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Chemerin in Arthritis: Molecular Basis, Clinical Implications, and Translational Perspectives

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Abstract: Against global aging and rising obesity, arthritis—a highly prevalent chronic musculoskeletal disease—causes high morbidity and disability, with unclear pathogenesis and no curative therapies. Chemerin, a dual chemokine-adipokine linking metabolic dysregulation to chronic inflammation, plays a pivotal role in arthritis progression, yet controversies persist over subtype-specific functions and its bidirectional effects. This review (covering literature from Jan 1997 to Mar 2026) shows aberrant chemerin overexpression in the serum and local joints of osteoarthritis(OA) and rheumatoid arthritis(RA) patients, which modulates disease via multiple pathways, while its mechanisms in gouty arthritis(GA) and spondyloarthritis(SpA) remain elusive. The Chemerin/ChemR23 axis is a promising therapeutic target; future studies should resolve existing controversies and fill knowledge gaps to clarify its precise regulatory mechanisms.

Keywords: Chemerin; ChemR23; Arthritis; Osteoarthritis; Rheumatoid arthritis; Gouty arthritis; Inflammation regulation; Cartilage degeneration

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1. Introduction

Arthritis, a highly prevalent chronic musculoskeletal disease globally, has rising incidence and disability rates amid population aging and growing obesity, severely impairing patients' quality of life and straining global healthcare. With the pathogenesis of its subtypes still incompletely elucidated and no curative treatments available, identifying core regulatory molecules and key signaling pathways remains a central research priority.

Chemerin (RARRES2), a dual adipokine and chemokine, has evolved from an inflammatory bystander to a key driver of joint destruction and immune dysregulation in arthritis. It exhibits marked subtype heterogeneity: it mediates chondrocyte metabolic disturbance and matrix degradation in OA, and regulates synovial fibroblast-like cell activation and immune cell recruitment in RA. Research on its roles

in GA and SpA remains limited, with underlying mechanisms not fully elucidated.

This paper systematically reviews chemerin research progress, analyzes its subtype-specific mechanisms, academic consensus and controversies, identifies key research gaps, and lays a theoretical basis for future targeted intervention strategies.

2. Discovery, nomenclature, and molecular biological characteristics of chemerin

2.1. Discovery and nomenclature evolution

Chemerin research began in the late 1990s. In 1997, Nagpal *et al.* first identified the tazarotene-induced gene product TIG-2, with its physiological function and ligand properties unclarified. In 2003, Wittamer *et al.* isolated the natural ligand of the orphan receptor ChemR23 (CMKLR1) from inflammatory ascites, formally named it chemerin, and confirmed the ligand-receptor relationship, initiating research on its immunomodulatory functions. In 2007, Goralski *et al.* further defined it as a novel adipokine mainly secreted by adipose tissue that regulates lipogenesis and energy metabolism, establishing a molecular link between metabolic syndrome and chronic inflammation [1].

2.2. Molecular structure and precursor processing mechanism

Chemerin is a 1–16 kDa, 163-amino acid protein comprising a signal peptide, core domain, and two terminal tails. Its precursor preprochemerin yields inactive prochemerin after signal peptide cleavage, which requires C-terminal processing by serine protease cascades to become active. Cryo-EM studies confirm its "reverse chemokine" activation mechanism: the C-terminal nonapeptide independently activates CMKLR1 and GPR1, while the N-terminal globular domain enhances the binding affinity of the full-length molecule. Chemerin-157 is the main mature active isoform [2].

2.3. Receptor system and signal transduction pathways

2.3.1. Receptors

Chemerin transmits signals through three homologous but functionally distinct G protein-coupled receptors: CMKLR1, GPR1, and CCRL2.

CMKLR1 is the primary functional receptor; upon ligand binding, it couples with Gi/o proteins to reduce intracellular cAMP levels, activates the MAPK/ERK, AKT, and PI3K pathways, and mediates β-arrestin-dependent signaling and receptor internalization. It is widely expressed in immune cells and adipose tissue.

GPR1 is a high-affinity receptor that exhibits weak classical G protein signaling and primarily functions through β-arrestin recruitment and receptor internalization. It is highly expressed in neural tissues and specific immune cell subsets, potentially contributing to neuroimmune regulation.

CCRL2, upon ligand binding, lacks classical G protein signaling and internalization activity; instead, it acts mainly as a "presentation receptor" by locally concentrating chemerin, thereby facilitating CMKLR1-mediated signaling and leukocyte recruitment at inflammatory sites.

2.3.2. Core signaling cascades

Upon chemerin binding, CMKLR1 mainly couples to Gi/o proteins, inhibiting adenylyl cyclase to reduce intracellular cAMP, while promoting IP3 production and calcium mobilization to activate PLC, PI3K,

MAPK, and RhoA/ROCK pathways. It also recruits β-arrestin to terminate GPCR signaling and mediate signaling complex assembly [3]. In contrast, GPR1 takes arrestin recruitment as its core signaling mechanism, mediating receptor internalization and activating alternative pathways such as MAPK, leading to more sustained cellular effects.

2.3.3. Downstream signaling axis

ERK1/2 (MAPK) pathway: The Chemerin/CMKLR1 axis can activate ERK1/2; in monocyte adhesion models, chemerin induces β2 integrin activation and triggers ERK1/2 phosphorylation, and blocking ERK eliminates the adhesion phenotype.

PI3K/Akt pathway: Upon binding to CMKLR1, chemerin activates PI3K/Akt; in macrophage-related studies, chemerin-induced phenotypes are mediated by Akt activation and its downstream transcription factor CEBPα (the CMKLR1/p-Akt/CEBPα axis).

NF-κB pathway: Chemerin/CMKLR1 can activate NF-κB; in tumor microenvironment research, chemerin enhances mesenchymal features of glioblastoma and activates NF-κB in tumor-associated macrophages (TAMs) via a CMKLR1-dependent NF-κB signaling pathway.

β-arrestin-related signaling: CMKLR1 mediates dual signaling through both G protein and arrestin pathways; in contrast, although GPR1 exhibits weak G protein signaling, it displays strong arrestin-dependent and -independent internalization characteristics.

3. Research progression of chemerin mechanisms in osteoarthritis

3.1. Establishment of chemerin-osteoarthritis correlation

Berg *et al.*(2010) demonstrated at the chondrocyte level that human articular chondrocytes synthesize chemerin and express CMKLR1; exogenous chemerin upregulates catabolic factors and matrix metalloproteinases, driving matrix degradation and mediating obesity-related inflammation in OA progression [4]. Huang *et al.*(2012) further confirmed clinically that chemerin is elevated in OA synovial fluid and synovium, positively correlating with disease severity.

3.2. Deepened mechanistic insights

3.2.1. Chemerin receptor expression and signaling networks

CMKLR1 is chemerin's primary functional receptor. In the OA joint microenvironment, it is highly expressed on macrophages and dendritic cells, and markedly upregulated in chondrocytes, synovial fibroblasts, and osteoclasts, acting as a key molecular link between systemic metabolic disorders and local joint pathology. Chemerin-CMKLR1 binding activates multiple downstream pathways, with NF-κB as the central inflammatory axis driving transcription of pro-inflammatory factors (IL-6, TNF-α) and matrix metalloproteinases to trigger local inflammatory cascades. It also upregulates TLR4 in synovial fibroblasts, induces CCL2 release to recruit immune cells, and forms an inflammatory amplification loop that exacerbates cartilage damage and degeneration.

3.2.2. Chemerin-mediated inflammation and cartilage matrix degradation

In OA pathogenesis, chemerin drives cartilage matrix degradation through both direct and indirect pathways. In vitro, recombinant chemerin induces macrophages and primary chondrocytes to secrete pro-inflammatory

cytokines (IL-6, TNF-α), upregulates MMP-1, MMP-3, and MMP-13 expression and activity, and degrades core cartilage matrix components including type II collagen and proteoglycans. Furthermore, chemerin synergizes with highly expressed IL-1β in OA synovial fluid: their co-stimulation enhances AKT and ERK phosphorylation, suppresses chondrocyte proliferation, reduces cell viability and accelerates apoptosis, amplifying inflammation-mediated cartilage damage via positive feedback.

3.2.3. Regulation of chondrocyte metabolism and survival by chemerin

As a metabolism-associated adipokine, chemerin directly disrupts chondrocyte energy metabolism. Studies show chemerin treatment sustains AKT and ERK pathway activation in chondrocytes, triggering glucose metabolic disturbances and mitochondrial dysfunction, which ultimately reduces chondrocyte proliferation and promotes apoptosis.

3.2.4. Chemerin-mediated periarticular bone remodeling

Beyond cartilage damage, OA features abnormal periarticular bone remodeling including subchondral bone sclerosis and osteophyte formation, with chemerin involved in regulating bone metabolic balance. It inhibits the canonical Wnt/β-catenin pathway and downregulates osteogenic transcription factors Runx2 and Osterix, suppressing mesenchymal stem cell osteogenic differentiation and bone formation. Meanwhile, it upregulates RANKL in osteoblasts and synovial cells, reduces OPG secretion, and elevates the RANKL/OPG ratio, promoting osteoclast differentiation and bone resorption [5]. In ovariectomized osteoporotic mice, endogenous chemerin deficiency improves intraosseous microvascular formation and bone formation markers, indicating chemerin may indirectly impair bone repair by inhibiting intraosseous angiogenesis, providing indirect mechanistic evidence for OA subchondral bone lesions.

3.2.5. Structural basis and biased signaling of Chemerin-CMKLR1 interaction

Secreted as an inactive precursor, chemerin yields functionally divergent active isoforms via C-terminal proteolytic cleavage, accounting for conflicting findings about its roles in OA and RA. The 2024 cryo-EM study first resolved the Chemerin-CMKLR1 complex structure and identified its “reverse topology, two-step binding site” activation mode. CMKLR1 mediates ligand-biased signaling: distinct isoforms selectively trigger G protein, Syk, or β-arrestin cascades to exert disparate effects, with C15 anti-inflammatory and C9 pro-inflammatory [6]. This finding clarifies chemerin’s functional ambiguity and inspires OA-targeted therapy design. Developing biased ligands or antagonists that block pro-inflammatory signals without disrupting protective functions represents a promising therapeutic strategy.

4. Research progress on chemerin molecular mechanisms in rheumatoid arthritis

RA is an autoimmune disorder marked by symmetric erosive polyarthritis, pathologically presenting synovial hyperplasia, immune cell infiltration, pannus formation, and progressive cartilage and bone destruction. Adipokine-mediated breakdown of the metabolic-immune axis is pivotal to its pathogenesis.

4.1. Chemerin precursor processing and multi-receptor regulatory network

In the RA inflammatory milieu, neutrophil-derived serine proteases cleave chemerin’s precursor into multiple

active isoforms, with chem157S being the most potent. Such post-translational modification diversity allows stage-specific fine regulation of pathological processes. Chemerin acts via three GPCRs (CMKLR1, GPR1, CCRL2) to form an intricate functional network in RA. CMKLR1, the principal functional receptor broadly expressed on immune and synovial cells, mediates most pro-inflammatory and chemotactic responses. CCRL2 has no canonical GPCR signaling capacity and acts mainly as a presentation receptor to concentrate local chemerin and boost the recruitment of CMKLR1-expressing cells.

4.2. Chemerin activates fibroblast-like synoviocytes to drive inflammation and matrix degradation

Synovial fibroblast-like cells (FLS) function as the core effector cells driving synovial hyperplasia, pannus growth and joint destruction in RA. Chemerin is more abundant in RA synovium than OA, localizing to the synovial lining and vessel walls, while its receptor CMKLR1 is detected on synovial macrophages, immature dendritic cells and FLS. Chemerin directly activates RA-FLS to secrete IL-6, CCL2 and MMP-3, upregulate TLR4, and boost migratory and invasive abilities, forming a pro-inflammatory vicious cycle of matrix breakdown and immune cell recruitment to worsen joint injury [7]. This activation relies on ERK1/2, p38 MAPK, and Akt pathways. TNFα and IFNγ further elevate chemerin expression in FLS, establishing a positive feedback loop to sustain disease progression.

4.3. Chemerin-mediated immune cell recruitment and activation

Chemerin triggers directional migration of macrophages and immature dendritic cells through CMKLR1 by suppressing intracellular cAMP and activating PI3K/Akt and ERK1/2 cascades [3]. CCRL2 concentrates local chemerin to amplify inflammation, and chemerin activates FLS to secrete pro-inflammatory mediators and matrix metalloproteinases, aggravating joint damage. It also stimulates the endothelial NF-κB pathway to upregulate adhesion molecules and facilitate monocyte adhesion and transendothelial migration. In macrophages, the Akt/CEBPα axis driven by chemerin promotes pro-inflammatory M1 polarization and tissue injury. Moreover, CMKLR1 is enriched on $CD8^+$ effector memory T cells; Chemerin recruits these cells and boosts TNF-α production [8]. The peripheral abundance of this T cell subset correlates positively with DAS28 scores in RA patients, marking its vital role in RA immune pathogenesis.

4.4. Clinical correlations between chemerin and RA disease phenotypes

Clinical evidence confirms chemerin closely correlates with RA disease activity and severity. Female RA patients exhibit drastically elevated serum chemerin, which positively associates with DAS28-CRP, swollen joint counts, and CRP. After adjustment for BMI, fat mass, and other confounders, high serum chemerin acts as an independent risk factor for moderate-to-severe RA activity [9]. Its concentrations also independently correlate with DAS28-ESR and the HAQ-DI disability index, unaffected by other adipokines, cytokines, or E-selectin. Chemerin is also highly enriched in RA synovial fluid and mainly derived from synovial fibroblasts [10].

5. Research status of chemerin in other arthritis subtypes

Direct investigations into chemerin in GA are scarce, with no large-cohort clinical data delineating its expression profiles in GA patients' serum and synovial fluid. Originally purified from pooled inflammatory

arthritis synovial fluid, chemerin is hypothesized to mediate intra-articular immune recruitment and inflammatory amplification in GA, given synovial fluid serves as the core niche for urate crystal deposition and acute inflammatory initiation. Nevertheless, its cellular origins and regulatory functions in neutrophil-mediated urate crystal phagocytosis and NET formation in GA require experimental validation. Likewise, chemerin's pathogenic contribution to SpA lacks solid direct evidence, with its expression patterns and biological functions still undetermined.

6. Conclusion

Chemerin is a pivotal adipokine that modulates metabolic homeostasis and innate immunity, representing a research hotspot in inflammatory arthritis. Synthesized as an inactive precursor, chemerin is activated by serine protease cleavage and acts via CMKLR1, GPR1, and CCRL2 receptors to regulate immune cell chemotaxis, pro-inflammatory cytokine secretion, and cartilage matrix remodeling. Clinically, chemerin is aberrantly upregulated in the serum, synovial fluid, and lesioned joint tissues of OA and RA patients, and its expression correlates strongly with disease activity, bone erosion, and cartilage degeneration. Accordingly, chemerin serves as a promising novel biomarker, and the chemerin-CMKLR1 axis is a viable target for arthritis therapy.

Current studies possess three major limitations: overrepresentation of OA and RA research with insufficient systematic evidence for GA and SpA; unclear subtype-specific downstream signaling and cellular mechanisms underlying chemerin's functional heterogeneity; and inadequate translational progress, as targeted interventions remain limited to preclinical models without clinical validation. Future research should prioritize multi-omics profiling of chemerin's spatiotemporal expression in joint tissues, clarification of its crosstalk with other adipokines, cross-subtype comparative studies to identify disease-specific mechanisms for precision therapy, and optimized preclinical evaluation to accelerate drug clinical translation.

In conclusion, multidimensional research will refine the theoretical framework of chemerin-mediated joint pathological injury, providing novel molecular targets and a theoretical basis for the precise diagnosis and treatment of inflammatory arthritis.

Disclosure statement

The authors declare no conflict of interest.

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