenic differentiation.[56] These aging-specific features substantially limit mechanistic interpretation and accurate prediction of BP therapeutic efficacy in elderly populations.

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Table 2 Core Regulatory Mechanisms of Black Phosphorus (BP) Nanomaterials in the Immunosenescent Bone Microenvironment

Type	Key Step	Key cells/Molecules	Mechanism	Specific Details	Effects	Ref.
Immune Remodeling	Regulation of M1/ M2 polarization	Macrophages	BP suppresses M1 polarization (↓ TNF-α, IL-6, IL-1β) and promotes M2 polarization (↑ IL-10, TGF-β, CD206), primarily via ROS scavenging and STAT6 pathway activation	PLGA/BP scaffolds significantly reduce the M1/M2 ratio; GelMA-BP scaffolds decrease TNF-α by ~60%; BP coatings increase bone formation area by ~47%	Relieves chronic inflammation and reprograms the microenvironment from a pro-inflammatory destructive state toward an anti-inflammatory regenerative state	[32,33,39,56,106,112]
	Regulation of Treg/ Th17 balance	T-cell subsets	Indirect modulation of the Treg/ Th17 ratio through regulation of antigen-presenting cell function, leading to suppression of IL-17 production and osteoclast activation	Nanoparticle intervention results in increased Treg proportions, reduced Th17 cells, and decreased IL-17 levels	Restores adaptive immune homeostasis and limits excessive inflammation and bone resorption	[32,33,56,88,89]
Anti-oxidative and Immune Exhaustion Reversal	ROS scavenging	ROS, mitochondria	Direct neutralization of excessive reactive oxygen species and improvement of mitochondrial function	BP demonstrates strong ROS-scavenging capacity; SOD activity is markedly reduced in aging microenvironments	Alleviates oxidative stress in immune cells, reverses immune exhaustion, and supports osteogenic activity	[47,90–92,113]
	Inhibition of the NLRP3 inflammasome	NLRP3/TXNIP/NF-κB	Blockade of the ROS–TXNIP–NLRP3 signaling axis, thereby suppressing downstream inflammatory cascades	Antioxidant strategies interrupt inflammatory signaling; Co nanozymes significantly inhibit NLRP3 assembly	Disrupts inflammatory amplification loops and mitigates tissue injury	[48–52,93,114]
Osteo–Immune Crosstalk Regulation	Activation of osteogenic signaling	Runx2, BMP-2, BMSCs	BP degradation releases PO_4^{3-}, enhancing mineralization and activating PI3K–AKT signaling	Phosphate ion release from BP significantly enhances mineral deposition	Promotes osteogenic differentiation of BMSCs and extracellular matrix formation	[29,32,33,104,105]
	Regulation of the RANKL/OPG axis	RANKL, OPG, osteoclasts	Suppression of inflammation-induced RANKL expression, restoration of the RANKL/OPG ratio, and reduction of osteoclast activity via M2 macrophage polarization	In OVX models, BMD increases by ~32%, accompanied by restoration of the M2/M1 ratio	Prevents excessive osteoclast activation and attenuates bone resorption	[32,33,39,107,115–120]

Senescence-Associated Pathway Modulation	SASP suppression	IL-6, IL-8, TNF-α, MMPs, G-CSF	Interference with SASP release and signal propagation through combined anti-inflammatory and antioxidative actions	SASP is a key driver of osteoporosis and joint degeneration	Slows chronic inflammatory accumulation and delays aging of the bone marrow microenvironment	[56,94–98]
	Modulation of the cGAS–STING pathway	cGAS, STING, IFN-I, TBK1, IRF3	Indirect restraint of excessive cGAS–STING activation; potential synergistic regulation via Mn^{2+} delivery	DNA damage → cytosolic DNA → cGAS–STING → IFN-I → SASP	Alleviates STING-driven inflammation and tissue damage	[55,99–102,121–123]
	Induction of reparative factors	IL-10, TGF-β	Promotion of anti-inflammatory and pro-reparative cytokine expression mediated primarily by M2 macrophages	M2 macrophages secrete IL-10 and TGF-β	Facilitates immune tolerance and tissue regeneration	[32,33,103]
Preclinical and Translational Applications	Immuno-friendly biomaterials	Aged bone defect models	BP-based scaffolds actively modulate immune responses to establish an immuno-friendly microenvironment	GelMA-BP scaffolds reduce TNF-α by ~60%; BP coatings enhance bone formation by ~47%	Shifts biomaterials from inert supports to active microenvironment modulators	[56,106]
	Personalized precision therapy	Degradation kinetics and drug delivery	Degradation rates tuned by BP thickness and size; photothermal-responsive delivery of IL-4 and BMP-2 combined with AI-assisted 3D printing	Degradation cycles range from hours to weeks; bone healing time shortened by ~35%	Matches aging-adapted regenerative rhythms and enables temporally precise interventions	[108,110,111]
	Treatment of degenerative bone diseases	OVX, RA, non-union models	Bidirectional regulation of immune–bone metabolic networks, balancing osteogenesis and inflammation suppression	OVX model BMD ↑~32%; CIA model IL-17A ↓~70%; non-union model bone continuity 93% vs 40% in controls	Improves refractory bone defects by intervening in disease progression through dual bone–immune axes	[47,107,108]

Notes: This table summarizes the major regulatory mechanisms of black phosphorus (BP) nanomaterials within the immunosenescent bone microenvironment. Evidence is primarily derived from in vitro and animal studies. "↑" and "↓" indicate upregulation and downregulation, respectively. "M1/M2" denote pro-inflammatory and anti-inflammatory macrophage phenotypes; "ROS" refers to reactive oxygen species; "SASP" denotes the senescence-associated secretory phenotype; "BMD" refers to bone mineral density; "OVX" indicates ovariectomized models; "RA" denotes rheumatoid arthritis; and "CIA" denotes collagen-induced arthritis.

Table 3 Key Challenges Associated with Black Phosphorus (BP)-Based Therapy

Challenge	Current Status	Strategies	Ref.
Complexity of aging immune mechanisms	Immune regulatory pathways in aging remain incompletely defined, and systematic investigations of BP–immune cell interactions (eg, macrophages and T cells) in immunosenescent contexts are limited	(1) Strengthen mechanistic studies on BP–immune cell interactions with a focus on aged immune microenvironments; (2) Employ surface engineering to modulate BP-induced immune responses and achieve controllable immune activation	[33,124,125]
Safety	Most available evidence is derived from short-term animal studies; long-term in vivo data on degradation, toxicity, immune responses, and biodistribution—particularly in aged models—are scarce	(1) Perform long-term toxicological and immunological evaluations using aged animal models; (2) Optimize BP surface modifications to improve biocompatibility and degradation stability	[126–129]
Clinical translation	Large-scale production remains challenging due to limited stability and pronounced batch-to-batch variability, hindering standardization and reproducibility	(1) Establish standardized synthesis and characterization protocols to enhance scalability; (2) Develop multifunctional composites and intelligent delivery systems to enable precise bone regeneration	[49,128,130,131]

Notes: This table summarizes the primary challenges hindering the clinical application of black phosphorus (BP) nanomaterials in aging-related bone disorders and outlines corresponding strategies to address immune complexity, safety concerns, and translational barriers.

Lack of Long-Term Safety Data

Age-related declines in metabolic capacity may predispose elderly individuals to long-term BP accumulation in vivo. Although existing studies generally report favorable biocompatibility, they are predominantly based on short-term observations.[107,132] In contrast, data on long-term in vivo degradation, toxicity, immune responses, and biodistribution remain limited, particularly in aged animal models.[126–129] Accordingly, extended-duration (>1 year) toxicological and immunological investigations are urgently required to comprehensively characterize the safety profile of BP-based interventions in elderly populations.

Unclear Clinical Translation Pathways

Most available studies employ rodent models,[32,47] whose physiological characteristics differ substantially from those of humans, thereby limiting direct clinical extrapolation. Furthermore, practical challenges, including difficulties in large-scale BP production, poor physicochemical stability, significant batch-to-batch variability, and insufficient standardization and controllability, continue to impede clinical translation.[49,128,130,131]

Future Perspectives

Over the next 5–10 years, increasing emphasis will be placed on elucidating BP–immune cell interactions, particularly involving macrophages and T cells, within the context of the aged osteoimmune microenvironment.[33,124,125] Advanced spatial transcriptomics will be applied to resolve the spatial organization, signaling pathways, and interaction networks among immune cells, bone cells, and vascular cells,[133,134] enabling construction of a three-dimensional BP-regulated "immune–bone–vascular" interaction atlas. In parallel, an "aged osteoimmune multi-omics database" will be established by integrating genomic, transcriptomic, proteomic, and metabolomic responses of elderly individuals under different BP-based interventions. This approach will facilitate identification of key biomarkers governing BP-mediated immunomodulatory efficacy.[56] On this basis, rational surface modification strategies can be developed to fine-tune BP-induced immune responses, thereby supporting bone regeneration therapies in elderly patients.

During the same period, long-term (>1 year) in vivo toxicological and immunological evaluations, together with the establishment of aged or large-animal models,[107,126–129,132] will enable more comprehensive safety assessments. Concurrently, standardized synthesis and characterization protocols will be implemented to enhance large-scale BP production and address issues of poor stability and pronounced batch-to-batch variability, ultimately accelerating clinical translation.[32,47,49,128,130,131]

Artificial intelligence (AI) is also expected to play an increasingly central role in BP research, spanning material design, therapeutic optimization, and safety evaluation. In intelligent nanomaterial development, AI-assisted machine learning and molecular modeling will support high-throughput screening and structural prediction, enabling optimization of BP nanoparticle size, surface modification, and drug-loading efficiency to improve stability, biocompatibility, and overall safety.[135] At the therapeutic level, AI algorithms will be used to predict drug release kinetics, targeting performance, and in vivo distribution of BP-based delivery systems, thereby enabling intelligent responsiveness to the tumor microenvironment. Such strategies have the potential to enhance bone regeneration while achieving precise drug delivery and improved anticancer efficacy.[135,136] In addition, AI-driven analyses of long-term follow-up and toxicological data will support early identification of potential safety risks, facilitate toxicity prediction and risk management, optimize clinical trial design, and ultimately improve clinical safety and therapeutic outcomes.[90,135] Collectively, these advances are expected to accelerate the clinical translation and implementation of BP-based therapies.

Looking ahead, further investigations will focus on layer-dependent immune response mechanisms of BP in the aged bone microenvironment. Systematic comparisons of macrophage polarization induced by BP with different layer numbers will be conducted to establish structure–activity relationships linking layer number, particle size, and immune response.[34,131] In parallel, continued attention will be given to interactions between BP and aging hallmarks, including its effects on mechanotransduction pathways in aged osteocytes and its antioxidant capacity to modulate epigenetic states of aged mesenchymal stem cells and autophagy–proteostasis networks, enabling more quantitative and precise evaluations.[75,79,83] Finally, machine learning approaches may be employed to construct temporal coupling models between BP degradation kinetics and dynamic changes in the aged osteoimmune microenvironment. When integrated with immunosenescence indicators in elderly patients, these models could support individualized response prediction systems, advancing precision therapy and maximizing the beneficial effects of BP.[110,135]

Table 3 summarizes the three major challenges associated with BP-based therapies and the corresponding strategic solutions.

Data Sharing Statement

The present study did not involve the generation or analysis of any datasets.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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