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RESEARCH ARTICLE

Adipokines Overview: The Major Component of Immune Dysregulation

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Abstract: Purpose of Review: Obesity is increasingly recognized as an immune endocrine disorder rather than only a metabolic condition. This review critically examines how adipokines particularly adiponectin, resistin, adipsin, and chemerin mediate the interplay between obesity and autoimmunity. Unlike previous reviews that broadly surveyed cytokines, our focus is on comparative roles of specific adipokines across multiple autoimmune diseases. Recent Findings: Evidence demonstrates that these adipokines exert dual and sometimes contradictory immunomodulatory effects, shaping both metabolic dysfunction and autoimmune activity. Elevated adiponectin, resistin, and adipsin are observed in systemic lupus erythematosus and rheumatoid arthritis, while chemerin strongly correlates with psoriasis and multiple sclerosis activity. However, the clinical interpretation is complicated by differential effects of adipokine isoforms and context-specific receptor signaling. Summary: A critical gap remains in distinguishing protective versus pathogenic adipokine actions and in understanding how adipose-derived versus tissue-localized adipokines differentially influence disease progression. Future research should standardize measurement of adipokine isoforms, explore causal pathways through longitudinal and mechanistic studies, and evaluate whether targeting adipokines could provide dual benefits in obesity-related and autoimmune disorders.

Keywords: Obesity, Autoimmunity, Adipokines, Inflammation, Immunometabolism

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Introduction

Obesity affects nearly half of the global adult population and is linked not only to metabolic syndromes such as type 2 diabetes and NAFLD but also to immune-mediated conditions, including Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), and Multiple Sclerosis (MS) [153,2]. Beyond genetics, diet, and the microbiome [3, 4], a central element in this connection is white adipose tissue as an active endocrine organ, releasing a range of adipokines that regulate both metabolism and immunity [5–7].

Previous reviews have extensively discussed cytokine-driven inflammation in obesity. However, few have systematically evaluated the comparative contributions of individual adipokines across autoimmune diseases. Most focus on single conditions (e.g., adiponectin in RA) or single pathways, leaving unresolved questions about:

(i) Why certain adipokines act pro-inflammatory in one disease and anti-inflammatory in another

(ii) How adipokine isoforms or receptor signaling determine these effects

(iii) Whether adipose-derived versus local tissue-derived adipokines play distinct pathogenic roles [8-10]. This review addresses these gaps by focusing on four adipokines adiponectin, resistin, adipsin, and chemerin that represent major but mechanistically diverse mediators of immune dysregulation

To guide readers, a schematic overview (Figure 1) is added in the introduction, summarizing hypothesized pathways by which adipokines link obesity to autoimmunity.

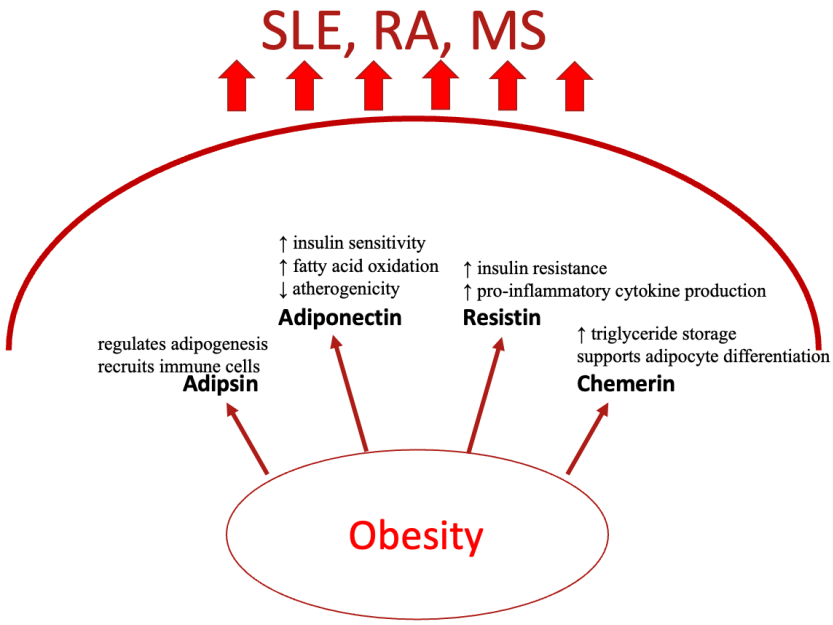

Fig. 1: Concept of the adipokines impact on autoimmune diseases

Methodology

This review followed a structured literature search to ensure comprehensive and transparent selection of studies. We searched PubMed, Scopus, and Web of Science from January 2019 to June 2025 using the terms “adipokine” AND “obesity” AND “autoimmunity”, along with specific adipokine names (adiponectin, resistin, adipsin, chemerin). Additional references were identified from bibliographies of included articles.

Inclusion criteria: original research and review articles in English that reported mechanistic, clinical, or translational findings on adipokines in the context of obesity and autoimmune diseases.

Exclusion criteria: non-peer-reviewed sources, animal studies without immune endpoints, and studies reporting only metabolic outcomes unrelated to autoimmunity.

A total of 263 studies were screened, and 173 were included. Data were synthesized narratively, with emphasis on mechanistic insights, cross-disease comparisons, and identification of gaps.

Adiponectin

Adiponectin demonstrates context-dependent actions in autoimmunity, shaped by isoform predominance, receptor engagement, and disease-specific immune environments. In SLE and RA, elevated (especially HMW) ApN correlates with

more severe disease, supporting a pathogenic role. In MS, reduced HMW ApN reflects a loss of protective signaling, supporting a neuroprotective role. In T1DM, the significance of elevated ApN remains ambiguous.

Rather than being inherently pro- or anti-inflammatory, ApN acts as a molecular switch, where the outcome depends on isoform ratios and receptor-specific signaling. Translational limitations remain, since murine models often differ from human biology, but accumulating human cohort data increasingly highlight the isoform-dependent nature of these effects. This integrated view clarifies apparent contradictions in the literature and underscores the importance of isoform-specific, large-scale human studies to determine whether ApN could serve as a biomarker or therapeutic target in autoimmune diseases [176].

Structure and Receptors

Adiponectin (ApN) is a 30-kDa adipokine secreted mainly by adipocytes, circulating in Low-Molecular-Weight (LMW), Middle-Molecular-Weight (MMW), and High-Molecular-Weight (HMW) forms [11-14]. These isoforms differ in bioactivity and receptor affinity. ApN acts through AdipoR1, AdipoR2, and T-cadherin, which vary in tissue distribution and downstream signaling. AdipoR1 preferentially activates AMPK pathways, AdipoR2 engages PPAR-α signaling, while T-cadherin binds HMW multimers and modulates cardiovascular and endothelial functions [15-19]. The diversity of isoforms and receptors provides a molecular basis for the apparently contradictory effects of ApN observed in immune regulation [20-24].

Adiponectin Impact on the Immune Function

Adiponectin (ApN) exerts pleiotropic effects on the immune system, with outcomes largely determined by its isoform, receptor engagement, and the inflammatory context [25, 26]. Its receptors, including AdipoR1, AdipoR2, and T-cadherin, are widely expressed on immune cells, enabling ApN to influence both innate and adaptive immunity in a highly context-dependent manner.

In monocytes and macrophages, ApN modulates cytokine production in opposing ways depending on the receptor pathway and molecular form. The globular form of ApN, acting through AdipoR1–MAPK/NF-κB signaling, stimulates secretion of TNF-α and IL-6, favoring classical M1-like polarization [27–29]. In contrast, full-length High Molecular Weight (HMW) ApN primarily signals through AdipoR2, leading to PPAR-α activation, upregulation of IL-10 and arginase-1, and the induction of anti-inflammatory M2-like macrophages [29]. Studies in ApN-deficient mice support this dualism: adipose tissue in these models contains increased numbers of M1 macrophages producing high levels of IL-6, MCP-1, and TNF-α, whereas reconstitution with HMW ApN restores an anti-inflammatory profile [27, 28]. Thus, the apparent contradictions in macrophage responses reflect isoform-specific and receptor-specific signaling rather than genuine inconsistencies.

Dendritic Cells (DCs) also demonstrate dual sensitivity to ApN. Engagement of AdipoR1 activates p38 MAPK and JNK pathways, enhancing IL-12 release and promoting polarization of naïve T cells into Th1 and Th17 subsets [30–32]. However, stimulation of AdipoR2 results in AMPK activation, which suppresses NF-κB activity, reduces expression of costimulatory molecules, and favors the induction of regulatory T cells (Tregs) [33–35]. These seemingly conflicting outcomes are partly explained by differences in DC generation methods, timing of ApN exposure, and differential receptor expression, underscoring the complexity of its immunoregulatory role.

Beyond antigen-presenting cells, ApN also influences lymphocytes. In T cells, adipocyte-derived ApN from high-fat diet-fed mice increases the frequency of IFN-γ^+ and IL-17^+ subsets, while under standard diet conditions ApN decreases the number of such pro-inflammatory T cells [36–38]. Moreover, CD4^+ T cells themselves can serve as a local source of ApN in transplanted hearts, suggesting a role in tissue-specific immune regulation [39–43]. B lymphocytes exhibit similarly heterogeneous responses: AdipoR1–ERK1/2 signaling enhances proliferation and plasma cell differentiation [44–46], whereas AdipoR2–AMPK signaling reduces antibody secretion [48, 49, 62]. These divergent effects likely reflect not only receptor usage but also the circulating balance of Low Molecular Weight (LMW), Medium Molecular Weight (MMW), and HMW isoforms.

Natural killer (NK) cells are also modulated by ApN. Short-term AdipoR1-driven STAT3 activation enhances IFN-γ release, promoting anti-viral and anti-tumor immunity [36–38]. Conversely, chronic exposure to ApN through sustained AMPK activation dampens NK cell cytotoxicity, demonstrating that ApN can both amplify and restrain NK activity depending on the temporal and metabolic context [39–43].

Taken together, these findings highlight that the apparently contradictory functions of ApN can be reconciled by considering isoform-specific signaling and receptor engagement. In general, LMW isoforms acting via AdipoR1 promote pro-inflammatory responses, while HMW isoforms engaging AdipoR2 and T-cadherin mediate anti-inflammatory and tolerogenic effects. This balance is critical in obesity, autoimmunity, and metabolic inflammation, where disruptions in isoform distribution and receptor signaling may tip the immune system toward either protective regulation or pathological activation (Table 2).

Adiponectin in Autoimmune Disorders

In Systemic Lupus Erythematosus (SLE), multiple large-scale patient studies and meta-analyses confirm elevated serum ApN levels compared with healthy controls [177]. Higher ApN correlates with disease activity scores, lupus nephritis, and inflammatory cytokine burden [178]. Importantly, some cohorts show disproportionate increases in HMW ApN, raising the possibility that isoform imbalance drives pathogenic inflammation rather than representing a protective compensation [179, 180]. In Rheumatoid Arthritis (RA), ApN is consistently elevated in serum and synovial fluid, where it correlates with disease activity, erosive progression, and radiographic damage [181,182]. Synovial fibroblasts exposed to ApN upregulate IL-6 and MMPs, providing a mechanistic link between ApN and joint destruction [183]. Again, elevated HMW fractions in RA patients point to isoform-specific pathogenicity [184].

By contrast, Multiple Sclerosis (MS) patients exhibit reduced ApN-particularly lower HMW isoforms compared to healthy controls [185]. This reduction correlates with increased disability scores and greater MRI lesion burden [186, 187]. Experimental Autoimmune Encephalomyelitis (EAE) models support a protective role: ApN-deficient mice develop more severe disease and heightened microglial activation [188, 189]. These findings suggest that in MS, HMW ApN provides neuroprotective and anti-inflammatory signaling that is lost in patients [190].

Human clinical data in type 1 Diabetes Mellitus (T1DM) remain more limited, but several cohorts demonstrate elevated ApN levels, particularly in patients with vascular complications [191]. Whether these elevations are compensatory (protective against endothelial dysfunction) or pathogenic (promoting chronic inflammation) is still unresolved [192].

Clinical Significance of Isoform Balance

Evidence across autoimmune and metabolic diseases emphasizes that total ApN measurements are insufficient. HMW isoforms are the most metabolically active, enhancing insulin sensitivity and vascular protection [193]. However, in SLE and RA, disproportionate increases in HMW ApN appear to coincide with greater inflammatory activity and tissue injury [194]. Conversely, in MS, reduced HMW/total ApN ratios predict worse outcomes [195]. Thus, the balance among isoforms and their receptor-specific signaling-likely determines whether ApN acts as a protective or pathogenic factor. Unfortunately, most clinical studies do not measure isoform distribution, which limits mechanistic interpretation. Addressing this gap in large patient cohorts is essential for clarifying ApN's role and therapeutic potential.

Resistin

Resistin shows divergent biological roles in mice versus humans: in mice, primarily a metabolic factor; in humans, primarily an immune mediator. Through CAP1- and TLR4-dependent signaling, resistin amplifies NF-κB–driven cytokine cascades and endothelial activation, linking it to chronic inflammation. In SLE and RA, elevated resistin consistently correlates with disease activity and tissue damage, supporting a pathogenic role. In MS, emerging evidence suggests resistin contributes to neuroinflammation. In T1DM, resistin's contribution remains ambiguous [196].

Overall, resistin should be considered not simply as an adipokine but as a pro-inflammatory cytokine-like factor in humans. Its strong associations with autoimmune activity, rather than obesity or insulin resistance, suggest that resistin may serve as both a biomarker of immune activation and a potential therapeutic target in chronic inflammatory disease [197].

Resistin Structure, Receptors, and Function

Resistin, a cysteine-rich secretory protein, was first identified in mice as an adipocyte-derived factor linking obesity to insulin resistance [59, 60]. Structurally, it forms homodimers stabilized by disulfide bonds, circulating as oligomeric complexes of varying bioactivity [61, 62]. In mice, resistin is produced mainly by adipocytes and contributes directly to glucose intolerance and insulin resistance [63, 64]. In humans, however, resistin is secreted predominantly by monocytes and macrophages, reflecting a fundamental species divergence that complicates translation of murine findings [65-68]. This difference explains why human studies show weak correlations with BMI and insulin resistance but consistent associations with inflammation and autoimmunity [69-71].

Resistin and Immune Mechanisms

Resistin exerts multiple pro-inflammatory effects in human immune cells, primarily through receptor-mediated signaling. Binding to adenylyl Cyclase–Associated Protein 1 (CAP1) activates cAMP–PKA–NF-κB signaling, which in turn upregulates the transcription of key cytokines, including TNF-α, IL-6, and IL-1β [72, 73]. In macrophages, resistin promotes TNF-α and IL-12 production via NF-κB–dependent mechanisms, while in monocytes it can enhance Toll-Like Receptor 4 (TLR4) signaling, thereby amplifying innate immune responses [74–76]. The release of resistin from peripheral blood mononuclear cells and infiltrating monocytes is itself triggered by inflammatory mediators such as IL-6, IL-1β, CRP, and TNF-α, creating a feed-forward loop that sustains inflammation [72–76].

Resistin also contributes to vascular inflammation and dysfunction. In endothelial cells, it induces the expression of adhesion molecules such as VCAM-1 and ICAM-1 through ERK1/2 and p38 MAPK activation, facilitating leukocyte recruitment to inflamed tissues and linking systemic inflammation to cardiovascular pathology [198].

Beyond its effects on innate immunity, resistin also influences adaptive immune responses. In dendritic cells, resistin promotes IL-12 production, which drives Th1 polarization [199]. In T cells, resistin enhances proliferation and IFN-γ secretion, further strengthening pro-inflammatory pathways [200]. In B cells, it upregulates BAFF expression, indirectly supporting autoantibody production, a process highly relevant to autoimmune disease [201]. However, not all evidence points uniformly toward a pro-inflammatory role. Some studies report that resistin can suppress cytokine production and reduce antigen uptake in monocyte-derived human dendritic cells, thereby promoting the expansion of regulatory T cells [77, 78].

Taken together, these findings establish resistin as a key mediator at the interface of metabolic stress and immune activation. Its ability to activate CAP1- and possibly TLR4-dependent pathways, amplify both innate and adaptive immune responses, and modulate endothelial activation positions resistin as a significant contributor to chronic inflammation and autoimmunity. Nevertheless, contradictory findings particularly regarding its potential tolerogenic effects in dendritic cells highlight the need for further mechanistic studies and large-scale human data to clarify whether resistin acts exclusively as a pro-inflammatory driver or also serves compensatory regulatory functions in specific contexts.

Resistin in Autoimmune Disorders

- Systemic Lupus Erythematosus (SLE): Several cohort studies demonstrate elevated serum resistin in SLE patients compared with controls [202,203]. High resistin correlates with disease activity indices, renal involvement, and systemic inflammation [204]. Mechanistically, resistin enhances Neutrophil Extracellular Trap (NET) formation and synergizes with type I IFN responses, both central to SLE pathogenesis [205]
- Rheumatoid Arthritis (RA): Resistin levels are elevated in both serum and synovial fluid, with synovial concentrations often exceeding systemic levels [206]. Locally, resistin stimulates fibroblast-like synoviocytes to produce IL-6, IL-8, and MMPs, promoting pannus formation and joint destruction [207,208]. Clinically, higher resistin associates with more severe joint damage and poor therapeutic response [209]
- Multiple Sclerosis (MS): Data are more limited, but increased resistin levels have been detected in the cerebrospinal fluid of MS patients and correlate with disability progression [210]. Experimental Autoimmune Encephalomyelitis (EAE) models suggest resistin may exacerbate neuroinflammation by promoting microglial activation and TNF-α release [211]
- Type 1 Diabetes Mellitus (T1DM): Results are heterogeneous: some studies report higher resistin in patients, especially those with microvascular complications, while others find no significant differences [212]. Resistin may contribute to β-cell dysfunction and vascular injury, but its role in T1DM remains less defined compared with SLE and RA [213]

Adipsin

Adipsin occupies a unique niche among adipokines, functioning both as an adipose-derived factor and as a complement system protease. In RA, adipsin contributes to local complement activation, driving synovial inflammation and joint destruction. In SLE, altered adipsin levels reflect complex interactions with systemic complement activity, though evidence is mixed. Translational studies highlight adipsin as both a disease biomarker and a potential therapeutic target, with complement inhibitors offering a rational strategy for intervention [214].

Future work must clarify tissue-specific sources of adipsin, standardize measurement approaches, and assess its predictive value in large autoimmune cohorts.

Adipsin Structure

Adipsin, also known as complement factor D, is a serine protease primarily secreted by adipocytes, macrophages, and hepatocytes. Structurally, it is a 28-kDa protein that plays an essential role in the alternative complement pathway, where it cleaves factor B in complex with C3b to generate the C3 convertase (C3bBb) [86-88]. This positions adipsin at the crossroads of adipose biology, innate immunity, and inflammation [89].

Adipsin and Immune Mechanisms

Adipsin, originally identified in adipose tissue by Spiegelman and colleagues in the late 1980s, was later recognized as complement factor D, a central enzyme of the alternative complement pathway [86, 87]. While most soluble complement proteins are synthesized in the liver, adipsin is predominantly produced in adipose tissue, underscoring its role at the interface between metabolism and immunity [88–90]. Along with complement Component 3 (C3) and Factor B, which are also expressed in adipose tissue at lower levels, adipsin drives activation of the alternative pathway. This results in the cleavage of C3 and the generation of biologically active fragments that link innate immunity with inflammatory signaling.

One of the major products of adipsin-mediated complement activation is C3a, an anaphylatoxin that promotes chemotaxis, increases vascular permeability, and recruits neutrophils and macrophages to inflamed sites [91, 92]. The C3a receptor (C3aR), expressed on both adipocytes and macrophages, is upregulated in the context of high-fat diet feeding. Mice deficient in C3aR display protection against metabolic disturbances, highlighting the importance of adipsin-driven C3a signaling in obesity-associated inflammation [91, 92]. A related metabolite, C3adesArg generated through exopeptidase activity acts as Acylation-Stimulating Protein (ASP), which regulates fatty acid uptake, glucose transport, and triglyceride synthesis in adipocytes, thereby linking complement activity to metabolic regulation [93, 94]. Through these pathways, adipsin not only amplifies innate immune responses but also directly influences energy balance and adipocyte function.

Adipsin further modulates immune cell polarization. In macrophages, complement activation through the adipsin–C3a axis enhances M1-like activation and stimulates pro-inflammatory cytokine production, contributing to tissue inflammation [91, 92]. In T cells, complement fragments generated downstream of adipsin indirectly shape activation and survival, thereby influencing adaptive immunity [215]. This dual role situates adipsin as both an immune amplifier and a metabolic regulator.

Experimental evidence supports its involvement in systemic inflammation and metabolic disease. In mice lacking adipsin, weight gain under high-fat diet conditions is attenuated, accompanied by reduced adipose tissue inflammation, fewer mast cells, and diminished crown-like structures [95, 96]. Despite these seemingly protective features, adipsin deficiency also results in impaired glucose tolerance due to insulinopenia from compromised pancreatic β-cell function [95, 96]. Conversely, restoration of adipsin in db/db mice using recombinant protein improves fasting glucose levels and glucose tolerance, effects mediated by C3a signaling [97–99]. These findings illustrate that adipsin can simultaneously exacerbate inflammatory responses while supporting metabolic homeostasis.

Clinically, adipsin levels are consistently elevated in autoimmune diseases such as Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA), particularly in patients with renal involvement such as lupus nephritis [202]. This observation reinforces its central contribution to complement activation in autoimmunity. Although its predominant activity aligns with pro-inflammatory mechanisms, emerging data suggest that adipsin also sustains β-cell function and metabolic regulation, highlighting its dual role as both a pathogenic and potentially protective mediator at the adipose–immune interface.

Adipsin in Autoimmune Disorders

- Rheumatoid Arthritis (RA): Elevated adipsin has been detected in synovial fluid and synovial tissue of RA patients [102]. Local adipsin drives complement activation, fueling joint inflammation and cartilage destruction [102]. Experimental arthritis models show that adipsin deficiency reduces disease severity, whereas adipose tissue transplants restore pathology, confirming that adipose-derived adipsin sustains RA progression [103]. Clinically, higher adipsin levels associate with more aggressive joint disease and may serve as a biomarker of synovial inflammation [104]
- Systemic Lupus Erythematosus (SLE): Altered adipsin levels have been reported in SLE, though findings remain inconsistent. Some studies describe increased circulating adipsin correlating with renal involvement and complement

activation, while others show reduced levels, potentially reflecting complement consumption in active disease [100,101]. This discrepancy highlights the need for isoform- and tissue-specific analyses in lupus cohorts

- Other autoimmune conditions: Limited data suggest possible roles for adipsin in multiple sclerosis and type 1 diabetes, but mechanistic evidence remains sparse. Complement dysregulation in these diseases makes adipsin a plausible contributor, though direct clinical evidence is lacking [105, 106]

Therapeutic and Biomarker Potential

Given its central role in the alternative complement pathway, adipsin represents a promising therapeutic target. Inhibitors of factor D are already in development for complement-mediated diseases such as paroxysmal nocturnal hemoglobinuria (PNH) and age-related macular degeneration [216, 217]. Similar strategies could be explored in RA and lupus to limit complement-driven tissue injury.

As a biomarker, synovial and serum adipsin levels may help identify patients with complement-driven inflammation, guiding personalized therapeutic approaches. Combining adipsin measurement with other adipokines (adiponectin, resistin, chemerin) could refine disease phenotyping in autoimmune disorders.

Chemerin

Chemerin acts at the intersection of adipose biology and immune regulation, with effects determined by isoform processing and receptor engagement (Tables 1 and 2). In psoriasis and RA, chemerin appears predominantly pathogenic, driving leukocyte recruitment and tissue destruction. In SLE, its role is less defined but correlates with systemic inflammation. In MS, experimental data support a contribution to neuroinflammation [218].

Overall, chemerin functions as both a chemoattractant and adipokine, positioning it as a candidate biomarker and therapeutic target in autoimmune disease. Future studies must clarify isoform-specific roles and optimize receptor-targeted interventions.

Chemerin Receptors and Function

Chemerin is a secreted protein that functions as both an adipokine and a chemoattractant cytokine. It is synthesized as an inactive precursor (prochemerin, 163 amino acids) and requires proteolytic cleavage by serine or cysteine proteases to generate active isoforms with distinct biological activities [107-111]. This processing creates structural diversity, explaining the context-dependent functions of chemerin in metabolic and immune regulation.

Table 1: Adipokines and Their Roles in Obesity and Autoimmune Disorders

Adipokine	Structure	Receptors	Functions in Obesity	Impact on Autoimmune Disorders	Evidence Strength / Model
Adiponectin	30-kDa protein, multimeric forms	AdipoR1, AdipoR2, T-cadherin	Increases insulin sensitivity, promotes fatty acid oxidation, anti-atherogenic	↑ in SLE (human plasma, murine lupus models); correlates with RA activity (synovial fluid); ↓ in MS (clinical cohorts)	Moderate–strong (multiple human cohorts; murine models)
Resistin	12.5-kDa cysteine-rich polypeptide	CAP1 (in humans)	Promotes insulin resistance, pro-inflammatory cytokine production	↑ in RA (synovial fluid, serum); ↑ in SLE (plasma, renal involvement); ↑ in psoriasis (human studies); role in MS unclear	Strong in human studies; limited mechanistic murine data
Adipsin	Complement factor D	C3aR	Promotes triglyceride storage; supports adipocyte differentiation	↑ in SLE (linked to renal involvement, human studies); ↑ in RA (synovial fluid, plasma); little data in MS/psoriasis	Moderate (human clinical data, complement studies)
Chemerin	Chemoattractant protein	CMKLR1, GPR1	Regulates adipogenesis, recruits immune cells	↑ in psoriasis (lesional skin, plasma); ↑ in MS (EAE mouse model, human CSF); ↑ in RA synovium; less consistent in SLE	Strong (psoriasis, MS); moderate (RA, SLE)

Chemerin signals through three receptors:

- CMKLR1 (ChemR23): the primary signaling receptor, mediating most metabolic and immunologic effects [112-114]
- GPR1: binds chemerin with high affinity, but its downstream functions remain less defined [115-116]
- CCRL2: a non-signaling receptor that sequesters chemerin at inflammatory sites, enhancing local gradients [117-119]

Table 2: Adipokines and Immune Function

Adipokine	Effects on Immune Cells	Pro-inflammatory Activity	Anti-inflammatory Activity
Adiponectin	Stimulates IL-6 and MCP-1 in synovial fibroblasts; promotes IL-10 in macrophages	↑ IL-6, ↑ TNF-α in joint tissues (RA)	↑ IL-10 in macrophages; promotes M2 polarization
Resistin	Stimulates TNF-α, IL-12 in macrophages; reduces antigen uptake by DCs	↑ TNF-α, ↑ IL-12 (human monocytes, RA synovial fluid)	Expands Tregs via DC modulation (limited data)
Adipsin	Enhances complement C3 convertase formation; recruits immune cells via C3a	↑ Complement activation, inflammation in lupus nephritis	Possible protective metabolic effects (controversial)
Chemerin	Recruits plasmacytoid DCs, macrophages, NK cells; promotes Th17 skewing	↑ DC trafficking in psoriasis; ↑ Th17 in EAE	Limited anti-inflammatory isoform data

Chemerin and Immune Mechanisms

Chemerin is secreted by adipocytes, endothelial cells, and inflammatory cells, acting as a molecular bridge between metabolic stress and immune activation. Its receptors are widely expressed on immune cell subsets, and their engagement shapes both innate and adaptive immune responses. CMKLR1 is found on plasmacytoid, myeloid, and immature dendritic cells, as well as on macrophages derived from monocytes, where it mediates their migration to inflamed tissues [120–124]. By binding to CMKLR1 on circulating plasmacytoid dendritic cells, chemerin recruits them into visceral white adipose tissue, where they release type I interferons, thereby promoting the proinflammatory polarization of resident macrophages [120–122]. In macrophages, CMKLR1 signaling activates MAPK and PI3K/AKT pathways, enhancing the production of proinflammatory cytokines such as TNF-α, IL-6, and IL-1β [219]. Research by Herova and colleagues further indicated that CMKLR1 is expressed predominantly on M1 macrophages, but not on M2 macrophages, supporting its role in recruiting classically activated macrophages to inflammatory sites [125].

Chemerin also functions as a potent chemoattractant for natural killer (NK) cells, guiding CD56CD16+ subsets to inflammatory locations, where their IFN-γ secretion amplifies local immune activation [126]. In addition, chemerin regulates dendritic cell function, as chemerin-activated DCs release IL-6 and IL-23, thereby promoting Th17 differentiation and supporting pro-inflammatory polarization of T cells [133]. Through this mechanism, chemerin indirectly shapes adaptive immune responses. CCRL2, a non-signaling chemerin receptor, is expressed on neutrophils, macrophages, T cells, mast cells, dendritic cells, and NK cells, where it stabilizes chemerin gradients at inflamed sites. Mice lacking CCRL2 exhibit heightened inflammatory responses to peritonitis, accompanied by increased accumulation of monocytes and neutrophils in the peritoneal cavity, underscoring the receptor's modulatory role in acute inflammation [126, 127].

In adipose tissue, chemerin exerts additional effects on metabolism by regulating adipocyte differentiation, glucose uptake, and lipolysis. Elevated circulating levels of chemerin, particularly in obesity and high-fat diet models, correlate with macrophage infiltration into adipose depots and the development of systemic insulin resistance. Thus, chemerin acts as a multifaceted mediator that connects adipose tissue dysfunction with both innate and adaptive immune responses, linking metabolic stress to chronic inflammation and autoimmune activation.

Chemerin in Autoimmune Disorders

- Psoriasis: Chemerin is highly expressed in psoriatic skin lesions, where it recruits plasmacytoid Dendritic Cells (pDCs) via CMKLR1 [128]. These pDCs release type I interferons, initiating the psoriatic inflammatory cascade. Serum chemerin levels correlate with Psoriasis Area and Severity Index (PASI) scores, suggesting a role as a disease activity biomarker [129]
- Systemic Lupus Erythematosus (SLE): Patients with SLE display elevated serum chemerin, correlating with disease activity and renal involvement [130]. Mechanistically, chemerin promotes macrophage and DC infiltration, sustaining type I IFN–driven immune activation [131,132]. However, isoform-specific data are lacking, and whether chemerin is pathogenic or compensatory remains unclear
- Rheumatoid Arthritis (RA): Chemerin is significantly increased in RA synovial fluid and tissue [133,134]. Locally, chemerin stimulates fibroblast-like synoviocytes to produce IL-6, IL-8, and MMPs, thereby promoting pannus formation and cartilage destruction [133]. Serum chemerin correlates with disease activity scores and joint erosion [133]. Elevated CMKLR1 expression in synovium further underscores the functional significance of this axis [133]

- Multiple Sclerosis (MS): Data are less consistent. Some studies report increased chemerin in cerebrospinal fluid and active brain lesions, suggesting a role in leukocyte recruitment [xx]. In Experimental Autoimmune Encephalomyelitis (EAE), CMKLR1 deficiency reduces disease severity, supporting a pathogenic role [135,136]

Therapeutic Implications

Given its dual roles in metabolism and immunity, chemerin has emerged as a therapeutic target. CMKLR1 antagonists and chemerin-neutralizing antibodies have shown efficacy in preclinical models of psoriasis and arthritis, reducing inflammatory cell recruitment and cytokine production [220]. Circulating chemerin and its active isoforms are also being explored as biomarkers for disease activity in psoriasis and RA [221]. However, the structural and isoform complexity of chemerin remains a barrier to clinical translation.

Cytokines

TNF-α Production and Activity

TNF-α was among the first cytokines recognized as being secreted by adipose tissue. Spiegelman and colleagues demonstrated that visceral white adipose tissue and spleen are primary endogenous sources of TNF-α in obese mouse models, with mRNA levels up to ten-fold higher in db/db compared with lean mice [137]. Similar findings were observed in ob/ob mice and Zucker rats, while human studies confirmed elevated TNF-α expression in adipose tissue and positive correlations with BMI [138, 139]. Although both adipocytes and macrophages contribute, adipose tissue macrophages (ATMs) are considered the main source [138, 139].

Structurally, TNF-α is first produced as a 26-kDa transmembrane monomer that can be cleaved by TNF-α Converting Enzyme (TACE) into a 17-kDa soluble form. Both variants form bioactive homotrimers. TNF-α exerts its effects through two receptors TNFR1 and TNFR2 which differ in their intracellular signaling domains [140, 141]. TNFR1 predominates in adipose tissue and activates NF-κB, MAPKs, ceramide synthesis, and apoptotic pathways [142–144].

Several triggers underlie increased TNF-α in obesity, including adipocyte stress and death, which recruit monocytes that differentiate into ATMs, and elevated circulating fatty acids, which potentiate cytokine release [145,146]. In turn, TNF-α alters the adipokine milieu by suppressing adiponectin and upregulating leptin and visfatin, amplifying local inflammation [147,148].

From an immunological perspective, acute TNF-α elevation enhances Th1 differentiation and effector responses, while chronic exposure leads to Treg suppression, low-grade inflammation, and heightened risk for autoimmunity [149,150]. Elevated TNF-α is a well-established pathogenic factor in rheumatoid arthritis and inflammatory bowel disease, forming the rationale for anti-TNF biologics. In obesity, persistent TNF-α signaling may prime immune dysregulation that contributes to autoimmune risk, positioning adipose tissue as an active participant in systemic autoimmunity.

IL-6 Structure and Function

IL-6 is a glycoprotein of ~21–28 kDa comprising four α-helices and several functional domains, including an N-terminal domain, a helical bundle, and a C-terminal region responsible for receptor interaction [151]. It binds to the IL-6 receptor α chain (IL-6Rα), which then complexes with gp130, triggering intracellular signaling. Two modes of signaling exist: Classic signaling, mediated by membrane-bound IL-6Rα and associated with regenerative and anti-inflammatory effects, and rans-signaling, mediated via soluble IL-6Rα and implicated in chronic inflammation and autoimmunity [152, 153].

Adipocytes and ATMs produce approximately one-third of circulating IL-6, making adipose tissue a substantial contributor [151–153]. Elevated IL-6 correlates with BMI and waist circumference, but its metabolic impact is paradoxical. In rodents, acute IL-6 administration impairs insulin signaling and increases triglycerides [154–156]. Yet IL-6 knockout mice develop obesity and insulin resistance, while IL-6 replacement reverses these phenotypes [157]. These discrepancies likely reflect tissue-specific and context-dependent IL-6 activity. For instance, myeloid-derived IL-6 in adipose tissue improves glucose tolerance and suppresses M1 macrophage polarization, whereas adipocyte-derived IL-6 fosters macrophage infiltration [157].

Beyond metabolism, IL-6 plays a central role in autoimmunity. In RA, IL-6 promotes Th17 differentiation and synovial inflammation, directly correlating with disease activity. In SLE, elevated IL-6 drives B-cell hyperactivity, autoantibody production, and nephritis severity. In MS, IL-6 amplifies Th17-driven neuroinflammation. The critical importance of IL-6 in autoimmune diseases is underscored by the clinical success of IL-6R inhibitors such as tocilizumab.

Thus, while IL-6 in obesity is often framed as a metabolic mediator, its dual signaling mechanisms protective in metabolic homeostasis but pathogenic in chronic inflammation place it at the crossroads between obesity-induced immune dysregulation and autoimmunity.

MCP-1 in Obesity and Autoimmunity

Monocyte chemoattractant protein-1 (MCP-1/CCL2) is a 13-kDa chemokine produced by endothelial cells, adipocytes, and macrophages, exerting its effects primarily through CCR2 [158–160]. CCR2A is expressed on mononuclear and vascular smooth muscle cells, whereas CCR2B dominates on monocytes and NK cells.

In obesity, MCP-1 is upregulated in adipose tissue and circulation, where it recruits monocytes that differentiate into ATMs, fueling inflammation and insulin resistance [161–163]. Interestingly, MCP-1 also supports local macrophage proliferation within adipose tissue, even in the absence of circulating monocytes, highlighting its dual role in recruitment and expansion [164]. However, contradictory findings exist some MCP-1 knockout studies show protection against insulin resistance and hepatic steatosis, while others do not [165]. These inconsistencies may reflect compensation by other chemokines or differences in diet-induced obesity models.

Mechanistically, MCP-1/CCR2 signaling favors M1 macrophage polarization, reduces M2 anti-inflammatory populations, and disrupts adipocyte–immune crosstalk, sustaining chronic inflammation. Systemically, elevated MCP-1 is linked to vascular dysfunction, atherosclerosis, and tissue infiltration in obesity, extending its role beyond adipose tissue.

In autoimmunity, MCP-1 contributes to leukocyte trafficking into inflamed tissues. In RA, high MCP-1 levels correlate with synovial macrophage infiltration and joint damage. In SLE, MCP-1 is associated with lupus nephritis and glomerular monocyte accumulation. In MS, MCP-1 expression in brain lesions facilitates monocyte infiltration and demyelination. Thus, MCP-1 bridges metabolic stress with systemic autoimmunity, positioning the MCP-1/CCR2 axis as a therapeutic target under investigation for both metabolic and autoimmune diseases.

Unclear Role of IL-10 in Obesity

IL-10 is a cytokine produced by a variety of cell types, including T helper 2 cells, macrophages, and B lymphocytes. While it impacts multiple cell types, its primary function is to modulate inflammation. IL-10 promotes the release of soluble TNF- α receptors and IL-1 receptor antagonists, which help to reduce the activity of pro-inflammatory cytokines. Additionally, it inhibits Th1 cell function by decreasing levels of TNF-α, IFN-γ, and IL-6 [166-168]. The specific role of IL-10 in adipose tissue, especially regarding its regulation and effects on White Adipose Tissue (WAT) metabolism and insulin sensitivity, remains unclear.

In studies involving non-obese diabetic mice, administration of IL-10 has been shown to delay the onset of diabetes and alleviate lipid-induced insulin resistance in skeletal muscle. In cases of obesity, both in human and murine models, WAT produces increased amounts of IL-10. This uptick in IL-10 levels is likely a response aimed at countering the ongoing production of pro-inflammatory cytokines in adipose tissue [169, 170]. However, research on circulating IL-10 levels in obesity presents conflicting findings; some studies report elevated levels in obese individuals, while others indicate lower levels. Given that IL-10 can act in a pro-inflammatory manner under certain conditions, further investigation is needed to fully understand its production in adipose tissue and its role in obesity [171-173].

Overall, there is limited understanding of this diverse group of molecules and their specific roles in obesity and autoimmune conditions. For example, angiopoietin-related protein 2 shows increased levels in obesity and supports the accumulation of immune cells in adipose tissue; however, its levels in autoimmune disorders remain unexamined. Omentin, which is found in reduced amounts in obesity, is associated with elevated levels of IL-4 and IL-13 and promotes Th2-type responses. Patients with psoriasis display decreased omentin levels, while those with lupus nephritis have elevated levels. It is still unclear whether omentin acts as a pro-inflammatory or anti-inflammatory factor in autoimmune diseases [174, 175].

Conclusion

Adipokines such as adiponectin, resistin, chemerin, and adipsin, alongside classical cytokines including TNF-α, IL-6, and MCP-1, form a complex signaling network that links adipose tissue dysfunction with systemic autoimmunity. Collectively, the evidence underscores that adipose tissue is not merely an inert energy reservoir but an active immune–endocrine organ capable of modulating inflammatory circuits and shaping autoimmune risk.

However, several methodological weaknesses limit the field. Most mechanistic insights still rely heavily on murine models, where adipokine biology often diverges from humans (e.g., resistin expression). Clinical studies are frequently constrained by small sample sizes, heterogeneity in disease stage and treatment status, and inconsistent assays for adipokine isoforms and receptors. These factors contribute to contradictory findings, such as adiponectin's dual anti- and pro-inflammatory roles or MCP-1's variable impact on insulin resistance. Addressing these gaps will require standardized methodologies, larger patient cohorts, and integration of multi-omics approaches.

A clearer translational outlook is now emerging. Adipokine profiling holds promise as a biomarker strategy to stratify patients by metabolic–immune risk. Isoform-specific assays for adiponectin and chemerin could help distinguish protective versus pathogenic activity. Therapeutically, interventions targeting the chemerin-CMKLR1 axis or adipsin/factor D-mediated complement activation represent novel strategies to dampen autoimmune inflammation, while modulation of IL-6 trans-signaling has already proven clinically effective. Importantly, lifestyle and pharmacological interventions that reduce adipose tissue inflammation such as weight loss, exercise, and insulin-sensitizing drugs may indirectly recalibrate adipokine balance and immune tolerance, providing a feasible adjunct to immunomodulatory therapies.

Looking forward, the most pressing need is to move beyond descriptive associations and toward causal, mechanistically informed studies that integrate metabolic and immune endpoints. Longitudinal cohort studies, combined with interventional trials that track adipokine dynamics alongside autoimmunity progression, will be essential. Such approaches may ultimately allow adipokines to serve not only as biomarkers of immune metabolic dysfunction but also as therapeutic targets that bridge obesity management and autoimmune disease treatment.

Key Points

- The interplay between obesity and autoimmune diseases highlights the role of adipose tissue as an endocrine organ influencing immune responses via adipokines
- Adipokines like adiponectin, resistin, adipsin, and chemerin exhibit both pro-inflammatory and anti-inflammatory effects that can impact metabolic health and autoimmunity
- Chronic low-grade inflammation associated with obesity is linked to the exacerbation of autoimmune conditions, suggesting a shared pathogenic mechanism
- Elevated levels of specific adipokines in certain autoimmune disorders indicate their potential as biomarkers and therapeutic targets for managing these conditions
- Understanding the nuanced roles of adipokines can lead to innovative strategies for treating comorbidities related to obesity and autoimmune diseases

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Author's Contributions

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Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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