Interleukin family in vascular calcification: molecular mechanisms and therapeutic perspectives

Yikun Zhao, Heng Li and Yuanyuan Guo*

Vascular Surgery Department, Fuwai Yunnan Cardiovascular Hospital, Kunming Medical University, Kunming, China

Vascular calcification (VC), characterized by pathological calcium deposition in arterial walls, is a major contributor to cardiovascular morbidity in chronic inflammatory diseases such as atherosclerosis, chronic kidney disease (CKD), and diabetes. Emerging evidence underscores the pivotal role of interleukin (IL) family cytokines in modulating VC through dual pro- and anti-calcific mechanisms. Pro-inflammatory IL members, including IL-1β, IL-6, IL-17A, and IL-29, drive osteogenic transdifferentiation of vascular smooth muscle cells (VSMCs) by activating pathways such as NF-κB, STAT3, NLRP3 inflammasomes, and Wnt/β-catenin. These pathways upregulate osteogenic markers (e.g., Runx2, BMP-2) and promote oxidative stress, matrix remodeling, and pyroptosis. Conversely, anti-inflammatory cytokines like IL-10 counteract calcification by suppressing inflammatory signaling, enhancing autophagy, and restoring mineral homeostasis. This review highlights the dynamic interplay between IL cytokines, metabolic dysregulation, and epigenetic modifications in VC pathogenesis. It advocates for multi-target approaches, such as combining TYK2/STAT3 inhibition with metabolic reprogramming, to disrupt pathological crosstalk. Future research must address spatiotemporal heterogeneity in IL signaling and optimize therapeutic specificity to translate mechanistic insights into clinical applications. Harnessing the IL family's dual roles offers transformative potential for mitigating VC while preserving immune integrity.

KEYWORDS

interleukin family, vascular calcification, osteogenic differentiation, inflammation, therapeutic targets

Introduction

Vascular calcification (VC), characterized by pathological calcium-phosphate deposition in arterial walls, is a hallmark of cardiovascular morbidity in chronic inflammatory diseases such as atherosclerosis, chronic kidney disease (CKD), and diabetes (1, 2). VC manifests as intimal calcification within atherosclerotic plaques or medial calcification (Mönckeberg's sclerosis), both independently predicting adverse outcomes like myocardial infarction and peripheral artery disease (3, 4). Intimal calcification destabilizes plaques, increasing rupture risk, while medial calcification reduces vascular compliance, exacerbating hypertension and heart failure (5). Patients with CKD exhibit accelerated VC progression due to phosphate metabolism imbalance and chronic inflammation. Among predialysis and late-stage CKD patients, the incidence of coronary artery calcification reaches 64%–77% (6). VC is not merely a passive degenerative process but an active cellular phenomenon involving

osteochondrogenic transdifferentiation of vascular smooth muscle cells (VSMCs) and metabolic-inflammatory crosstalk (7). Emerging evidence underscores VC as a dynamic interplay between mineral dysregulation, oxidative stress, and immune activation, positioning it as a critical therapeutic target in cardiovascular pathology (2, 8).

Chronic inflammation is central to VC pathogenesis, with pro-inflammatory cytokines of the interleukin (IL) family orchestrating osteogenic progression of VSMCs (9). IL-1β and IL-6 synergistically activate pathways such as NF-κB and STAT3, upregulating osteogenic markers (e.g., Runx2, BMP-2) and promoting matrix remodeling (9, 10). IL-17A amplifies oxidative stress via Wnt/β-catenin signaling, while IL-18 induces pyroptosis through NLRP3 inflammasome activation, releasing calcification-primed matrix vesicles (11, 12). Conversely, anti-inflammatory cytokines like IL-37 counteract calcification by suppressing NF-κB and enhancing autophagy (13). The IL family's dual roles highlight its regulatory complexity: pro-calcific members drive VSMC senescence and mineralization, while protective cytokines restore mineral homeostasis (14). Clinical studies in CKD patients have shown that elevated IL-6 levels are associated with arterial calcification. Separately, preclinical studies in urotensin-deficient mice indicate that increased IL-1β contributes to this pathology. These findings highlight the prognostic value of both cytokines (15, 16).

This review systematically examines the IL family's dual mechanisms in VC, emphasizing translational potential. We explore how IL-1β, IL-6, and IL-17A promote osteogenic transformation, while IL-10 and IL-37 mitigate calcification via metabolic reprogramming. Emerging strategies, such as IL-6 trans-signaling inhibition (sgp130Fc) and NLRP3 targeting, demonstrate efficacy in preclinical models but face challenges in clinical specificity (15, 17). By integrating molecular insights with clinical evidence, we aim to identify precision therapeutic avenues for modulating IL-driven vascular pathology, addressing

spatiotemporal heterogeneity in cytokine signaling and optimizing immune-metabolic balance (4, 18).

This Figure 1 illustrates how dendritic cells (DCs), upon interacting with naïve T cells, release multiple cytokines (e.g., IL-1β, IL-6, IL-8, IL-17A/F, IL-24, IL-29, IL-4, IL-3, IL-18, IL-37, IL-10), which regulate the osteogenic differentiation and calcification of VSMCs via signaling pathways such as BMP2/Runx2, JAK/STAT, and Wnt/β-catenin. Certain cytokines can simultaneously exhibit both pro- and anti-calcific properties, ultimately influencing the progression of VC and calcium-phosphorus homeostasis.

Molecular mechanisms of vascular calcification

Osteogenic transdifferentiation of VSMCs

The osteogenic transdifferentiation of VSMCs represents a pivotal pathological event in VC, driven by transcriptional reprogramming, metabolic remodeling, and inflammatory crosstalk. Central to this process is the activation of the master transcriptional regulator Runx2, which orchestrates the expression of osteogenic markers such as bone morphogenetic protein-2 (BMP-2) and alkaline phosphatase (ALP) (19). The synergistic interaction between BMP-2/SMAD and Wnt/β-catenin pathways amplifies calcification: BMP-2 induces SMAD1/5 phosphorylation to facilitate β-catenin nuclear translocation, while Wnt signaling enhances Runx2 transcription via KLF4-PFKFB3-mediated glycolytic reprogramming, providing bioenergetic support for phenotypic switching (20). Recent studies highlight the regulatory role of Cdon, a Wnt antagonist, which attenuates calcification by disrupting β-catenin-Runx2 binding through its Ig2 domain (21). Epigenetic modulation further refines this process, as SIRT6 deacetylates Runx2 to promote its nuclear export and proteasomal degradation, thereby suppressing osteogenic differentiation (19). Pro-inflammatory cytokines, notably IL-29 and IL-6, exacerbate calcification via JAK2/STAT3 signaling, which upregulates BMP-2 expression and enhances Runx2 transcriptional activity through STAT3-Tyr705 phosphorylation (22, 23). Metabolic perturbations, such as O-GlcNAcylation mediated by O-GlcNAc transferase (OGT), stabilize β-catenin to potentiate Wnt signaling, accelerating VSMC mineralization (24). These findings underscore a multidimensional regulatory network, identifying actionable targets—including Cdon-Ig2, SIRT6 activators, and OGT inhibitors—for therapeutic intervention in VC.

The progression of VC is governed by synergistic interactions between metabolic derangements and inflammatory signaling. Hyperphosphatemia activates monocytes via the phosphate transporter PiT-1, triggering TNF-α and IL-6 release to establish a pro-inflammatory microenvironment that accelerates VSMC osteogenic differentiation (25). Phosphate overload synergizes with IL-6 to induce senescence-associated calcification through the IL-6/sIL-6R/STAT3/p53 axis, a process partially reversible by resveratrol (26). Emerging evidence highlights the role of

leukemia inhibitory factor (LIF) in amplifying phosphate-driven calcification via the TYK2/STAT3 pathway, with TYK2 inhibition by deucravacitinib—a clinically approved immunosuppressant—significantly attenuating VC in CKD models (27). Furthermore, caspase-1 inhibitor VX-765 mitigates hyperphosphatemia-induced VSMC calcification by suppressing STAT3 phosphorylation and pyroptosis-related NLRP3/GSDMD activation (11). These findings underscore the therapeutic potential of targeting metabolic-inflammatory hubs, particularly TYK2 and STAT3 signaling nodes, to disrupt pathological crosstalk in VC.

Emerging evidence highlights the complexity of VC as a process governed by intersecting epigenetic, metabolic, and inflammatory axes. Recent studies identify SIRT6 and SIRT7 as critical epigenetic regulators that mitigate osteogenic transdifferentiation by deacetylating Runx2 and suppressing oxidative stress-induced senescence, respectively (19, 28). Metabolic dysregulation is further modulated by mitochondrial phosphate carrier (PiC), which drives calcification via ERK1/2-mTOR-dependent superoxide generation, while inhibition of PiC with butyl malonate attenuates VC in CKD model (29). The discovery of ARSE as a promoter of VSMC calcification through Wnt/β-catenin signaling underscores the role of genetic variants in VC pathogenesis, with ARSE knockdown reducing aortic mineralization (30). Therapeutic innovation is exemplified by 4-octyl itaconate (4-OI), which activates HMOX-1 to counteract oxidative stress and inflammation in calcified VSMCs (31), and Moscatilin, a natural compound targeting IL13RA2/STAT3-WNT3/β-catenin crosstalk to inhibit osteogenic differentiation (32). Additionally, calprotectin inhibition via paquinimod disrupts RAGE/TLR4 signaling, offering a translational strategy for CKD-associated VC (33). These findings collectively map a multidimensional network encompassing mitochondrial dynamics, epigenetic reprogramming, and inflammatory cascades, positioning targeted inhibition of PiC, ARSE, and calprotectin as promising avenues for clinical intervention.

Role of inflammation and oxidative stress

Pro-inflammatory mechanisms and targeting strategies in vascular calcification

IL-1β

IL-1β, a pivotal pro-inflammatory cytokine, drives VC through NLRP3 inflammasome-pyroptosis axis activation and transcriptional reprogramming of VSMCs. Under hyperphosphatemic conditions, IL-1β activates NF-κB signaling to upregulate Runx2 and BMP2 expression, promoting osteogenic transdifferentiation of VSMCs (34). Clinical studies demonstrate elevated serum IL-1β levels in CKD patients correlate with coronary calcification scores, while NLRP3 inhibition with MCC950 suppresses IL-1β secretion and attenuates calcification (35). Mechanistically, IL-1β induces gasdermin D-mediated

pyroptosis, releasing calcification-primed matrix vesicles (MVs) as nucleation sites—a process reversible by caspase-1 inhibitor VX-765 (11). Recent advances reveal a feedforward loop between IL-1β and transcription factor TCF21: TCF21 enhances IL-1β production via ERK1/2-β-catenin signaling, while IL-1β amplifies osteogenic gene transcription through STAT3 activation (9). Therapeutically, the natural compound ligustrazine mitigates coronary calcification by inhibiting caspase-3/GSDME-dependent pyroptosis and IL-1β release in murine models (36). Additionally, Elabela, an endogenous peptide, suppresses IL-1β-driven inflammation via PPAR-γ/FDX1 signaling, offering a novel regulatory axis for VC intervention (37). These findings not only delineate IL-1β's multifaceted role in VC but also validate NLRP3 inhibitors (e.g., MCC950), pyroptosis blockers (e.g., VX-765), and natural compounds as promising translational strategies targeting IL-1β signaling.

IL-6

IL-6 emerges as a pivotal mediator in VC, driving osteogenic transdifferentiation of VSMCs via the JAK2/STAT3 signaling axis. Clinical studies demonstrate that elevated serum IL-6 levels in CKD patients correlate with coronary artery calcification (CAC) progression and cardiovascular mortality, with high IL-6 tertiles exhibiting a 2.2-fold increased risk of death (38). Mechanistically, IL-6 induces STAT3-Tyr705 phosphorylation, promoting Runx2 nuclear translocation and BMP2 upregulation while suppressing osteoprotegerin (OPG) secretion, thereby disrupting the mineralization balance (22). Hyperphosphatemia exacerbates this process by activating PiT-1 receptors on monocytes, triggering IL-6 release and establishing a self-reinforcing inflammatory-calcific loop (25). Recent advances reveal a feedforward mechanism involving transcription factor TCF21, which enhances IL-6 expression via ERK1/2-β-catenin signaling, while IL-6 reciprocally amplifies STAT3 activation to potentiate osteogenic gene transcription (9). Therapeutic interventions targeting this axis show promise: JAK inhibitors like tofacitinib attenuate aortic calcification by blocking IL-6R/gp130 signaling (39), while the natural compound Ptd-1 suppresses IL-6/STAT3 crosstalk and ERK/β-catenin interactions to reduce VSMC mineralization (40). Additionally, the SGLT2 inhibitor empagliflozin mitigates IL-6-driven inflammation through AMPK/Nrf2 pathway activation, highlighting its potential in CKD-associated VC (41). These findings underscore IL-6 as a multidimensional therapeutic target, with combinatorial strategies addressing both inflammatory and metabolic pathways offering novel avenues for clinical translation.

IL-6 inhibitors, exemplified by tocilizumab, demonstrate significant efficacy in managing various inflammatory conditions but carry notable risks. In polyarticular or systemic juvenile idiopathic arthritis (pJIA/sJIA), long-term subcutaneous tocilizumab maintained disease control, achieving inactive disease in up to 92% of sJIA patients; however, serious adverse events, including infections, occurred in 13.6% of pJIA and 13.2% of sJIA patients (42). For refractory Takayasu arteritis, tocilizumab provided a substantial steroid-sparing effect, with 46.4% of patients reducing glucocorticoid doses to less than half their

pre-study relapse dose, alongside improved quality-of-life metrics and no new safety signals during extended treatment (43). In giant cell arteritis, intravenous tocilizumab (6–7 mg/kg) sustained remission without flares, though 16.7% of patients experienced serious adverse events (44). These findings underscore its potent anti-inflammatory effects balanced against infection-related risks.

IL-8

IL-8, a potent chemoattractant cytokine, accelerates VC by orchestrating neutrophil infiltration and matrix metalloproteinase-9 (MMP-9)-mediated degradation of calcification inhibitors. In CKD, elevated serum IL-8 levels correlate with VC severity, driven by hyperphosphatemia-induced endothelial cell (EC) secretion of IL-8, which suppresses osteopontin (OPN) expression in VSMCs and compromises intrinsic anti-calcific defenses (45). Mechanistically, phosphate overload activates the JAK-STAT pathway in VSMCs, triggering IL-8 release and MMP-9 activation to degrade matrix Gla protein (MGP), thereby facilitating hydroxyapatite deposition (39). Clinically, the phosphate binder sucroferric oxyhydroxide (SO) reduces serum IL-8 levels and attenuates calciprotein particle (CPP)-mediated endothelial inflammation in dialysis patients (46). Genetic interventions, such as GALNT3 overexpression, mitigate VC by O-GalNAc glycosylation of TNFR1 to inhibit NF-κB signaling and downregulate IL-8 expression (10). Furthermore, neutralization of IL-8 via monoclonal antibodies reverses the pro-calcific effects of uremic toxins like lanthionine, highlighting IL-8's role as a mediator of toxin-driven mineralization (47). These findings position IL-8-CXCR1/2 axis inhibition and upstream JAK-STAT/NF-κB modulation as promising strategies to disrupt inflammation-mediated calcification cascades.

IL-17

The IL-17 family cytokines, particularly IL-17A and IL-17F, promote VC by amplifying oxidative stress and inflammatory cascades. *In vitro* studies reveal that IL-17A enhances aortic calcification in a dose-dependent manner, primarily through inducing reactive oxygen species (ROS) and activating the Wnt/β-catenin pathway, which drives osteogenic differentiation of VSMCs (12). In chronic inflammatory skin disorders such as psoriasis and atopic dermatitis, overexpression of IL-17A/F exacerbates endothelial dysfunction and arterial stiffness, thereby accelerating atherosclerosis (45). Animal studies demonstrate a dose-dependent pro-calcific effect of IL-17A in murine ex vivo aortic calcification models. Intriguingly, another study reported that IL-17A requires co-application with IP-10 (CXCL10) to promote coronary artery calcification *in vitro*, suggesting a potential role of coordinated regulation by endothelial or inflammatory cells (48). Neutralizing IL-17A reduces neutrophil infiltration and aortic oxidative stress, restoring vascular elasticity (49). Clinically, IL-17 inhibitors (e.g., secukinumab) ameliorate both psoriatic lesions and atherosclerotic plaque burden, highlighting their potential cardioprotective effects (50). Collectively, targeting IL-17 receptors and downstream JAK/STAT signaling represents a promising therapeutic strategy to mitigate calcification associated with chronic inflammatory and metabolic disorders.

IL-24

IL-24, a pro-inflammatory cytokine, has recently emerged as a potent driver of VC through multi-pathway activation. Kawada et al. first demonstrated that iron overload synergizes with TNF-α to upregulate IL-24 expression in human aortic smooth muscle cells (HASMCs), inducing calcification that is reversible by anti-IL-24 antibodies, establishing IL-24 as a critical mediator of iron-dependent mineralization. Mechanistically, IL-24 activates the STAT3 signaling pathway, upregulating osteogenic markers Runx2 and BMP-2, while enhancing the Wnt/β-catenin axis to promote osteochondrogenic transdifferentiation of VSMCs (51). On this basis, studies have shown that the expression of osteogenic markers is increased in the aortic tissue of iron overload rats, and the increase of IL-24 may play a role in the process of iron promoting calcification (52). Clinically, IL-24 is overexpressed in calcified vessels of CKD patients, correlating positively with serum iron levels and inflammatory markers (e.g., hsCRP), suggesting its potential as a biomarker for iron dysregulation-associated calcification. However, the spatiotemporal specificity of IL-24 receptor signaling in atherosclerotic calcification remains poorly defined, and targeted therapies face challenges such as receptor promiscuity and inefficient nanoparticle delivery across calcified plaques.

IL-24 engages in bidirectional crosstalk with classical inflammatory and metabolic pathways through context-dependent mechanisms. In Th17 cells, IL-17A induces IL-24 via NF-κB activation, creating an autocrine negative feedback loop that suppresses GM-CSF and IL-17F production to limit immunopathology (53). Paradoxically, IL-24 itself promotes mitochondrial STAT3 accumulation through interaction with Grim19 (a complex I component), driving IL-10 production that further constrains Th17 pathogenicity (54). In stromal compartments, IL-17A directly upregulates IL-24 in skin fibroblasts and keratinocytes, amplifying keratinocyte proliferation in psoriasis through coordinated induction of IL-19/IL-24 (55). Hypoxia integrates with this signaling via HIF-1α stabilization, which converges with STAT3 activation in epithelial progenitors to induce IL-24 during tissue repair (56). Pathologically, IL-24 exacerbates renal fibrosis by inducing TGF-β1, PDGF-B, and CTGF in tubular cells, while IL-20 receptor beta (IL-20RB) deficiency attenuates fibrotic gene expression in obstructive nephropathy (57). This positions IL-24 as a nodal regulator bridging immune activation, metabolic stress, and fibrocalcific responses.

IL-29

IL-29, a member of the type III interferon family, has recently emerged as a key driver of VC through activation of the JAK2/STAT3/BMP2 signaling axis. Previous studies have shown that IL-29 inhibits osteoclastogenesis by activating the STAT signaling pathway, blocking NF-κB activation and NFATc1 translocation, and inhibiting downstream osteoclastogenic gene expression (58). According to a recent study reveals elevated IL-29 expression in calcified carotid arteries of patients with coronary artery disease or CKD, where it positively correlates with bone morphogenetic

protein 2 (BMP2) level (23). Mechanistically, IL-29 binds to its specific receptor IL-28Rα, triggering JAK2/STAT3 pathway activation, which induces osteogenic transdifferentiation of VSMCs and accelerates hydroxyapatite deposition. *in vitro* and ex vivo studies demonstrate that pharmacological inhibition of IL-28Rα or JAK2 significantly attenuates VSMC calcification and suppresses BMP2 expression, highlighting the therapeutic potential of targeting the IL-29/IL-28Rα axis to disrupt calcification cascades in vascular pathologies.

IL-29 mediates bidirectional regulation through crosstalk with canonical inflammatory pathways. In the osteoarthritis microenvironment, IL-29 significantly enhances synovial fibroblast production of IL-1β, IL-6, and MMP-3 through MAPK/NF-κB pathways (but not JAK-STAT), accelerating cartilage degradation (59). This tissue-specific regulatory pattern demonstrates IL-29's capacity to selectively engage STAT or MAPK/NF-κB pathways according to microenvironmental context, enabling precise immunomodulation balancing immune homeostasis and inflammatory responses.

Anti-calcification mechanisms and therapeutic targeting in vascular pathology

IL-10

IL-10, a pivotal anti-inflammatory cytokine, exerts inhibitory effects on VC by suppressing pro-inflammatory signaling and modulating mineralization homeostasis. In Apolipoprotein E knockout (ApoE$^{-/-}$) mice, exogenous inorganic pyrophosphate (PPi) supplementation significantly elevates serum IL-10 levels while reducing pro-calcific cytokines such as TNF-α and IL-6, thereby attenuating atheromatous calcification progression (60). Mechanistically, IL-10 activates the STAT3/SOCS3 axis to inhibit NF-κB-driven transcription, downregulating osteogenic differentiation markers (e.g., Runx2, BMP2) in VSMCs (61). Preclinical studies further demonstrate that T cell-mediated immunomodulation (e.g., mCRAMP immunization) enhances IL-10 secretion by CD8$^+$ T cells, reducing atherosclerotic plaque calcification incidence from 56% to 0% ($p = 0.003$) and fostering an anti-inflammatory microenvironment (62). Additionally, IL-10 upregulates Klotho expression, counteracting FGF23 signaling to preserve calcium-phosphate equilibrium and inhibit hydroxyapatite crystallization. These findings underscore the therapeutic potential of IL-10-targeted strategies—including recombinant IL-10 administration or PPi mimetics—to disrupt both inflammatory and mineralization cascades in VC.

Dual roles in vascular calcification: context-dependent mechanisms and therapeutic implications

IL-4 and Il-13

IL-4 and IL-13, as Th2 cytokines, exhibit spatiotemporal dual roles in VC through microenvironment-dependent mechanisms. A 2023 study demonstrated that eosinophil-derived cationic proteins (e.g., ECP) directly promote vascular smooth muscle cell (VSMC) osteogenic differentiation via the BMPR-1A/1B-Smad1/5/8-Runx2 axis, while IL-4 and IL-13 showed no direct pro-calcific effects in this process (63). Conversely, in diabetic models, IL-13 drives VSMC osteogenic transdifferentiation through the CHI3L1-IL-13Ra2-JAK1-STAT3 pathway, with H3K18 lactylation amplifying this signal to increase calcification (64). Paradoxically, IL-4 correlates with hand VC severity and all-cause mortality in rheumatoid arthritis (RA) patients (HR = 1.41, 95% CI 1.12, 1.78; $P = 0.004$) (65), yet short-term IL-4 exposure upregulates osteoprotegerin (OPG) via STAT6 to inhibit calcification, whereas chronic exposure induces Cbfa1-mediated osteogenic differentiation (66). Furthermore, alternative macrophages (M2) in calcified plaques express elevated IL-4 receptors and suppress osteoclastic activity via IL-10 secretion (67), while IL-13 promotes calcification through crosstalk between WNT3/β-catenin and STAT3 pathways (32). This functional dichotomy arises from metabolic heterogeneity: hyperlactate diabetic microenvironments epigenetically enhance IL-13 signaling, whereas chronic inflammation balances IL-4-driven fibrotic and anti-calcific responses via M2 polarization. Therapeutic strategies targeting IL-13Ra2 antagonism or H3K18 lactylation inhibition may offer precision interventions to mitigate VC progression.

IL-18

IL-18, a pro-inflammatory cytokine, exhibits context-dependent dual roles in VC, with its effects intricately linked to microenvironmental signaling crosstalk. Clinical studies demonstrate a strong positive correlation between serum IL-18 levels and coronary artery calcium scores (r = 0.91, $p < 0.001$), mediated via TRPM7 channel activation and ERK1/2 signaling, which upregulate osteogenic markers Runx2 and BMP-2 in VSMCs (68, 69). In CKD, IL-18 exacerbates aortic calcification through p38 MAPK pathway activation, correlating with increased aortic pulse wave velocity (aoPWV) (29, 70). Mechanistically, IL-18 enhances VSMC osteochondrogenic transdifferentiation via SGK1-dependent pathways, while SGK1 inhibition attenuates calcification (71). Furthermore, IL-18 amplifies pyroptosis by activating the NLRP3/caspase-1/GSDMD axis, fostering a pro-calcific microenvironment (11, 36). Paradoxically, IL-18-driven inflammatory responses may indirectly suppress calcification by inducing autophagic clearance of apoptotic bodies (72). Notably, Elabela counteracts IL-18-associated cuproptosis and VC by activating PPAR-γ/FDX1 signaling (37). These paradoxical effects underscore IL-18's spatiotemporal duality: while predominantly pro-calcific via TRPM7, SGK1, and pyroptotic pathways, its inflammatory milieu may trigger compensatory anti-calcific mechanisms. Targeting downstream effectors (e.g., TRPM7 inhibitors, SGK1 antagonists) rather than IL-18 itself may optimize therapeutic precision, balancing anti-inflammatory efficacy with calcification mitigation.

IL-37

IL-37, a unique anti-inflammatory member of the IL-1 cytokine family, emerging evidence highlights IL-37's dual role in

TABLE 1 Role of IL family in the process of VC.

IL Family member	Role in VC	Mechanistic pathways	Clinical relevance	Cited authors
IL-1β	Pro-calcific	Activates NLRP3 inflammasome-pyroptosis (gasdermin D); upregulates Runx2/BMP2 via NF-κB; TCF21 feedforward loop	Elevated in CKD patients; NLRP3 inhibition (MCC950) and ligustrazine reduce calcification	(9, 11, 34–37)
IL-6	Pro-calcific	JAK2/STAT3 activation; TCF21-ERK1/2-β-catenin synergy; suppresses OPG	High IL-6 tertiles predict 2.2-fold mortality risk in CKD; JAK inhibitors (tofacitinib) show efficacy	(9, 22, 25, 38–44)
IL-8	Pro-calcific	JAK-STAT-mediated MMP-9 activation; GALNT3 overexpression inhibits NF-κB	Phosphate binders (sucroferric oxyhydroxide) reduce IL-8 in dialysis patients	(10, 39, 45–47)
IL-17A/F	Pro-calcific	Wnt/β-catenin & ROS pathways; synergizes with IP-10 (CXCL10) for coronary calcification	IL-17 inhibitors (secukinumab) reduce plaque burden in psoriasis	(12, 45, 48–50)
IL-24	Pro-calcific	STAT3/Wnt activation; iron overload synergizes with TNF-α	Overexpressed in CKD calcified vessels; correlates with serum iron/hsCRP	(51–57)
IL-29	Pro-calcific	JAK2/STAT3/BMP2 axis via IL-28Rα receptor	Elevated in CAD/CKD carotid arteries	(23, 58, 59)
IL-10	Anti-calcific	STAT3/SOCS3-mediated NF-κB suppression; Klotho upregulation	Exogenous pyrophosphate elevates IL-10, reducing calcification in ApoE$^{-/-}$ mice	(60–62)
IL-4/IL-13	Dual role	IL-13: CHI3L1-IL-13Ra2-JAK1-STAT3; IL-4: STAT6-OPG transient inhibition	IL-4 correlates with hand VC severity in RA (HR = 1.41 mortality)	(63–67)
IL-18	Dual role	TRPM7/ERK1/2 & SGK1 pathways; NLRP3/caspase-1/GSDMD pyroptosis	Serum IL-18 correlates with coronary calcium scores (r = 0.91); Elabela counteracts	(11, 29, 36, 37, 68–72)
IL-37	Dual role	Inhibits EndMT via Notch1/p38 MAPK-NF-κB; Smad3 binding in ox-LDL stress	Elevated in severe CAC patients; paradoxically linked to hsCRP	(13, 73–76)
IL-33	Indirect pro-calcific	sST2 (decoy receptor) correlates with atherosclerosis; co-localizes with NLRP3	IL-33/ST2l axis implicated in plaque destabilization	(77–81)

HR, indicates hazard ratio; and RR, relative risk.

VC, balancing anti-inflammatory protection with compensatory biomarker elevation in advanced disease. Preclinical studies demonstrate IL-37 suppresses pro-calcific pathways by inhibiting endothelial-to-mesenchymal transition (EndMT) through Notch1/p38 MAPK-NF-κB signaling, thereby reducing smooth muscle cell activation and extracellular matrix remodeling in coronary artery model (73). This aligns with findings that IL-37 attenuates ox-LDL-induced endothelial osteogenic differentiation and endoplasmic reticulum stress via Smad3 binding, suggesting direct anti-calcification mechanisms (74). However, clinical observations reveal elevated plasma IL-37 levels in patients with severe coronary artery calcification (CAC), showing positive correlations with Agatston scores and inflammatory markers like hsCRP (75, 76). This paradox may reflect IL-37's compensatory upregulation in chronic inflammation, as evidenced by its predominant expression in macrophages and VSMCs within calcified lesions. While IL-37 demonstrates therapeutic potential in mitigating early calcification drivers like EndM (73), its sustained elevation in advanced disease might indicate either a failed protective response or biomarker utility for monitoring calcification progression (13). These findings underscore the need for phase-specific evaluation of IL-37's role in VC pathophysiology.

Roles that may be overlooked

IL-33

IL-33, a pro-inflammatory cytokine of the IL-1 family, although direct evidence linking IL-33 to VC remains limited, emerging insights into its receptor ST2 suggest potential regulatory roles in calcification-related pathways. The IL-33/ST2 axis has been implicated in fibrocalcific processes, as soluble ST2 (sST2) correlates with coronary artery calcium scores and serves as a biomarker for atherosclerosis severity (77). In carotid atherosclerotic plaques, transmembrane ST2l overexpression on macrophages in symptomatic patients suggests its involvement in plaque destabilization, potentially creating a microenvironment conducive to calcification (78). Notably, IL-33 binding to ST2l exhibits cardioprotective effects by counteracting fibrosis in rheumatic valvular disease, while sST2 acts as a decoy receptor that exacerbates fibrotic remodeling—a precursor to calcification (79). This dual receptor dynamic may influence VC progression, particularly through macrophage-mediated inflammatory pathways. In peripheral arterial disease, IL-33 co-localizes with NLRP3 inflammasome components in calcified vessels, implicating IL-33-associated inflammation in calcification initiation (80). However, the therapeutic potential of modulating this axis remains unclear, as ACE inhibitors reduce sST2 levels but show limited correlation with calcification regression in clinical trials (81). These findings collectively suggest IL-33 may exert context-dependent effects on VC through receptor-specific signaling and inflammatory crosstalk, warranting further mechanistic investigation.

This Figure 2 illustrates the interplay between inflammatory cytokines and osteogenic/chondrogenic transdifferentiation in VC. Pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF-α) activate NF-κB and MAPK pathways, driving VSMCs toward an osteoblast-like phenotype and promoting calcium phosphate deposition. Key regulatory factors (e.g., OPG/RANKL, MGP) modulate these processes, either facilitating or inhibiting calcification. Exogenous stimuli (e.g., oxidative stress, dyslipidemia) exacerbate this cycle, leading to vascular dysfunction and disease progression. This model highlights the inflammatory-calcification crosstalk and potential therapeutic targets.

FIGURE 1
Schematic diagram illustrating the dual roles of IL family members in promoting or inhibiting VC.
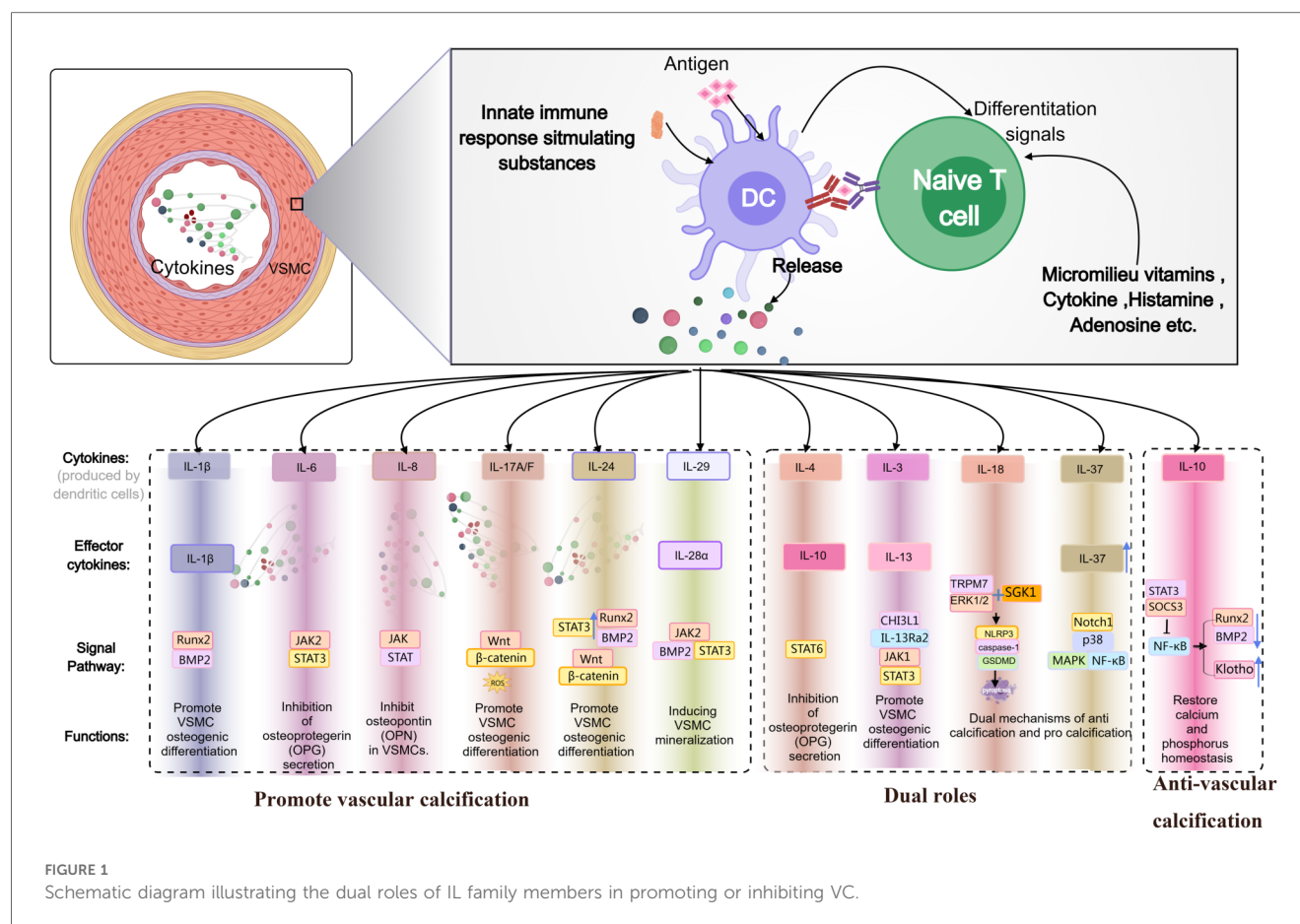
This Table 1 briefly outlines the pro-calcific or anti-calcific roles of various ILs in the VC process, along with their principal molecular pathways (e.g., BMP2/Runx2, JAK/STAT, Wnt/β-catenin, and the NLRP3 inflammasome) and clinical relevance. Reference numbers are provided for further consultation.

Prospects and challenges

The IL family exhibits marked functional heterogeneity in VC, dynamically regulated by microenvironmental cues. Functional heterogeneity within vascular microenvironments critically regulates calcification processes through dynamic interactions between cellular components and extracellular matrix (ECM) signaling. Single-cell proteomic profiling reveals that smooth muscle cell (SMC) phenotypic switching under altered shear stress involves Notch1/p38 MAPK-NF-κB signaling, with IL-37 suppressing pro-inflammatory EndMT to mitigate calcification (73). The ECM composition directly modulates SMC behavior, as demonstrated by reduced LTBP1 expression in unstable atherosclerotic plaques, which promotes SMC calcification through disrupted TGF-β signaling (82). NLRP3 inflammasome activation in macrophages adjacent to calcified areas creates a pro-osteogenic niche via IL-1β and TNF-α secretion, with pharmacological inhibition of NLRP3 attenuating VC in CKD

models (35, 80). Microenvironmental phosphate overload induces SMC pyroptosis through potassium efflux-dependent NLRP3 activation, independent of canonical IL-1β signaling (83). Dynamic co-culture models reveal endothelial-SMC crosstalk amplifies calcification through TGF-β1/SIRT1 axis modulation, highlighting microenvironment-dependent phenotypic plasticity (84). Exosomal miR-302d-5p from endothelial cells suppresses SMC osteogenesis via Wnt3 inhibition in a m6A-dependent manner, illustrating epigenetic regulation within the vascular wall microenvironment (85). These findings underscore the spatial and temporal complexity of microenvironmental regulation in VC.

Precision therapeutic strategies

Innovations in nanodelivery systems

Recent advancements in nanodelivery systems have significantly enhanced the targeting efficacy and therapeutic outcomes for VC. For calcific aortic valve disease (CAVD), Chen et al. developed PAR2-targeted magnetic nanocargoes that achieved dual-active targeting through PAR2-specific hexapeptides and magnetic field navigation, effectively suppressing osteogenic differentiation of valvular interstitial cells and alleviating calcification in *Ldlr(-/-)*mice (86). In abdominal aortic aneurysm (AAA) therapy, Hu et al. engineered
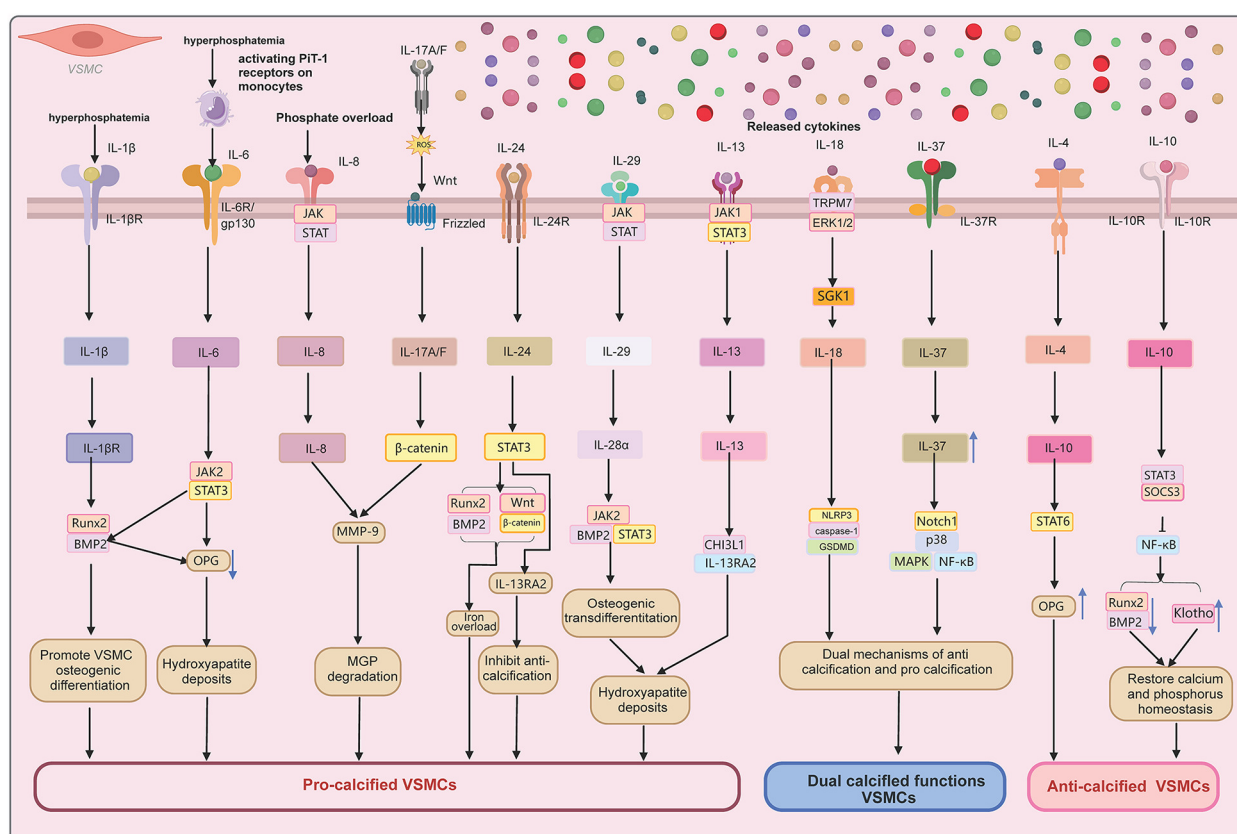
FIGURE 2
Molecular pathways of IL cytokines in VC.

α-cyclodextrin-based LaCD nanoparticles, which mitigated neutrophilic inflammation and NETosis, significantly improving vascular structural integrity. Functionalization with alendronate further enhanced targeting capability and therapeutic efficacy (87). For diabetic VC, Li et al. designed mitochondria-targeted nanodrugs (T4O@TPP/PEG-PLGA) that utilized TPP ligands for precise mitochondrial delivery, reducing oxidative stress induced by hyperglycemia and restoring mitochondrial morphology in animal models (88). Additionally, Mo et al. reported a dual-targeting virus-like nanocage (EVMS@R-HNC) that bound integrin αvβ3 on macrophages and smooth muscle cells, synergistically inhibiting inflammatory microenvironment dysregulation while preserving contractile function, offering a multifaceted solution for complex vascular pathologies (89). Zhang et al. further demonstrated through spatial conformation analysis that cyclic RGD exhibited superior αvβ3 integrin binding specificity compared to linear RGD, providing molecular insights for optimizing targeted nanocarrier design (90).

But nanocarriers face significant challenges in targeting efficiency and biosafety. PEGylated and CD-47-functionalized magnetic nanoporous silica nanoparticles paradoxically accumulated primarily in the liver and spleen (86% of administered dose) rather than infected implant sites, with severe inflammation-driven off-target distribution in murine models (91). Polymeric PLGA-PEG nanoparticles induced sublethal

hepatotoxicity *in vitro*, where redox-responsive variants (RR-NPs) triggered reactive oxygen species (ROS) surges and impaired albumin/urea production, while non-redox-responsive nanoparticles (nRR-NPs) additionally caused DNA damage in hepatocytes despite comparable cellular uptake (92). These findings underscore unresolved targeting inaccuracies and organ-specific toxicity risks.

Potential for multi-target synergistic intervention

Multi-target synergistic strategies demonstrate promising potential in addressing the multifactorial pathogenesis of VC. Aierken et al. identified that inhibition of iron transporters Slc39a14/Slc39a8 alleviated ferroptosis in VSMCs by mitigating iron overload, revealing novel targets at the intersection of metabolism and oxidative stress (93). Chen et al. demonstrated that oleoylethanolamide (OEA) suppressed STING1-mediated mitochondrial DNA damage and cellular senescence via Nrf2 activation while modulating the PPARα-dependent autophagy-ferroptosis axis, achieving multi-dimensional anti-calcification effects in diabetic models (94). Shen et al. reported that the natural compound thonningianin A activated L-type calcium channels to induce autophagy, downregulating RUNX2/BMP2 expression, and validated its synergistic effects via Cav1.2 α1C targeting in type 2 diabetes mellitus (T2DM) models (95). Furthermore, Sun et al. discovered that TFEB activation

enhanced autophagic flux and the Nrf2 antioxidant system, suppressing diabetic VC through the POSTN-TGFβR1-YAP/TAZ pathway, highlighting the integration of transcriptional regulatory networks for multi-target intervention (96). These studies collectively suggest that coordinated modulation of metabolic dysregulation, oxidative stress, and epigenetic remodeling may form the cornerstone of future precision therapies.

Clinical challenges in balancing anti-inflammatory and immunosuppressive risks

The central role of anti-inflammatory therapy in managing chronic inflammatory diseases necessitates a delicate balance with immunosuppression-related risks. Datta-Mannan et al. reported that the oral IL-17A small-molecule inhibitor LY3509754 significantly reduced IL-17A activity but induced lymphocytic hepatitis and drug-induced liver injury (DILI) in high-dose cohorts (400–1,000 mg), underscoring the imperative for rigorous hepatic safety monitoring when targeting the IL-17 pathway (97). In phase III trials for hidradenitis suppurativa, Kimball et al. demonstrated that the dual IL-17A/F inhibitor bimekizumab achieved a 52% HiSCR50 response rate, yet elevated risks of oral candidiasis and opportunistic infections highlighted the need for immune status-based dosing optimization (98). A Nordic multicenter study by Glintborg et al. comparing secukinumab with TNF inhibitors revealed doubled hospitalization rates for infections with secukinumab (IR 5.0 vs. 2.3/100 patient-years for adalimumab), though attenuated after confounding adjustment, advocating personalized infection risk stratification (99). Azadeh et al. meta-analysis of IL-17 inhibitors in ankylosing spondylitis identified significantly increased mucosal/opportunistic infection risks (RD = 0.09, p = 0.02), recommending adjunct antifungal prophylaxis (100). Smolen et al. found the IL-6 inhibitor olokizumab non-inferior to adalimumab in rheumatoid arthritis but associated with higher infection rates (~70%), emphasizing the need to reconcile target specificity with systemic immunosuppression (101). Collectively, precision biomarker stratification (e.g., IL-23/Th17 axis activity), dynamic immune monitoring, and stepwise dose titration emerge as critical strategies to optimize the anti-inflammatory-immunosuppression risk-benefit ratio.

Conclusion

The roles of IL family members in VC are complex and diverse. They can either exacerbate the calcification process by promoting inflammation and cell transformation or protect against it by modulating immune responses and reducing oxidative stress. Given the crucial role of IL signaling pathways in calcification, targeting IL family signaling pathways holds significant therapeutic potential. Inhibiting pro-calcification cytokines or

activating protective cytokine pathways could provide novel interventions for VC-related diseases. However, to achieve this goal, further in-depth research is needed to better understand the mechanisms of action, signaling networks, and relationships of IL family members with VC, to develop more effective targeted strategies for clinical treatment.

Author contributions

YZ: Investigation, Data curation, Writing – review & editing, Writing – original draft, Visualization, Conceptualization. HL: Resources, Writing – original draft, Investigation, Writing – review & editing. YG: Writing – review & editing, Project administration, Writing – original draft, Validation, Supervision, Funding acquisition.

Funding

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that Generative AI was used in the creation of this manuscript. I declare that AI is only used for grammar correction and initial polishing.

Publisher's note

References

1. St Hilaire C. Medial arterial calcification: a significant and independent contributor of peripheral artery disease. *Arterioscler Thromb Vasc Biol*. (2022) 42(3):253–60. doi: 10.1161/ATVBAHA.121.316252

2. Zhang H, Li G, Yu X, Yang J, Jiang A, Cheng H, et al. Progression of vascular calcification and clinical outcomes in patients receiving maintenance dialysis. *JAMA Netw Open*. (2023) 6(5):e2310909. doi: 10.1001/jamanetworkopen.2023.10909

3. Shioi A, Morioka T, Shoji T, Emoto M. The inhibitory roles of vitamin K in progression of vascular calcification. *Nutrients*. (2020) 12(2):583. doi: 10.3390/nu12020583

4. Sutton NR, Malhotra R, St Hilaire C, Aikawa E, Blumenthal RS, Gackenbach G, et al. Molecular mechanisms of vascular health: insights from vascular aging and calcification. *Arterioscler Thromb Vasc Biol*. (2023) 43(1):15–29. doi: 10.1161/ATVBAHA.122.317332

5. Lanzer P, Hannan FM, Lanzer JD, Janzen J, Raggi P, Furniss D, et al. Medial arterial calcification. JACC state-of-the-art review. *J Am Coll Cardiol*. (2021) 78(11):1145–65. doi: 10.1016/j.jacc.2021.06.049

6. Hutcheson JD, Goettsch C. Cardiovascular calcification heterogeneity in chronic kidney disease. *Circ Res*. (2023) 132(8):993–1012. doi: 10.1161/CIRCRESAHA.123.321760

7. Lin X, Shan SK, Xu F, Zhong JY, Wu F, Duan JY, et al. The crosstalk between endothelial cells and vascular smooth muscle cells aggravates high phosphorus-induced arterial calcification. *Cell Death Dis*. (2022) 13(7):650. doi: 10.1038/s41419-022-05064-5

8. Lee SJ, Lee IK, Jeon JH. Vascular calcification-new insights into its mechanism. *Int J Mol Sci*. (2020) 21(8):2685. doi: 10.3390/ijms21082685

9. Zhao XK, Zhu MM, Wang SN, Zhang TT, Wei XN, Wang CY, et al. Transcription factor 21 accelerates vascular calcification in mice by activating the IL-6/STAT3 signaling pathway and the interplay between VSMCs and ECs. *Acta Pharmacol Sin*. (2023) 44(8):1625–36. doi: 10.1038/s41401-023-01077-8

10. Wang YK, Li SJ, Zhou LL, Li D, Guo LW. GALNT3 protects against vascular calcification by reducing oxidative stress and apoptosis of smooth muscle cells. *Eur J Pharmacol*. (2023) 939:175447. doi: 10.1016/j.ejphar.2022.175447

11. Duan Y, Peng Z, Zhong S, Zhou P, Huang H, Li J, et al. VX-765 ameliorates CKD VSMC calcification by regulating STAT3 activation. *Eur J Pharmacol*. (2023) 945:175610. doi: 10.1016/j.ejphar.2023.175610

12. Hiramatsu-Asano S, Mukai T, Akagi T, Uchida HA, Fujita S, Nakano K, et al. IL-17A promotes vascular calcification in an ex vivo murine aorta culture. *Biochem Biophys Res Commun*. (2022) 604:83–7. doi: 10.1016/j.bbrc.2022.03.051

13. McCurdy S, Yap J, Irei J, Lozano J, Boisvert WA. IL-37-a putative therapeutic agent in cardiovascular diseases. *Qjm*. (2022) 115(11):719–25. doi: 10.1093/qjmed/hcab011

14. Qian Y, Li L, Sun Z, Liu J, Yuan W, Wang Z. A multi-omics view of the complex mechanism of vascular calcification. *Biomed Pharmacother*. (2021) 135:111192. doi: 10.1016/j.biopha.2020.111192

15. Alesutan I, Luong TTD, Schelski N, Masyout J, Hille S, Schneider MP, et al. Circulating uromodulin inhibits vascular calcification by interfering with pro-inflammatory cytokine signalling. *Cardiovasc Res*. (2021) 117(3):930–41. doi: 10.1093/cvr/cvaa081

16. Kamińska J, Stopiński M, Mucha K, Jędrzejczak A, Gołębiowski M, Niewczas MA, et al. IL 6 but not TNF is linked to coronary artery calcification in patients with chronic kidney disease. *Cytokine*. (2019) 120:9–14. doi: 10.1016/j.cyto.2019.04.002

17. Rose-John S, Jenkins BJ, Garbers C, Moll JM, Scheller J. Targeting IL-6 trans-signalling: past, present and future prospects. *Nat Rev Immunol*. (2023) 23(10):666–81. doi: 10.1038/s41577-023-00856-y

18. Villa-Bellosta R. Vascular calcification: key roles of phosphate and pyrophosphate. *Int J Mol Sci*. (2021) 22(24):13536. doi: 10.3390/ijms222413536

19. Li W, Feng W, Su X, Luo D, Li Z, Zhou Y, et al. SIRT6 protects vascular smooth muscle cells from osteogenic transdifferentiation via Runx2 in chronic kidney disease. *J Clin Invest*. (2022) 132(1). doi: 10.1172/JCI150051

20. Zhang X, Zheng B, Zhao L, Shen J, Yang Z, Zhang Y, et al. KLF4-PFKFB3-driven glycolysis is essential for phenotypic switching of vascular smooth muscle cells. *Commun Biol*. (2022) 5(1):1332. doi: 10.1038/s42003-022-04302-y

21. Ahn BY, Jeong Y, Kim S, Zhang Y, Kim SW, Leem YE, et al. Cdon suppresses vascular smooth muscle calcification via repression of the wnt/Runx2 axis. *Exp Mol Med*. (2023) 55(1):120–31. doi: 10.1038/s12276-022-00909-7

22. Ballester-Servera C, Cañes L, Alonso J, Puertas-Umbert L, Vázquez-Sufuentes P, Taurón M, et al. Upregulation of NOR-1 in calcified human vascular tissues: impact on osteogenic differentiation and calcification. *Transl Res*. (2024) 264:1–14. doi: 10.1016/j.trsl.2023.09.004

23. Hao N, Zhou Z, Zhang F, Li Y, Hu R, Zou J, et al. Interleukin-29 accelerates vascular calcification via JAK2/STAT3/BMP2 signaling. *J Am Heart Assoc*. (2023) 12(1):e027222. doi: 10.1161/JAHA.122.027222

24. Xu L, Liu B, Ma H, Qi E, Ma J, Chang T, et al. O-GlcNAc transferase promotes vascular smooth muscle calcification through modulating wnt/β-catenin signaling. *Faseb j*. (2024) 38(24):e70271. doi: 10.1096/fj.202401649RR

25. Ding M, Zhang Q, Zhang M, Jiang X, Wang M, Ni L, et al. Phosphate overload stimulates inflammatory reaction via PiT-1 and induces vascular calcification in uremia. *J Ren Nutr*. (2022) 32(2):178–88. doi: 10.1053/j.jrn.2021.03.008

26. Xu D, Zeng F, Han L, Wang J, Yin Z, Lv L, et al. The synergistic action of phosphate and interleukin-6 enhances senescence-associated calcification in vascular smooth muscle cells depending on p53. *Mech Ageing Dev*. (2019) 182:111124. doi: 10.1016/j.mad.2019.111124

27. Alesutan I, Razazian M, Luong TTD, Estepa M, Pitigala L, Henze LA, et al. Augmentative effects of leukemia inhibitory factor reveal a critical role for TYK2 signaling in vascular calcification. *Kidney Int*. (2024) 106(4):611–24. doi: 10.1016/j.kint.2024.07.011

28. Yu H, Xie Y, Lan L, Ma S, Mok SWF, Wong IN, et al. Sirt7 protects against vascular calcification via modulation of reactive oxygen species and senescence of vascular smooth muscle cells. *Free Radic Biol Med*. (2024) 223:30–41. doi: 10.1016/j.freeradbiomed.2024.07.021

29. Kiu Weber CI, Duchateau-Nguyen G, Solier C, Schell-Steven A, Hermosilla R, Nogoceke E, et al. Cardiovascular risk markers associated with arterial calcification in patients with chronic kidney disease stages 3 and 4. *Clin Kidney J*. (2014) 7(2):167–73. doi: 10.1093/ckj/sfu017

30. de Vries PS, Conomos MP, Singh K, Nicholson CJ, Jain D, Hasbani NR, et al. Whole-genome sequencing uncovers two loci for coronary artery calcification and identifies ARSE as a regulator of vascular calcification. *Nat Cardiovasc Res*. (2023) 2(12):1159–72. doi: 10.1038/s44161-023-00375-y

31. Dong Q, Liu F, Zhu J, Li M, Chen A, Feng L, et al. 4-Octyl itaconate inhibits vascular calcification partially via modulation of HMOX-1 signaling. *Eur J Pharmacol*. (2024) 985:177122. doi: 10.1016/j.ejphar.2024.177122

32. Zhang T, Zhu M, Ma J, Liu Z, Zhang Z, Chen M, et al. Moscatilin inhibits vascular calcification by activating IL13RA2-dependent inhibition of STAT3 and attenuating the WNT3/β-catenin signalling pathway. *J Adv Res*. (2025) 68:445–57. doi: 10.1016/j.jare.2024.02.020

33. Amaya-Garrido A, Brunet M, Buffin-Meyer B, Piedrafita A, Grzesiak L, Agbegbo E, et al. Calprotectin is a contributor to and potential therapeutic target for vascular calcification in chronic kidney disease. *Sci Transl Med*. (2023) 15(712):eabn5939. doi: 10.1126/scitranslmed.abn5939

34. Shen J, Zhao M, Zhang C, Sun X. IL-1β in atherosclerotic vascular calcification: from bench to bedside. *Int J Biol Sci*. (2021) 17(15):4353–64. doi: 10.7150/ijbs.66537

35. Chen A, Lan Z, Li L, Xie L, Liu X, Yang X, et al. Sodium-glucose cotransporter 2 inhibitor canagliflozin alleviates vascular calcification through suppression of nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 inflammasome. *Cardiovasc Res*. (2023) 119(13):2368–81. doi: 10.1093/cvr/cvad119

36. Yang H, Xu G, Li Q, Zhu L. Ligustrazine alleviates the progression of coronary artery calcification by inhibiting caspase-3/GSDME mediated pyroptosis. *Biosci Trends*. (2024) 18(5):482–91. doi: 10.5582/bst.2024.01096

37. Qi RQ, Chen YF, Cheng J, Song JW, Chen YH, Wang SY, et al. Elabela alleviates cuproptosis and vascular calcification in vitaminD3- overloaded mice via regulation of the PPAR-γ/FDX1 signaling. *Mol Med*. (2024) 30(1):223. doi: 10.1186/s10020-024-00997-3

38. Roy N, Rosas SE. IL-6 is associated with progression of coronary artery calcification and mortality in incident dialysis patients. *Am J Nephrol*. (2021) 52(9):745–52. doi: 10.1159/000518652

39. Macrì F, Vigorito I, Castiglione S, Faggiano S, Casaburo M, Fanotti N, et al. High phosphate-induced JAK-STAT signalling sustains vascular smooth muscle cell inflammation and limits calcification. *Biomolecules*. (2023) 14(1):29. doi: 10.3390/biom14010029

40. Wei X, Shen Z, Zhu M, Fang M, Wang S, Zhang T, et al. The pterostilbene-dihydropyrazole derivative ptd-1 ameliorates vascular calcification by regulating inflammation. *Int Immunopharmacol*. (2023) 125(Pt B):111198. doi: 10.1016/j.intimp.2023.111198

41. Lu CW, Lee CJ, Hsieh YJ, Hsu BG. Empagliflozin attenuates vascular calcification in mice with chronic kidney disease by regulating the NFR2/HO-1 anti-inflammatory pathway through AMPK activation. *Int J Mol Sci*. (2023) 24(12):10016. doi: 10.3390/ijms241210016

42. Nakaoka Y, Isobe M, Tanaka Y, Ishii T, Ooka S, Niiro H, et al. Long-term efficacy and safety of tocilizumab in refractory takayasu arteritis: final results of the randomized controlled phase 3 TAKT study. *Rheumatology (Oxford)*. (2020) 59(9):2427–34. doi: 10.1093/rheumatology/kez630

43. Schmitt C, Brockwell L, Giraudon M, Zucchetto M, Christ L, Bannert B, et al. Intravenous tocilizumab for the treatment of giant cell arteritis: a phase Ib dose-ranging pharmacokinetic bridging study. *Arthritis Res Ther*. (2022) 24(1):133. doi: 10.1186/s13075-022-02815-9

44. Brunner HI, Ruperto N, Ramanan AV, Horneff G, Minden K, Calvo Penades I, et al. Long-term efficacy and safety of subcutaneous tocilizumab in clinical trials of polyarticular or systemic juvenile idiopathic arthritis. *Rheumatology (Oxford)*. (2024) 63(9):2535–46. doi: 10.1093/rheumatology/keae180

45. Bouabdallah J, Zibara K, Issa H, Lenglet G, Kchour G, Caus T, et al. Endothelial cells exposed to phosphate and indoxyl sulphate promote vascular calcification through interleukin-8 secretion. *Nephrol Dial Transplant*. (2019) 34(7):1125–34. doi: 10.1093/ndt/gfy325

46. Thiem U, Hewitson TD, Toussaint ND, Holt SG, Haller MC, Pasch A, et al. Effect of the phosphate binder sucroferric oxyhydroxide in dialysis patients on endogenous calciprotein particles, inflammation, and vascular cells. *Nephrol Dial Transplant*. (2023) 38(5):1282–96. doi: 10.1093/ndt/gfac271

47. Perna AF, Russo L, D'Esposito V, Formisano P, Bruzzese D, Vigorito C, et al. Lanthionine, a novel uremic toxin, in the vascular calcification of chronic kidney disease: the role of proinflammatory cytokines. *Int J Mol Sci*. (2021) 22(13):6875. doi: 10.3390/ijms22136875

48. Chang SF, Liu SF, Chen CN, Kuo HC. Serum IP-10 and IL-17 from Kawasaki disease patients induce calcification-related genes and proteins in human coronary artery smooth muscle cells *in vitro*. *Cell Biosci*. (2020) 10:36. doi: 10.1186/s13578-020-00400-8

49. Lin IC, Suen JL, Huang SK, Chou MH, Kuo HC, Lo MH, et al. Involvement of IL-17 A/IL-17 receptor A with neutrophil recruitment and the severity of coronary arteritis in Kawasaki disease. *J Clin Immunol*. (2024) 44(3):77. doi: 10.1007/s10875-024-01673-1

50. von Stebut E, Reich K, Thaçi D, Koenig W, Pinter A, Körber A, et al. Impact of secukinumab on endothelial dysfunction and other cardiovascular disease parameters in psoriasis patients over 52 weeks. *J Invest Dermatol*. (2019) 139(5):1054–62. doi: 10.1016/j.jid.2018.10.042

51. Kawada S, Nagasawa Y, Kawabe M, Ohyama H, Kida A, Kato-Kogoe N, et al. Iron-induced calcification in human aortic vascular smooth muscle cells through interleukin-24 (IL-24), with/without TNF-alpha. *Sci Rep*. (2018) 8(1):658. doi: 10.1038/s41598-017-19092-1

52. Song Y, Yang N, Si H, Liu T, Wang H, Geng H, et al. Iron overload impairs renal function and is associated with vascular calcification in rat aorta. *Biometals*. (2022) 35(6):1325–39. doi: 10.1007/s10534-022-00449-7

53. Chong WP, Mattapallil MJ, Raychaudhuri K, Bing SJ, Wu S, Zhong Y, et al. The cytokine IL-17A limits Th17 pathogenicity via a negative feedback loop driven by autocrine induction of IL-24. *Immunity*. (2020) 53(2):384–97.e5. doi: 10.1016/j.immuni.2020.06.022

54. Sie C, Kant R, Peter C, Muschaweckh A, Pfaller M, Nirschl L, et al. IL-24 intrinsically regulates Th17 cell pathogenicity in mice. *J Exp Med*. (2022) 219(8): e20212443. doi: 10.1084/jem.20212443

55. Xu X, Prens E, Florencia E, Leenen P, Boon L, Asmawidjaja P, et al. Interleukin-17A drives IL-19 and IL-24 expression in skin stromal cells regulating keratinocyte proliferation. *Front Immunol*. (2021) 12:719562. doi: 10.3389/fimmu.2021.719562

56. Liu S, Hur YH, Cai X, Cong Q, Yang Y, Xu C, et al. A tissue injury sensing and repair pathway distinct from host pathogen defense. *Cell*. (2023) 186(10):2127–43.e22. doi: 10.1016/j.cell.2023.03.031

57. Pap D, Veres-Székely A, Szebeni B, Rokonay R, Ónody A, Lippai R, et al. Characterization of IL-19, -20, and -24 in acute and chronic kidney diseases reveals a pro-fibrotic role of IL-24. *J Transl Med*. (2020) 18(1):172. doi: 10.1186/s12967-020-02338-4

58. Peng Q, Luo A, Zhou Z, Xuan W, Qiu M, Wu Q, et al. Interleukin 29 inhibits RANKL-induced osteoclastogenesis via activation of JNK and STAT, and inhibition of NF-κB and NFATc1. *Cytokine*. (2019) 113:144–54. doi: 10.1016/j.cyto.2018.06.032

59. Xu L, Peng Q, Xuan W, Feng X, Kong X, Zhang M, et al. Interleukin-29 enhances synovial inflammation and cartilage degradation in osteoarthritis. *Mediators Inflamm*. (2016) 2016:9631510. doi: 10.1155/2016/9631510

60. Gu W, Wei Y, Tang Y, Zhang S, Li S, Shi Y, et al. Supplement of exogenous inorganic pyrophosphate inhibits atheromatous calcification in apolipoprotein E knockout mice. *Heliyon*. (2023) 9(8):e19214. doi: 10.1016/j.heliyon.2023.e19214

61. Bohara S, Bagheri A, Ertugral EG, Radzikh I, Sandlers Y, Jiang P, et al. Integrative analysis of gene expression, protein abundance, and metabolomic profiling elucidates complex relationships in chronic hyperglycemia-induced changes in human aortic smooth muscle cells. *J Biol Eng*. (2024) 18(1):61. doi: 10.1186/s13036-024-00457-w

62. Chernomordik F, Cercek B, Lio WM, Mihailovic PM, Yano J, Herscovici R, et al. The role of T cells reactive to the cathelicidin antimicrobial peptide LL-37 in acute coronary syndrome and plaque calcification. *Front Immunol*. (2020) 11:575577. doi: 10.3389/fimmu.2020.575577

63. Meng Z, Zhang S, Li W, Wang Y, Wang M, Liu X, et al. Cationic proteins from eosinophils bind bone morphogenetic protein receptors promoting vascular calcification and atherogenesis. *Eur Heart J*. (2023) 44(29):2763–83. doi: 10.1093/eurheartj/ehad262

64. Zhu Y, Chen JC, Zhang JL, Wang FF, Liu RP. A new mechanism of arterial calcification in diabetes: interaction between H3K18 lactylation and CHI3L1. *Clin Sci (Lond)*. (2025) 139(2):115–30. doi: 10.1042/CS20243122

65. Solow EB, Yu F, Thiele GM, Sokolove J, Robinson WH, Pruhs ZM, et al. Vascular calcifications on hand radiographs in rheumatoid arthritis and associations with autoantibodies, cardiovascular risk factors and mortality. *Rheumatology (Oxford)*. (2015) 54(9):1587–95. doi: 10.1093/rheumatology/kev027

66. Hofbauer LC, Schrader J, Niebergall U, Viereck V, Burchert A, Hörsch D, et al. Interleukin-4 differentially regulates osteoprotegerin expression and induces calcification in vascular smooth muscle cells. *Thromb Haemost*. (2006) 95(4):708–14. doi: 10.1160/TH05-12-0800

67. Chinetti-Gbaguidi G, Daoudi M, Rosa M, Vinod M, Louvet L, Copin C, et al. Human alternative macrophages populate calcified areas of atherosclerotic lesions and display impaired RANKL-induced osteoclastic bone resorption activity. *Circ Res*. (2017) 121(1):19–30. doi: 10.1161/CIRCRESAHA.116.310262

68. Zhang K, Zhang Y, Feng W, Chen R, Chen J, Touyz RM, et al. Interleukin-18 enhances vascular calcification and osteogenic differentiation of vascular smooth muscle cells through TRPM7 activation. *Arterioscler Thromb Vasc Biol*. (2017) 37(10):1933–43. doi: 10.1161/ATVBAHA.117.309161

69. Zhang Y, Zhang K, Zhang Y, Zhou L, Huang H, Wang J. IL-18 mediates vascular calcification induced by high-fat diet in rats with chronic renal failure. *Front Cardiovasc Med*. (2021) 8:724233. doi: 10.3389/fcvm.2021.724233

70. Porazko T, Kúzniar J, Kusztal M, Kúzniar TJ, Weyde W, Kuriata-Kordek M, et al. IL-18 is involved in vascular injury in end-stage renal disease patients. *Nephrol Dial Transplant*. (2009) 24(2):589–96. doi: 10.1093/ndt/gfn486

71. Schelski N, Luong TTD, Lang F, Pieske B, Voelkl J, Alesutan I. SGK1-dependent stimulation of vascular smooth muscle cell osteo-/chondrogenic transdifferentiation by interleukin-18. *Pflugers Arch*. (2019) 471(6):889–99. doi: 10.1007/s00424-019-02256-5

72. Liu H, Zhang X, Zhong X, Li Z, Cai S, Yang P, et al. Puerarin inhibits vascular calcification of uremic rats. *Eur J Pharmacol*. (2019) 855:235–43. doi: 10.1016/j.ejphar.2019.05.023

73. Zhao P, Yao Q, Zhang PJ, The E, Zhai Y, Ao L, et al. Single-cell RNA-Seq reveals a critical role of novel pro-inflammatory EndMT in mediating adverse remodeling in coronary artery-on-a-chip. *Sci Adv*. (2021) 7(34):eabg1694. doi: 10.1126/sciadv.abg1694

74. Zhang C, Huang X, Xie B, Lian D, Chen J, Li W, et al. The multi-protective effect of IL-37-Smad3 against ox-LDL induced dysfunction of endothelial cells. *Biomed Pharmacother*. (2024) 172:116268. doi: 10.1016/j.biopha.2024.116268

75. Chai M, Zhang HT, Zhou YJ, Ji QW, Yang Q, Liu YY, et al. Elevated IL-37 levels in the plasma of patients with severe coronary artery calcification. *J Geriatr Cardiol*. (2017) 14(5):285–91. doi: 10.11909/j.issn.1671-5411.2017.05.013

76. Yu K, Min X, Lin Y, Huang Y, Huang S, Liu L, et al. Increased IL-37 concentrations in patients with arterial calcification. *Clin Chim Acta*. (2016) 461:19–24. doi: 10.1016/j.cca.2016.07.011

77. Oh J, Park S, Yu HT, Chang HJ, Lee SH, Kang SM, et al. Lack of superiority for soluble ST2 over high sensitive C-reactive protein in predicting high risk coronary artery calcium score in a community cohort. *Yonsei Med J*. (2016) 57(6):1347–53. doi: 10.3349/ymj.2016.57.6.1347

78. Marzullo A, Ambrosi F, Inchingolo M, Manca F, Devito F, Angiletta D, et al. ST2l Transmembrane receptor expression: an immunochemical study on endarterectomy samples. *PLoS One*. (2016) 11(5):e0156315. doi: 10.1371/journal.pone.0156315

79. Ambari AM, Setianto B, Santoso A, Radi B, Dwiputra B, Susilowati E, et al. Angiotensin converting enzyme inhibitors (ACEIs) decrease the progression of cardiac fibrosis in rheumatic heart disease through the inhibition of IL-33/sST2. *Front Cardiovasc Med*. (2020) 7:115. doi: 10.3389/fcvm.2020.00115

80. Bartoli-Leonard F, Zimmer J, Sonawane AR, Perez K, Turner ME, Kuraoka S, et al. NLRP3 inflammasome activation in peripheral arterial disease. *J Am Heart Assoc*. (2023) 12(6):e026945. doi: 10.1161/JAHA.122.026945

81. Ambari AM, Setianto B, Santoso A, Radi B, Dwiputra B, Susilowati E, et al. Randomised controlled trial into the role of ramipril in fibrosis reduction in rheumatic heart disease: the RamiRHeD trial protocol. *BMJ Open*. (2021) 11(9): e048016. doi: 10.1136/bmjopen-2020-048016

82. Aherrahrou R, Baig F, Theofilatos K, Lue D, Beele A, Örd T, et al. Secreted protein profiling of human aortic smooth muscle cells identifies vascular disease associations. *Arterioscler Thromb Vasc Biol*. (2024) 44(4):898–914. doi: 10.1161/ATVBAHA.123.320274

83. Ho LC, Chen YH, Wu TY, Kao LZ, Hung SY, Liou HH, et al. Phosphate burden induces vascular calcification through a NLRP3-caspase-1-mediated pyroptotic pathway. *Life Sci*. (2023) 332:122123. doi: 10.1016/j.lfs.2023.122123

84. Ceccherini E, Persiani E, Cabiati M, Guiducci L, Del Ry S, Gisone I, et al. A dynamic cellular model as an emerging platform to reproduce the complexity of human vascular calcification *in vitro*. *Int J Mol Sci*. (2024) 25(13):7427. doi: 10.3390/ijms25137427

85. Shan SK, Lin X, Wu F, Li CC, Guo B, Li FX, et al. Vascular wall microenvironment: endothelial cells original exosomes mediated melatonin-suppressed vascular calcification and vascular ageing in a m6A methylation dependent manner. *Bioact Mater*. (2024) 42:52–67. doi: 10.1016/j.bioactmat.2024.08.021

86. Chen J, Ren T, Xie L, Hu H, Li X, Maitusong M, et al. Enhancing aortic valve drug delivery with PAR2-targeting magnetic nano-cargoes for calcification alleviation. *Nat Commun.* (2024) 15(1):557. doi: 10.1038/s41467-024-44726-0

87. Hu K, Zhong L, Lin W, Zhao G, Pu W, Feng Z, et al. Pathogenesis-guided rational engineering of nanotherapies for the targeted treatment of abdominal aortic aneurysm by inhibiting neutrophilic inflammation. *ACS Nano.* (2024) 18(8):6650–72. doi: 10.1021/acsnano.4c00120

88. Li J, Lan T, Guo Q, Zhang C, Lu X, Hu X, et al. Mitochondria-targeted natural antioxidant nanosystem for diabetic vascular calcification therapy. *Biomacromolecules.* (2024) 25(7):4329–43. doi: 10.1021/acs.biomac.4c00375

89. Mo F, Wang C, Li S, Li Z, Xiao C, Zhang Y, et al. A dual-targeting, multi-faceted biocompatible nanodrug optimizes the microenvironment to ameliorate abdominal aortic aneurysm. *Adv Mater.* (2024) 36(33):e2405761. doi: 10.1002/adma.202405761

90. Zhang Z, Li S, Wang H, Shan Y. The effects of the carrier and ligand spatial conformation on RNA nanodrug cell delivery. *Anal Chem.* (2024) 96(32):13226–33. doi: 10.1021/acs.analchem.4c02270

91. Harting H, Herrmann T, Ehlert N, Meißner J, Angrisani N, Reifenrath J. Comparison of accumulation and distribution of PEGylated and CD-47-functionalized magnetic nanoporous silica nanoparticles in an *in vivo* mouse model of implant infection. *PLoS One.* (2025) 20(5):e0321888. doi: 10.1371/journal.pone.0321888

92. Powell LG, Alexander C, Stone V, Johnston HJ, Conte C. An *in vitro* investigation of the hepatic toxicity of PEGylated polymeric redox responsive nanoparticles. *RSC Adv.* (2022) 12(20):12860–70. doi: 10.1039/D2RA00395C

93. Aierken Y, He H, Li R, Lin Z, Xu T, Zhang L, et al. Inhibition of Slc39a14/Slc39a8 reduce vascular calcification via alleviating iron overload induced ferroptosis in vascular smooth muscle cells. *Cardiovasc Diabetol.* (2024) 23(1):186. doi: 10.1186/s12933-024-02224-z

94. Chen Z, Sun X, Li X, Liu N. Oleoylethanolamide alleviates hyperlipidaemia-mediated vascular calcification via attenuating mitochondrial DNA stress triggered autophagy-dependent ferroptosis by activating PPARα. *Biochem Pharmacol.* (2023) 208:115379. doi: 10.1016/j.bcp.2022.115379

95. Shen J, Zhang C, Liu Y, Zhao M, Wang Q, Li P, et al. L-type calcium ion channel-mediated activation of autophagy in vascular smooth muscle cells via thonningianin A (TA) alleviates vascular calcification in type 2 diabetes mellitus. *Eur J Pharmacol.* (2023) 959:176084. doi: 10.1016/j.ejphar.2023.176084

96. Sun XJ, Xiao SJ, Ma WQ, Jin H, Ren LQ, Yao YY, et al. Activation of TFEB protects against diabetic vascular calcification by improving autophagic flux and activating Nrf2 antioxidant system. *Am J Physiol Endocrinol Metab.* (2025) 328(6):E924–39. doi: 10.1152/ajpendo.00161.2023

97. Datta-Mannan A, Regev A, Coutant DE, Dropsey AJ, Foster J, Jones S, et al. Safety, tolerability, and pharmacokinetics of an oral small molecule inhibitor of IL-17A (LY3509754): a phase I randomized placebo-controlled study. *Clin Pharmacol Ther.* (2024) 115(5):1152–61. doi: 10.1002/cpt.3185

98. Kimball AB, Jemec GBE, Sayed CJ, Kirby JS, Prens E, Ingram JR, et al. Efficacy and safety of bimekizumab in patients with moderate-to-severe hidradenitis suppurativa (BE HEARD I and BE HEARD II): two 48-week, randomised, double-blind, placebo-controlled, multicentre phase 3 trials. *Lancet.* (2024) 403(10443):2504–19. doi: 10.1016/S0140-6736(24)00101-6

99. Glintborg B, Di Giuseppe D, Wallman JK, Provan SA, Nordström D, Hokkanen AM, et al. Is the risk of infection higher during treatment with secukinumab than with TNF inhibitors? An observational study from the nordic countries. *Rheumatology (Oxford).* (2023) 62(2):647–58. doi: 10.1093/rheumatology/keac358

100. Azadeh H, Alizadeh-Navaei R, Rezaiemanesh A, Rajabinejad M. Immune-related adverse events (irAEs) in ankylosing spondylitis (AS) patients treated with interleukin (IL)-17 inhibitors: a systematic review and meta-analysis. *Inflammopharmacology.* (2022) 30(2):435–51. doi: 10.1007/s10787-022-00933-z

101. Smolen JS, Feist E, Fatenejad S, Grishin SA, Korneva EV, Nasonov EL, et al. Olokizumab versus placebo or Adalimumab in rheumatoid arthritis. *N Engl J Med.* (2022) 387(8):715–26. doi: 10.1056/NEJMoa2201302