



Roles of Altered Macrophages and Cytokines: Implications for Pathological Mechanisms of Postmenopausal Osteoporosis, Rheumatoid Arthritis, and Alzheimer's Disease

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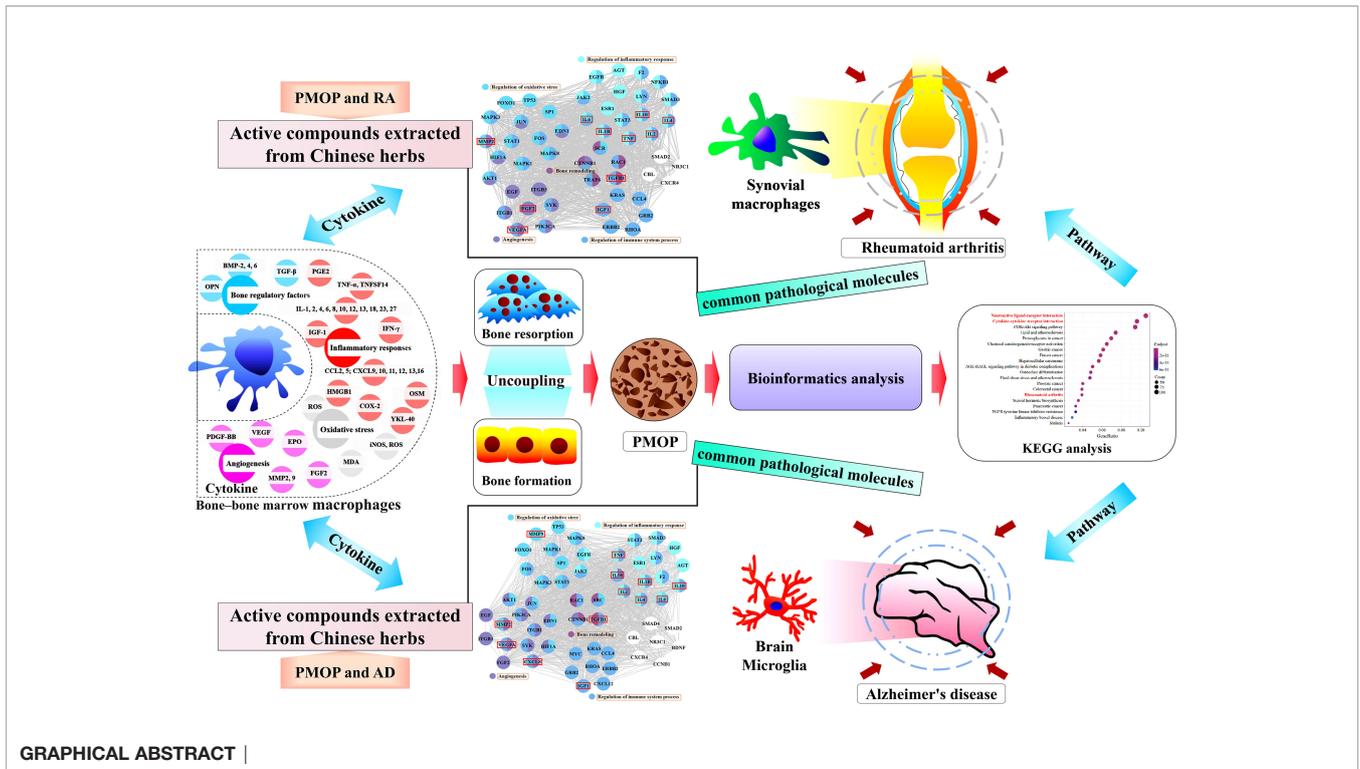
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Postmenopausal osteoporosis (PMOP) is characterized by the uncoupling of bone resorption and bone formation induced by estrogen deficiency, which is a complex outcome related to estrogen and the immune system. The interaction between bone and immune cells is regarded as the context of PMOP. Macrophages act differently on bone cells, depending on their polarization profile and secreted paracrine factors, which may have implications for the development of PMOP. PMOP, rheumatoid arthritis (RA), and Alzheimer's disease (AD) might have pathophysiological links, and the similarity of their pathological mechanisms is partially visible in altered macrophages and cytokines in the immune system. This review focuses on exploring the pathological mechanisms of PMOP, RA, and AD through the roles of altered macrophages and cytokines secretion. First, the multiple effects on cytokines secretion by bone-marrow (BM) macrophages in the pathological mechanism of PMOP are reviewed. Then, based on the thought of "different tissue-same cell type-common pathological molecules-disease pathological links-drug targets" and the methodologies of "molecular network" in bioinformatics, highlight that multiple cytokines overlap in the pathological molecules associated with PMOP vs. RA and PMOP vs. AD, and propose that these overlaps may lead to a pathological synergy in PMOP, RA, and AD. It provides a novel strategy for understanding the pathogenesis of PMOP and potential drug targets for the treatment of PMOP.

Keywords: postmenopausal osteoporosis, macrophages, cytokines, rheumatoid arthritis, Alzheimer's disease



GRAPHICAL ABSTRACT |

INTRODUCTION

Postmenopausal osteoporosis (PMOP) is a systemic chronic bone metabolic disease caused by the uncoupling of bone resorption and bone formation with estrogen deficiency (1, 2). Estrogen is also involved in the control of immune function, leading to a chronic low-grade pro-inflammatory phenotype under estrogen deficiency with altered cytokine expression and immune cell profiles in PMOP (3–5). Bone and immune system are functionally linked by complex molecular networks, in which accumulating evidence suggests that macrophages either directly or indirectly through the secretion of various cytokines, coordinate the coupling between osteoblasts and osteoclasts (6, 7). The relationship among estrogen, macrophages, and the skeleton could help in understanding the complex mechanism of PMOP.

The complex crosstalk between bone and immune cells plays an indispensable role in the pathogenesis of PMOP. Immunomodulatory imbalances and functional alterations are also part of the pathological conditions of PMOP, rheumatoid arthritis (RA), and Alzheimer’s disease (AD). Immunological studies have demonstrated that different tissue-resident cells of the macrophage lineage, such as bone-bone marrow (BM) macrophages, synovial macrophages, and microglia, are responsible for pathological changes in PMOP, RA, and AD, respectively. The existence of pathological links in PMOP, RA, and AD may be explained by searching for the common molecular network mediated by bone-BM macrophages, synovial macrophages, and microglia to provide a novel strategy for potential drug targets for the treatment of PMOP.

DIVERSITY OF PHENOTYPES AND FUNCTIONS OF MACROPHAGES

Macrophages, which are immune cells with heterogeneous phenotypes and complex functions, can be divided into circulating and resident macrophages (8, 9). Primitive hematopoiesis is a source of macrophages in embryos, and the majority of resident macrophages originate from yolk sac erythro-myeloid progenitors (10, 11). Bone-BM macrophages, synovial macrophages, and microglia play a key role in maintaining tissue homeostasis; phagocytosis and removal of cellular debris and foreign substances; tissue repair, regeneration, and remodeling; and the development and resolution of inflammation (12–15). Under physiological conditions, the bone-BM contains multiple different resident macrophage populations, including osteal macrophages, hematopoietic stem cell niche macrophages, and erythroblast island macrophages (16, 17). Macrophages have remarkable plasticity that allows them to respond efficiently to environmental signals and change their phenotypes.

Macrophages are activated, polarized, and subsequently secreted various cytokines (Supplementary Table S1) that are involved in coupling of bone resorption and bone formation under exposure to various types of stimuli. Under exposure to lipopolysaccharide (LPS) or T-helper 1 cytokines, such as interferon-gamma or granulocyte macrophage-colony stimulating factor, alone or in combination, macrophages are activated towards an M1 functional program to produce toxic effector molecules (such as inflammatory cytokines, reactive oxygen, and nitrogen species), which participate in polarized

T-helper 1 responses, regulate oxidative stress, and evoke inflammatory responses (18–21). Conversely, T-helper 2 cytokines, such as interleukin (IL)-4 or IL-13, can induce macrophages to polarize into the M2 type including M2a, M2b, M2c, and M2d, and play a central role in polarized T-helper 2 responses, the dampening of inflammation, angiogenesis, immunoregulation, and the remodeling of tissues (11, 22–25). The diversity of the phenotypes and functions of macrophages makes them play important different roles in inflammatory, immune, and metabolic diseases, such as PMOP, RA, and AD.

ROLE OF CYTOKINES SECRETED BY BONE-BM MACROPHAGES IN COUPLING OF BONE RESORPTION AND BONE FORMATION

Macrophages Directly Regulate Coupling of Bone Resorption and Bone Formation

Macrophages play a pivotal role in the coupling of bone resorption and bone formation. Paracrine cytokines, such as transforming growth factor- β (TGF- β), bone morphogenetic protein (BMP)-2, BMP-4, BMP-6, and osteopontin, are secreted by activated macrophages, which have a direct and critical impact on the physiological and pathological regulation of bone (**Supplementary Table S2**). On the one hand, fusion between cells of the monocyte/macrophage lineage leads to the formation of osteoclasts, which are the only cells with the ability to dissolve bone tissue (26). On the other hand, ablation of macrophages leads to loss of endosteal osteoblasts, reduction in the number of bone marrow mesenchymal stem cells (BMSCs), decrease in the ability of BMSCs to differentiate into osteoblasts, and attenuation of parathyroid hormone-induced trabecular bone anabolism (27–30). The macrophage-osteoclast axis plays an essential role in osteoimmunity, regulating the coupling of bone resorption and bone formation (31).

Uncoupling of Bone Resorption and Bone Formation: Cytokines Mediate Inflammatory Responses

Although macrophages in bone-BM are not directly adjacent to osteoblasts, they can alter the BM microenvironment by mediating an inflammatory response to affect bone synthesis and catabolism. Osteocytes are regulated by macrophages that secrete inflammatory mediators to control the coupling of bone resorption and bone formation (**Supplementary Table S3**). Macrophages are vital modulators of inflammation that rapidly change their phenotypes and functions in response to local microenvironmental signals and also play various roles in both the induction and resolution of inflammation, such as clearing dead cells and debris, presenting antigens, and recruiting, and activating other immune cells (7, 32–34). Skeletal homeostasis depends on the balance between the classically active M1 type and the alternatively active M2 type (35, 36). M2 activation appears to be blunted in macrophages from

postmenopausal women, leading to an increased M1/M2 response ratio (32). In ovariectomized (OVX) mice, polarization of M1 macrophages was increased whereas polarization of M2 macrophages was disturbed (37). Therefore, changes in macrophage-derived cytokines and their phenotypes linked with inflammation are critical regulators of bone resorption and bone formation, supporting the theory that the immune system significantly contributes to the pathological mechanism of inflammation-mediated bone-loss.

Uncoupling of Bone Resorption and Bone Formation: Cytokines Mediate Oxidative Stress

After menopause, due to the influence of estrogen deficiency, the level of oxidative stress in the body increases, which causes the imbalance in bone reconstruction and leads to osteoporosis (38–40). Macrophages secrete regulatory factors related to oxidative stress, such as reactive oxygen species (ROS), nitric oxide (NO), and inducible nitric oxide synthase, which induce pathological changes in the differentiation process and activity of bone cells, ultimately leading to the uncoupling of bone resorption and bone formation (**Supplementary Table S4**). The oxidative stress level in PMOP depends on the relationship between ROS and the endogenous antioxidant defense system (41, 42). One of the most damaging effects of ROS is lipid peroxidation, whose end product, malondialdehyde, is a potential biomarker of oxidative stress (43). NO, catalyzed by nitric oxide synthase, is also an integral part of the response to oxygen deprivation and has been confirmed to be a key regulator of bone homeostasis (44–46). The effects of these factors highlight the diversity of the roles of macrophages in regulating bone homeostasis. Further studies are needed to clarify the molecular mechanisms underlying the relationship among macrophages, oxidative stress and PMOP.

Uncoupling of Bone Resorption and Bone Formation: Cytokines Mediate Angiogenesis

Bone is a highly vascularized tissue, and bone homeostasis depends on the coupling between bone and blood vessels. The skeletal microvasculature system plays an important role in the metabolism of BM microenvironment, osteogenesis, and maintenance of the balance between bone formation and bone resorption. Basic and clinical studies have found that the decrease in local blood supply is related to PMOP. In the OVX mouse model, the number of microvessels, the type H vessels, and the expression of vascular endothelial growth factor (VEGF) are all significantly reduced (47, 48). Macrophages are key cellular components in the BM microenvironment that regulate bone homeostasis and angiogenesis. In bone repair, macrophages can remove dead neutrophils at the injured site after fracture, and release cytokines, such as VEGF, erythropoietin, platelet-derived growth factor-BB, matrix metalloproteinase 2 (MMP2), MMP9, and fibroblast growth factor 2 (FGF2) (**Supplementary Table S5**), so as to initiate the repair cascade that suppresses the pro-inflammatory

responses and promotes angiogenic responses (49, 50). During the inflammatory phase of bone repair, the recruitment of macrophages is related to angiogenesis, and their numbers are strongly correlated with the density of blood vessels (51). Moreover, the coordinated conversion of the pro-inflammatory M1 and anti-inflammatory M2 phenotypes in macrophages determines the efficiency of bone regeneration to a great extent (52). Given their intimate involvement in vascular formation, an understanding of the multilayered contributions of macrophages to bone repair and fracture healing is also accumulating.

BIOINFORMATICS IDENTIFIED SHARED PATHOLOGICAL MOLECULES IN PMOP, RA, AND AD

Bioinformatics Revealed Potential Pathological Links in PMOP, RA, and AD

Because the physiological and immune functions are reduced in postmenopausal women, in addition to the need to prevent osteoporosis, the prevalence of RA and AD is also quite noteworthy. A large number of clinical and basic studies have confirmed the association in PMOP, RA, and AD. With the help of bioinformatics analysis methods (**Supplementary Methods of Bioinformatics**), we integrated multiple databases to screen the differential genes of PMOP, and then performed enrichment analysis of the Kyoto Encyclopedia of Genes and Genomes

(KEGG) pathway, which was also enriched in the RA and AD pathways (**Figure 1** and **Table 1**). Simultaneously, the two signaling pathways of neuroactive ligand-receptor interaction and cytokine-cytokine receptor interaction also undergo significant changes. Like PMOP, the pathological mechanisms of RA and AD are also closely associated with two resident macrophages: synovial macrophages and brain microglia, respectively. Therefore, we pose the question of what role do macrophages play in the “two-pairs of disease links”. Searching for significant common-targets in PMOP, RA, and AD may have a particularly practical meaning in providing guidance for the prevention and control of PMOP, RA, and AD.

Common Pathological Molecules Between PMOP and RA: A Molecular Perspective of Cytokines Secreted From Bone-BM Macrophages and Synovial Macrophages

The immune cells involved in RA, macrophages, are the most numerous immune cells found in the RA synovium and play a key role in immune/inflammatory reactions and bone loss by paracrine signaling or *via* direct cell-cell contact (53–56). In addition, synovial macrophages are involved in pathological processes such as matrix degradation, oxidative stress, and angiogenesis in RA (57–59).

Among other features, RA is characterized by systemic bone loss, and the risk of osteoporosis is high in patients with RA, especially in postmenopausal women (60–62). Therefore, to clarify the pathological links between PMOP and RA, we used

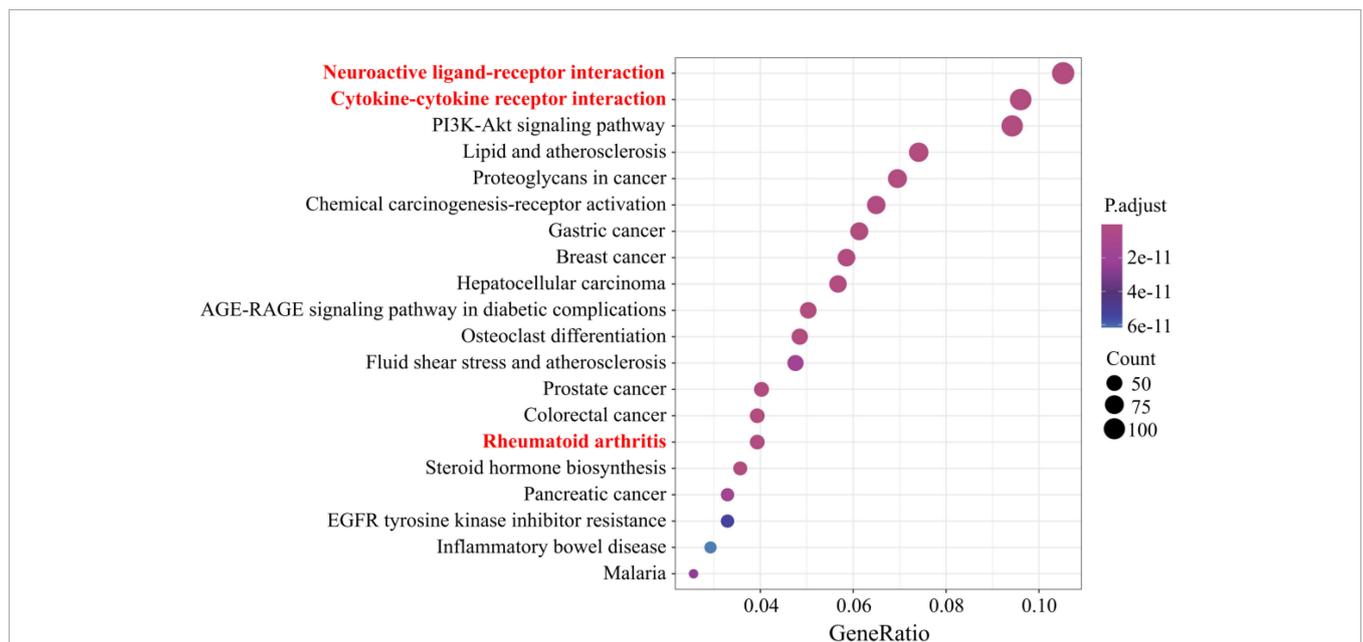


FIGURE 1 | Top 20 Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment candidate targets of differential genes in postmenopausal osteoporosis. Pathways with significant changes (false discovery rate [FDR] < 0.05) were identified. The vertical coordinates represent the KEGG pathway with significant enrichment, and the horizontal coordinates represent the gene ratio, which refers to the ratio of enriched genes to all target genes. The color of the bubble graph indicates the significance of the enriched KEGG pathway, the color gradient represents the size of the *P*-value, and the size of each dot represents the number of genes.

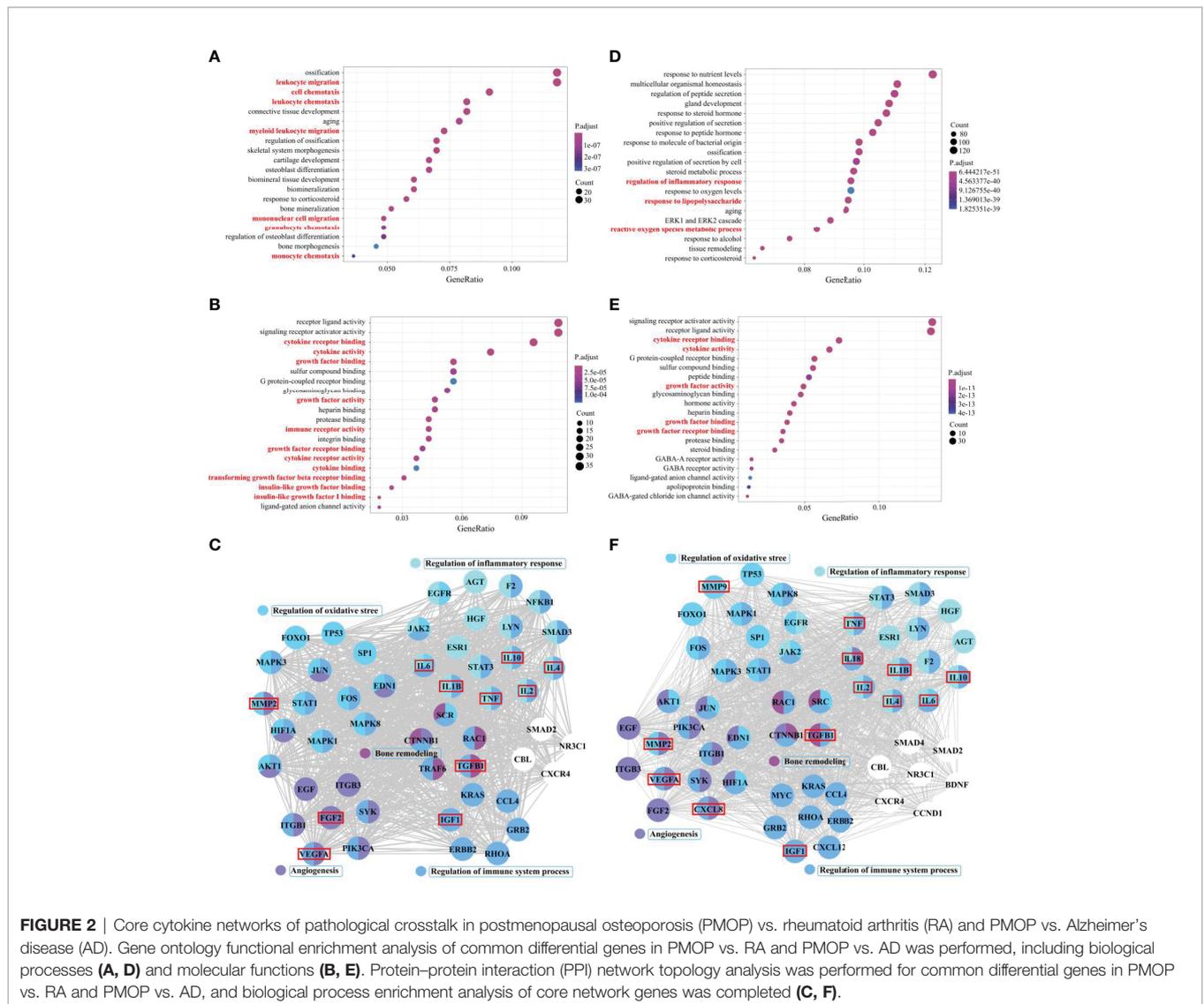
TABLE 1 | Results of KEGG enrichment analysis of RA and AD pathways.

Description	Gene Ratio	Bg Ratio	P-value	P-adjust	Q-value
Rheumatoid arthritis (hsa05323)	43/1093	93/8112	1.25E-14	3.13E-13	1.48E-13
Alzheimer's disease (hsa05010)	66/1093	384/8112	0.019899217	0.039433384	0.01871717

bioinformatics analysis methods (**Supplementary Methods of Bioinformatics**) to search for common pathological molecules between them.

The results are summarized as follows: among biological processes, it is enriched in leukocyte migration, cell chemotaxis, leukocyte chemotaxis, myeloid, mononuclear cell migration, granulocyte chemotaxis, monocyte chemotaxis, and other processes. (**Figure 2A**). Among molecular functions, it is enriched in cytokine receptor binding, cytokine activity, growth factor binding, growth factor activity, immune receptor activity, growth factor receptor binding, cytokine receptor activity,

cytokine binding, TGF- β receptor binding, insulin-like growth factor (IGF) binding, IGF-1 binding, and other functions (**Figure 2B**). The results show that the immune system and immune cells play important regulatory roles in the occurrence of PMOP and RA. Although the results did not directly enrich macrophage-related functions in the top 20 Gene Ontology functions, the related functions enriched in cells (such as TGF- β and IGF-1) still had great directivity. Cytokines secreted by macrophages, including TGF- β 1, IL-1 β , IL-2, IL-4, IL-6, IL-10, tumor necrosis factor (TNF), IGF-1, VEGFA, FGF2 and MMP2, which are associated with the functions of regulation of immune



system process, bone remodeling, regulation of inflammatory response, response to oxidative stress, and angiogenesis, were screened from the protein–protein interaction (PPI) core network, as described above (**Figure 2C**).

As in PMOP, an imbalanced network of cytokines secreted by synovial macrophages plays a key role in the pathogenesis of RA. Among them, secretion of TNF- α , IL-1 β , IL-2, and IL-6, or a combined deficiency of IL-4 and IL-10, promotes and sustains inflammation, while also acting to promote bone erosion (63, 64). In addition, TGF- β , TNF- α , IGF-1, VEGF, FGF2, and MMP2 are involved in the hypervascularization as well as the pannus formation observed in RA (65–67). As a result, the imbalanced cytokine network could provide clues to identify pathological links between the two diseases and potentially suggest some shared pharmacological prevention and treatment.

Common Pathological Molecules between PMOP and AD: A Molecular Perspective of Cytokines Secreted From Bone-BM Macrophages and Microglia

Microglia may play a significant role in the pathogenesis of AD, which is characterized by deposition of β -amyloid plaques, hyperphosphorylation of tau protein, oxidative damage, neuroinflammation, vascular remodeling, autophagy, and mitochondrial dysfunction (68–71). AD and PMOP are frequently seen to coincide in clinical practice, and their possible relationship, concurrent occurrence, and linking mechanism have recently been highlighted (72–74). Prevention of osteoporosis should be considered as part of the treatment of patients with AD, especially in postmenopausal women, and conversely, prevention of AD should be considered in patients with various degrees of bone loss.

Microglia show altered morphology and reduced arborization, and their activation increases with the progression of AD (75, 76). Activated microglia exhibit many morphologic and immunophenotypic features of peripheral macrophages, such as pro-inflammatory M1 and immunosuppressive M2 phenotypes (77, 78). Activated microglia assume diverse phenotypes, which mediate the different pathological processes of AD by releasing various substances, such as inflammatory cytokines, growth factors, chemokines, neurotrophins, and superoxide (79–82).

We also used bioinformatics analysis methods (**Supplementary Methods of Bioinformatics**) to search for common pathological molecules between PMOP and AD. Among biological processes, it's enriched in the regulation of inflammatory response, response to LPS, ROS metabolic process, and other processes (**Figure 2D**). Among molecular function, it is enriched in the cytokine receptor binding, cytokine activity, growth factor activity, growth factor binding and receptor binding, and other functions (**Figure 2E**). Cytokines secreted by macrophages, including TGF- β 1, IL-1 β , IL-2, IL-4, IL-6, IL-10, IL-18, TNF, IGF-1, C-X-C motif chemokine ligand 8 (CXCL8), VEGFA, FGF2, MMP2, and MMP9, which are also associated with the functions of regulation of immune system process, bone remodeling, regulation of inflammatory response, response to oxidative stress, and angiogenesis, were screened from the PPI core network, as described above (**Figure 2F**).

The results indicated that the pathological changes in bone-BM macrophage-mediated PMOP are partially similar to the pathological changes in microglia-mediated AD.

The delicate balance between their pro-inflammatory and anti-inflammatory actions and their neurotoxic and neuroprotective actions determines the role of microglia in AD. Microglia activate and drive inflammatory processes by inducing the pro-inflammatory molecules, such as IL-1 β , IL-6, IL-18, and TNF- α , leading to accumulation of extracellular amyloid- β peptides, tau hyperphosphorylation, and activation of other inflammatory participants (83, 84). They also produce various anti-inflammatory, chemokines and growth factors, such as IL-2, IL-4, IL-10, CXCL8, FGF2, IGF-1, and TGF- β 1, which have been shown to exert neuroprotective effects against amyloid- β -induced neurodegeneration (85–88). Other microglia-derived factors such as VEGFA, MMP2, and MMP9, are associated with disruption of the blood-brain barrier, leading to neuroinflammation and progression of AD (89–91). Combined with the role of macrophages in PMOP mentioned above, simultaneous tracing of the common pathological molecular network associated with cytokines (bone-BM macrophages and microglia) in PMOP and AD may reveal the key pathological links between the two diseases.

EXPLORATION OF MULTIFUNCTIONAL POTENTIAL ACTIVE COMPONENTS FROM CHINESE HERBS TARGETING COMMON PATHOLOGICAL MOLECULES OF PMOP, RA, AND AD

Because of the common pathological molecules of PMOP, RA, and AD, it is of great importance to seek effective drugs to prevent the occurrence of complications. Chinese herbs have anti-PMOP, anti-RA and anti-AD properties due to their actions against multiple targets, pathways, and systems. Therefore, taking the cytokines secreted by macrophages as the entry point, combined with the results of bioinformatics analysis, we summarized potential active components extracted from Chinese herbs, such as icariin, quercetin, and naringin, which were simultaneously applied in the treatment of PMOP, RA, and AD (**Tables 2 and 3**). From the side, this also reflects the roles of altered macrophages and cytokines on PMOP, RA, and AD.

CONCLUSIONS AND PERSPECTIVES

PMOP is caused by dysregulation of the homeostatic connection between bone and the immune system, leading to bone loss. This review has outlined the direct and indirect effects of cytokines secreted by bone-BM macrophages on the coupling of bone resorption and bone formation. The principal mechanisms of these effects include inflammatory/immune responses, angiogenesis, and oxidative stress. Some overlapping cytokines of PMOP, RA, and AD in bioinformatics analysis may immunologically link two diseases, serving as either shared

TABLE 2 | Summary of potential active components from Chinese herbs to be applied in PMOP and RA.

Active component from Chinese herbs	Targets	Pharmacodynamic mechanism in PMOP	Ref	Pharmacodynamic mechanism in RA	Ref
Icariin	IL-6 IL-1 β TNF- α PGE2 MMP9	a. Diminished LPS induced IL-6 and TNF- α on osteoclasts, and decreased PGE2 production by inhibiting COX-2. b. Inhibited IL-1 β in OVX rats. c. Reduced MMP-9 in RANKL-induced osteoclast formation from RAW 264.7 cells. d. Reduced MDA in hypoxia-induced oxidative damage of osteoblasts.	(92–94)	a. Inhibited IL-6, TNF- α , and IL-1 β in RA-FLS cells. b. Wangbi capsule, whose main effective substances include icariin, reduced PGE2 and IL-1 β in adjuvant induced arthritis rat model. c. Inhibited MMP in induction of type II collagen-induced arthritis. d. Reduced MDA levels in LPS-induced synovitis.	(95–98)
Luteolin	NO TNF- α IL-6	a. Decreased the 3-morpholinosydnonimie-induced production of NO, TNF- α , and IL-6 in osteoblasts.	(99)	a. Reduced NO, TNF- α , and IL-6 in LPS-induced RAW 264.7 macrophages and ConA-induced T lymphocytes.	(100)
Quercetin	TNF- α IL-6	a. Significantly decreased TNF- α in OVX rat model. b. Reduced IL-6 and TNF- α in RANKL-induced osteoclasts.	(101, 102)	a. Down-regulated the content of TNF- α , IL-1 β and IL-6 in collagen-induced arthritis mice.	(103)
Naringin	NO TNF- α	a. Enhanced NO synthesis in OVX rat model. b. Prevented TNF- α -inhibited BMSCs osteogenic differentiation of BMSCs.	(104, 105)	a. All flavonoids, including naringin, inhibited NO production from LPS-induced macrophage cells. b. Inhibited IL-6 and IL-1 β in TNF- α -induced RA-FLS.	(106, 107)

TABLE 3 | Summary of potential active components from Chinese herbs to be applied in PMOP and RA.

Active component from Chinese herbs	Targets	Pharmacodynamic mechanism in PMOP	Ref	Pharmacodynamic mechanism in AD	Ref
Icariin	COX-2 PEG2 TNF- α NO MDA ROS	a. Inhibited LPS-induced bone resorption and TNF- α expression, also inhibited COX-2 and PGE2 synthesis on osteoblasts or osteoclasts. b. Increased NO production in BMSCs and osteoblasts, and inhibited osteoclast-mediated bone resorption. c. Reduced production of ROS and MDA in osteoblasts.	(92, 94, 108, 109)	a. Decreased expression of TNF- α and COX-2 in hippocampus of rats with LPS-induced brain dysfunction. b. Inhibited the release of ROS, NO, and PGE2 in microglia. c. Reduced MDA content in hippocampus of aluminum-poisoned rats.	(110–112)
Naringin	NO TNF- α	a. Enhanced NO synthesis in OVX rats. b. TNF- α : as shown in Table 2 .	(104, 105)	a. Reduced hippocampal NO production in a mouse model of AD. b. Reduced TNF- α levels in ICV-STZ rats.	(113, 114)
Quercetin	ROS TNF- α	a. Protected against TNF- α -induced impairments in BMSCs osteogenesis. b. Reduced ROS and TNF- α levels when coculturing osteoblast-osteoclast or triculturing osteoblast-osteoclast-endothelial cells on hydroxyapatite loaded with quercetin.	(115, 116)	a. Reduced ROS and TNF- α levels in high-cholesterol-fed aged mice. b. Reduced TNF- α and -IL-6 expression and reversed neurodegeneration to restore memory function.	(117, 118)

susceptibility factors or molecular links. Therefore, based on the thought of “different tissue (bone-BM, synovial, and brain)-same cell type (macrophages)-common pathological molecules (cytokines)-disease pathological links (PMOP vs. RA and PMOP vs. AD)-drug targets (active compounds extracted from Chinese herbs)” and the methodologies of “molecular network” in bioinformatics, may lead to a paradigm shift in the understanding of the pathogenesis, prophylaxis, and treatment of PMOP.

AUTHOR CONTRIBUTIONS

XHL and YX identified the focus and overall direction of the review. Funding acquisition XHL and HY; Sources, XHL;

Methodology, XZ, JZ, YH, HZ, DX, XL, WC, XW, SW, and XHL; Supervision, XHL; Writing—original draft, YX, HY, and XHL; Writing—review & editing, YX, HY, XZ, JZ, YH, HZ, DX, XL, WC, XW, SW, and XHL. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2022.876269/full#supplementary-material>

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