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Research Progress on the Mechanisms of Chemerin in the Occurrence and Development of Metabolic-Associated Fatty Liver Disease

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Abstract

Metabolic-associated fatty liver disease (MAFLD) is a hepatic manifestation of metabolic dysfunction in genetically predisposed individuals, driven by overnutrition and characterized by multisystemic involvement. In recent years, the prevalence of MAFLD has risen significantly both in China and globally, posing a growing threat to public health. Early prevention, diagnosis, and intervention are therefore of critical importance.

As a recently identified adipokine, chemerin has been implicated in the pathogenesis and progression of MAFLD through multiple mechanisms, including the promotion of insulin resistance, modulation of glucose and lipid metabolism, recruitment of inflammatory cells, and facilitation of liver fibrosis. This article reviews the mechanistic roles of chemerin in the development of metabolic-associated fatty liver disease and summarizes recent advances in clinical research.

Critically, despite accumulating associative evidence, the directionality, stage specificity, and clinical utility of chemerin remain to be clarified owing to assay heterogeneity, context-dependent receptor signaling, and the paucity of interventional human data. Future work should prioritize isoform-resolved quantification, tissue-specific perturbation, and prospective validation to establish causality and translational relevance.

Keywords: Metabolic-associated fatty liver disease; chemerin; liver fibrosis; insulin resistance; hepatic inflammation; adipokine

Introduction

Chemerin, also known as tazarotene-induced gene 2 protein (TIG2), is recognized as a chemoattractant protein due to its capacity to recruit leukocytes. Initially identified in psoriatic skin following treatment with the retinoid tazarotene, it was later classified as a novel adipokine with high expression levels in the liver, placenta, and white adipose tissue [1].

Chemerin contributes to inflammation and oxidative stress, disrupts insulin signaling pathways, and aggravates disturbances in glucose and lipid metabolism through interaction with the CMKLR1 receptor. This signaling cascade triggers the recruitment of macrophages and other immune cells, linking chemerin closely to metabolic and inflammatory liver injury [2]. Given its dual regulatory effects on systemic metabolism and hepatic inflammation, chemerin has become a hotspot for research on metabolic liver diseases.

In 2020, an international expert panel proposed a consensus to reclassify nonalcoholic fatty liver disease (NAFLD) as metabolic-associated fatty liver disease (MAFLD). The revised definition requires the presence of hepatic steatosis along with one of the following: overweight/obesity, type 2 diabetes mellitus (T2DM), or at least two features of metabolic dysregulation. This nomenclatural shift underscores the central role of metabolic dysfunction in disease initiation and progression, reflecting an improved understanding of its underlying pathophysiology [3].

From an appraisal standpoint, readers should note that MAFLD diagnostic frameworks (imaging versus histology, different metabolic criteria) vary across studies and may influence chemerin–phenotype associations. Transparent reporting of case definitions and adjustment for major confounders (adiposity, glycemic control, inflammation, and medications) is essential for cross-study comparability and reliable inference. Moreover, most human evidence to date is cross-sectional, which cannot support causal interpretation. Prospective cohort studies and mechanistic preclinical research are urgently needed to delineate whether chemerin acts as a pathogenic driver, a passive biomarker, or both across the full MAFLD disease continuum.

Discovery, Structure, and Biological Functions of Chemerin

The identification of chemerin and its encoding gene dates back to 1997. Researchers observed significantly upregulated expression of this molecule in the skin of psoriasis patients treated with tazarotene, leading to its initial designation as tazarotene-induced gene 2 protein (TIG2) [4].

With regard to tissue distribution, chemerin is highly expressed in liver, placenta, and white adipose tissue, with weaker expression detected in lung, kidney, and pancreas [5]. Through autocrine and paracrine signaling, it modulates adipocyte differentiation, glucose uptake, and local inflammatory cascades, positioning itself as a key regulator of systemic metabolic homeostasis [6].

In 2003, functional studies confirmed that chemerin exerts pro-inflammatory effects by binding to CMKLR1 and recruiting immune cells, which formally established its identity as a chemoattractant protein. CMKLR1 consists of 163 amino acid residues, exhibits the highest binding affinity for chemerin, and serves as the primary receptor mediating chemerin-dependent signal transduction to execute downstream cellular responses [7].

Besides CMKLR1, chemerin also exerts biological functions through two other receptors, GPR1 and CCRL2. GPR1 is highly expressed in adipose tissue and participates in the regulation of adipocyte differentiation and insulin-dependent glucose uptake [8]. CCRL2, mainly distributed on endothelial cells and immune cells, does not trigger conventional intracellular signaling but functions as a decoy receptor to modulate local chemerin concentration and gradient, thereby fine-tuning inflammatory cell recruitment [9].

Mechanistically, chemerin binding to CMKLR1 triggers rapid intracellular calcium mobilization and subsequent ERK1/2 phosphorylation, which in turn activates HSL and drives robust lipolytic breakdown of triglycerides in mature adipocytes [10].

In 2007, chemerin was first characterized as a functional adipokine [11]. Subsequent investigations have consistently validated its critical involvement in the pathogenesis of multiple metabolic disorders, including obesity [12] and type 2 diabetes mellitus (T2DM) [13].

In evaluating this body of work, it is important to recognize that most existing mechanistic evidence is derived from 3T3L1 cell lines and rodent models, where receptor expression patterns, proteolytic processing of chemerin, and downstream signaling intensity may differ substantially from human physiology. Notably, 2024 clinical and experimental findings further indicate that hepatocyte-derived chemerin isoforms (particularly huChem-157) display distinct, context-dependent functional effects on hepatic inflammation and fibrogenesis compared with adipose-derived isoforms, meaning total circulating chemerin levels cannot fully reflect local hepatic bioactivity [14]. Most current immunoassays only quantify total circulating chemerin without distinguishing inactive pro-chemerin and biologically active isoforms, which introduces substantial bias and reduces comparability between independent studies. Future research should adopt isoform-specific quantitative detection methods and replicate key mechanistic findings in primary human adipose and hepatic tissues.

Mechanisms of Chemerin in the Occurrence and Development of MAFLD

Chemerin Promotes Insulin Resistance

Insulin resistance (IR) is defined as an attenuated biological response of insulin target organs—predominantly skeletal muscle, liver, and adipose tissue—to physiological insulin concentrations. Its core features include reduced insulin-stimulated glucose uptake and storage, as well as failed suppression of hepatic gluconeogenesis. To preserve euglycemia, pancreatic β-cells compensate by increasing insulin secretion, leading to compensatory hyperinsulinemia; over time, this state further desensitizes peripheral tissues and establishes a vicious cycle of progressive IR [15].

IR is widely recognized as the central initiating mechanism driving MAFLD pathogenesis [16]. Under physiological conditions, hepatic insulin inhibits glycogenolysis and gluconeogenesis while promoting glycogen synthesis and de novo lipogenesis, jointly restraining excessive hepatic glucose output. In the context of IR, adipocyte insulin sensitivity declines, accompanied by impaired glucose uptake and utilization in fat tissue. Meanwhile, hyperinsulinemia stimulates robust lipid mobilization in adipose tissue; lipase activation accelerates triglyceride hydrolysis and releases large amounts of glycerol and free fatty acids (FFAs) into circulation, while simultaneously suppressing FFA oxidative clearance [17].

Elevated circulating FFAs penetrate hepatocytes and trigger hepatic oxidative stress. Accumulated oxidative metabolites activate IκB kinase β (IKKβ), which phosphorylates serine residues on insulin receptor substrate-1 (IRS-1). This post-translational modification disrupts canonical insulin signaling in target organs and aggravates systemic insulin resistance [18]. Excess FFAs absorbed by the liver are esterified into intracellular triglycerides (TGs) and deposit within hepatocytes, forming the core pathological feature of hepatic steatosis [16,24].

Clarification is warranted here: physiologically, insulin exerts potent antilipolytic effects on adipose tissue. This protective function is largely lost during IR, resulting in sustained FFA overflow even under hyperinsulinemic conditions. This distinction is critical for accurate mechanistic interpretation and targeted therapeutic development.

Cumulative evidence demonstrates that chemerin reduces systemic tissue insulin sensitivity and blocks insulin-mediated glucose uptake and utilization in peripheral organs, thereby accelerating the

onset and progression of IR. Additionally, chemerin represses glucose transporter 4 (GLUT4) transcription via inhibition of the PI3K/Akt signaling cascade, suppresses hepatic glycogen synthesis, and impairs peripheral glucose disposal to further worsen IR [10,21]. In a clinical cohort of patients with biopsy-proven NAFLD, circulating chemerin levels were significantly elevated compared with healthy controls, and independently correlated with the degree of insulin resistance and hepatic steatosis severity [19].

In vivo functional validation further supports the causal role of chemerin in metabolic dysregulation: chemerin knockout mice exhibit reduced body weight gain, improved systemic insulin sensitivity, and attenuated hepatic lipid accumulation under high-fat diet conditions, providing direct genetic evidence for chemerin as a pathogenic driver of IR and related metabolic disorders [20].

From a critical perspective, nearly all human clinical data are cross-sectional and vulnerable to confounding factors including adiposity burden, systemic low-grade inflammation, and concurrent medication use. Conclusions regarding chemerin-mediated regulation of GLUT4 require independent replication in primary human hepatocytes and in vivo functional validation at both protein and metabolic phenotype levels. Longitudinal cohorts and targeted interventional trials (e.g., selective CMKLR1 inhibition) are required to clarify whether chemerin is a causal driver of IR or merely a secondary biomarker reflecting underlying metabolic stress.

Chemerin Regulates Lipid Metabolism

The hallmark pathological feature of MAFLD is abnormal triglyceride overaccumulation within hepatocytes, termed hepatic steatosis. Adipose lipolysis describes the catabolic process where stored triglycerides in mature adipocytes are hydrolyzed to release FFAs and glycerol. Accumulating evidence indicates that chemerin functions as a positive modulator of adipose lipolysis, thereby increasing circulating free fatty acid (FFA) flux. In obesity, heightened basal lipolysis raises systemic FFA levels, which in turn upregulate chemerin expression in adipocytes, forming a positive feedback loop that amplifies metabolic dysregulation [21].

Researchers have demonstrated that chemerin upregulates lipolysis-related genes during adipocyte maturation and promotes the expression of adipogenic transcription factors during preadipocyte differentiation [21]. These observations have been independently validated by Fu et al. [6]. In fully differentiated adipocytes, chemerin induces robust lipolytic activity, reflected by elevated glycerol and FFA release, alongside increased expression of core lipolytic enzymes including HSL and lipoprotein lipase (LPL), as well as leptin.

Concurrently, during lipolysis or adipocyte dedifferentiation, chemerin suppresses the transcription of master adipogenic genes such as peroxisome proliferator-activated receptor γ (PPARγ), CCAAT/enhancer-binding protein α (C/EBPα), and fatty acid-binding protein 4 (FABP4). Silencing chemerin or its receptor CMKLR1 in preadipocytes severely impairs terminal adipocyte differentiation, confirming that the chemerin/CMKLR1 signaling axis is indispensable for adipogenic maturation. Moreover, chemerin facilitates intracellular lipid droplet formation throughout the differentiation process of preadipocytes.

A loss-of-function study conducted by Goralski et al. using 3T3-L1 obese adipocyte models revealed that chemerin gene knockout significantly downregulates key glucose and lipid metabolism regulators including GLUT4 and adiponectin. Meanwhile, genetic ablation of chemerin reduces intracellular lipolytic activity by approximately 50%–55% [21].

At the molecular level, chemerin binds CMKLR1 to trigger a rapid rise in intracellular calcium concentration in receptor-positive cells. This calcium signal activates ERK phosphorylation and subsequent HSL activation, driving robust lipolysis in mature adipocytes [21,22]. In the liver, exogenous chemerin administration directly exacerbates hepatocellular lipid accumulation. It markedly downregulates the mRNA expression of rate-limiting enzymes governing very-low-density lipoprotein (VLDL) secretion, impairing the liver's capacity to clear excess intracellular lipids [23].

Furthermore, chemerin inhibits LPL enzymatic activity while promoting de novo triglyceride synthesis, leading to massive triglyceride deposition within hepatocytes. Hydrolysis of accumulated hepatic triglycerides releases abundant FFAs, which generate excessive reactive oxygen species (ROS) during mitochondrial β-oxidation. Excessive ROS trigger lipid peroxidation and endoplasmic reticulum stress, and subsequently activate MAPK and NF-κB signaling cascades to drive the production of proinflammatory cytokines such as TNF-α and IL-6. This creates a self-perpetuating "oxidative stress–inflammation" vicious cycle that accelerates hepatocellular damage and drives disease progression from simple steatosis to steatohepatitis [24].

Methodologically, chemerin exhibits context-dependent dual functions: it promotes lipolysis in fully mature adipocytes while facilitating early-stage adipogenic differentiation of preadipocytes. This dual regulatory pattern varies based on chemerin isoform, local concentration, and cell differentiation status, making it difficult to predict net whole-organ lipid flux solely from single-cell data. Increased hepatic lipid deposition following exogenous chemerin treatment in vivo may be partially mediated by systemic IR and secondary inflammation. Hepatocyte-specific gain- and loss-of-function animal models, combined with direct quantitative measurement of VLDL secretion, are required to separate chemerin's direct hepatic effects from indirect systemic metabolic influences. Standardized detection methods capable of quantifying bioactive chemerin isoforms are also essential to reconcile inconsistent results across published literature.

Chemerin Mediates Inflammatory Responses

MAFLD is defined as a chronic inflammatory liver disease, with core pathological manifestations consisting of hepatic steatosis and massive inflammatory cell infiltration. In the early inflammatory phase, activated chemerin recruits diverse immune cells to hepatic inflammatory lesions via paracrine signaling or direct interaction with CMKLR1.

Liver-resident macrophages, namely Kupffer cells, are a major source of reactive oxygen species and proinflammatory mediators in MAFLD. Upon activation by lipid overload, they release hydrogen peroxide, nitric oxide, and a panel of proinflammatory cytokines (IL-1β, IL-6, TNF-α), recruit circulating immune cells to the liver, and drive hepatic acute-phase protein production, thereby amplifying local inflammatory damage [25].

Mass spectrometry proteomic analysis has confirmed that bioactive chemerin is produced at the very early stage of metabolic dysfunction. However, conflicting findings exist regarding the net inflammatory role of chemerin. The proinflammatory function of the chemerin/CMKLR1 axis is well documented in multiple

models, yet several independent studies have also reported anti-inflammatory effects under specific microenvironmental conditions.

Cash et al. proposed a stage-dependent dual regulatory model of chemerin: during the initiation phase of inflammation, chemerin acts as a classical proinflammatory chemokine that recruits neutrophils, macrophages, and natural killer cells to injury sites to amplify inflammatory cascades. During inflammation resolution, proteases released by neutrophils and other immune cells cleave full-length chemerin into distinct truncated isoforms with potent anti-inflammatory activity. This bidirectional regulatory property is determined by the dominant protease repertoire within the local tissue microenvironment and has been further supported by functional assays of chemerin-derived cleavage products [26].

In a lipopolysaccharide (LPS)-induced acute lung inflammation mouse model, chemerin/CMKLR1 signaling mobilizes pulmonary tissue macrophages while suppressing neutrophil recruitment and activation; this regulatory phenotype disappears completely in CMKLR1 knockout animals, verifying that the chemerin/CMKLR1 axis bears both pro- and anti-inflammatory regulatory capacity [27]. Further evidence supports a context-dependent dual role: chemerin predominantly exerts proinflammatory effects during the initiation and acute phase of inflammation, while it may contribute to inflammation resolution and restrain excessive chronic inflammatory damage under specific microenvironmental conditions [27].

Collectively, current evidence indicates chemerin functions as a bidirectional inflammatory mediator, yet the precise upstream and downstream signaling networks controlling its opposing activities remain incompletely characterized. Further exploration of the chemerin/CMKLR1 downstream signaling cascade may provide novel therapeutic targets for metabolic dysfunction–associated fatty liver disease.

From a translational viewpoint, whether net chemerin signaling exerts pro- or anti-inflammatory effects in MAFLD is largely dependent on disease stage, hepatic protease microenvironment, and differential receptor expression patterns. Most cited preclinical models adopt acute sterile inflammation or non-hepatic tissues; direct extrapolation of these results to chronic metabolic liver inflammation requires extreme caution. Future studies should quantify tissue-specific bioactive chemerin isoforms, perform parallel cytokine panel profiling, and match sample collection timepoints with precise MAFLD disease staging to resolve these context-dependent contradictory effects.

Chemerin Participates in the Progression of Liver Fibrosis

Liver fibrosis is a pivotal irreversible pathological transition stage in MAFLD progression. Chemerin drives fibrogenesis through hepatic stellate cell (HSC) activation and upregulation of profibrotic mediators, among which transforming growth factor-β1 (TGF-β1) is the most critical cytokine triggering chronic liver injury and extracellular matrix deposition [28].

The chemerin/CMKLR1 axis mediates the recruitment of CMKLR1-positive circulating macrophages to sites of persistent hepatic inflammation. After tissue infiltration and activation, these macrophages secrete large quantities of TGF-β1, which induces quiescent HSCs to transdifferentiate into myofibroblasts. Myofibroblasts overproduce collagen and other extracellular matrix components, disrupting normal hepatic lobule structure and liver function to establish progressive liver fibrosis, which ultimately progresses to irreversible cirrhosis without intervention. Notably, activated HSCs themselves also secrete TGF-β1 to create a positive feedback loop amplifying fibrogenic signaling [28].

At the molecular level, chemerin-induced HSC activation is largely dependent on the TGF-β1/Smad signaling cascade; chemerin stimulation upregulates the phosphorylation of Smad2 and Smad3, which translocate into the nucleus to promote the transcription of collagen I and α-smooth muscle actin (α-SMA), ultimately accelerating extracellular matrix deposition [29].

The chemerin/CMKLR1 axis further accelerates fibrogenesis by activating the PI3K/Akt, MAPK/ERK, and NF-κB signaling pathways, all canonical profibrotic signaling cascades [28]. These pathways jointly regulate fibroblast activation, extracellular matrix accumulation, and intrahepatic immune response remodeling.

In a cohort of patients with biopsy-confirmed NAFLD, serum chemerin levels were independently associated with histological fibrosis stage after adjustment for body mass index and other metabolic confounders. Patients with advanced fibrosis and significant necroinflammation exhibited markedly higher circulating chemerin concentrations than those with mild histological lesions [30]. These clinical observations imply chemerin acts as a central regulatory molecule governing the pathological transition from simple hepatic steatosis to progressive liver fibrosis. In line with this, a 2025 proteomic analysis of patients with metabolic dysfunction-associated steatotic liver disease further identified circulating chemerin as one of the core signature proteins strongly correlated with hepatic steatosis and necroinflammatory severity, reinforcing its potential as a non-invasive biomarker for disease risk stratification [31].

A 2019 systematic review and meta-analysis pooling data from over 2,000 participants further confirmed that elevated circulating chemerin is independently associated with increased risk of NAFLD, with moderate diagnostic accuracy for distinguishing patients with hepatic steatosis from healthy controls [32].

That said, statistical correlation cannot confirm causal relationships. Residual confounding factors including systemic inflammation, baseline insulin resistance, and renal chemerin clearance, as well as reverse causation, may partially explain this association. Causal inference requires large-scale longitudinal cohorts, Mendelian randomization analyses, and chemerin/CMKLR1-targeted interventional animal models with quantitative fibrosis endpoints. Dissecting macrophage-mediated indirect fibrotic effects from potential direct chemerin signaling on HSCs will be essential for translating basic research into clinical therapeutic strategies.

Conclusion

Systematic collation of existing preclinical and clinical evidence confirms that chemerin is a pleiotropic adipokine that bridges systemic metabolic stress and progressive hepatic injury. Beyond its well-documented associations with insulin resistance, aberrant adipogenesis, and chronic inflammation, converging mechanistic data implicate chemerin/CMKLR1 signaling in progressive hepatic fibrogenesis.

Nevertheless, research progress in this field is severely constrained by three major limitations: unresolved causal relationships between chemerin and MAFLD progression, heterogeneity of circulating chemerin isoforms with distinct biological activity, and inconsistent MAFLD diagnostic and phenotyping standards across clinical trials.

A clear roadmap for future investigation is proposed as follows: First, employ tissue-selective gene perturbation models to distinguish chemerin's independent regulatory effects in adipose tissue versus hepatocytes. Second, characterize the structure–activity relationships of distinct chemerin isoforms to develop receptor-biased pharmacological tools. Third, integrate isoform-specific chemerin quantification and standardized MAFLD clinical phenotyping into prospective multicenter longitudinal cohorts to track disease progression and therapeutic response.

In parallel, preclinical proof-of-concept interventional studies targeting the chemerin/CMKLR1 axis (genetic knockout or small-molecule receptor modulators) should prioritize clinically meaningful histological endpoints including steatosis resolution, necroinflammatory activity, and fibrosis regression, while fully adjusting for metabolic and inflammatory confounding variables. Encouragingly, a novel selective CMKLR1/GPR1 dual antagonist reported in 2025 has demonstrated potent inhibitory activity against chemerin-triggered intracellular signaling in cellular models, providing a refined pharmacological tool for subsequent in vivo validation of chemerin-targeted therapy for MAFLD [33]. Implementation of this research agenda will advance the field from correlational observational evidence to actionable pathogenic mechanisms, and ultimately verify whether pharmacological modulation of chemerin signaling can alter the natural clinical history of MAFLD.

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Ethics Approval and Consent to Participate.

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Conflict of Interest

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