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LETTERS

Chemerin and male reproduction: 'a tangled rope' connecting metabolism and inflammation

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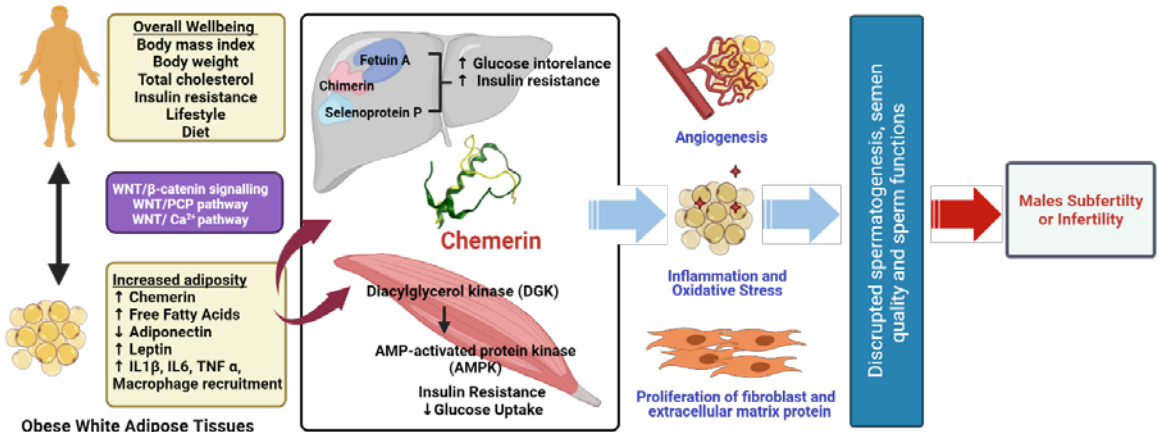
Review Article

ABSTRACT



Adipokines are peptides produced mainly by the fat tissue adipocytes and their levels are sensitive to alterations in metabolic state. While there is little known about the impact of adipokines on male reproductive control, both animal-based experimental data and clinical research suggest that they can influence numerous male fertility indices. Chemerin is a newly found adipokine which is generally recognized as a chemoattractant and chemokine. Chemerin has been correlated with inflammatory reactions and metabolic imbalances, as seen in various metabolic syndromes. A sex dimorphic chemerin expression pattern has also been shown with greater levels in men in comparison to women. Chemerin can thus be offered as a potential new candidate in the connection among metabolic disorders, inflammation and male reproduction. The present article explores the multidimensional metabolic and inflammatory roles of chemerin and discusses its impact upon the male reproduction.

Keywords: adipokine, chemerin, inflammation, male fertility, obesity

INTRODUCTION

Chemerin is a novel protein, well characterised for its chemotactic and adipokine properties.[1] Increased serum chemerin levels are a contributing factor to metabolic syndrome.[2] Chemerin is anticipated to have a multifaceted role in the development of complicated metabolic syndrome in humans by modulating meta-inflammation, adipocyte plasticity, and glucose metabolism.[1, 3] Metabolic syndrome and obesity are a growing public health concern in Western nations due to its numerous consequences, including sleep apnea, atherosclerosis, pessimism, orthopaedic disorders, diabetes mellitus, and infertility.

Male infertility (shown as poor semen quality) worldwide is shown to be increasing with passing decades.[4-10] The association of male infertility with obesity has recently received a lot of attention,[11,12] adipokines may have a role in the underlying mechanisms that lead to obesity-related male infertility.[13-16] Obesity is marked by excessive deposition of white adipose tissues, which highly express chemerin and exaggerate the obesity-induced systemic inflammation. This may lead to induction of oxidative stress,[17,18] which adversely affects the reproductive hormonal regulatory axis[19] as well as can mediate direct disruption to male reproductive tissues.[18]

Chemerin expression is evident in male reproductive tissues, and besides being involved in metabolism and inflammation, chemerin has been found to inversely correlate with Leydig cell functions, testosterone levels, as well as sperm functions.[20-22] The present review discusses how chemerin associates with male

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reproduction and whether its metabolic and inflammatory roles correspond to its effects on male fertility.

CHEMERIN AND ITS RECEPTORS

Chemerin expression and its receptors

Chemerin, a multifunctional protein, recognized particularly for its chemotactic and adipokine characteristics, is encoded by the gene retinoic acid receptor responder 2 (RARRES2), tazarotene-induced gene 2 protein (TIG2), or RAR-responsive protein TIG2.[1] The protein originates as a 163 residue pre-prochemerin, then undergoes N-terminal truncation and resulting a 143 residue prochemerin.[23] Several chemerin isoforms with distinct functions have been identified to date. Cleavage at the C-terminus by inflammatory serine proteases, tryptase, elastase, and plasmin, as well as carboxypeptidases, results in isoform formation. Chemerin isoforms are named after the C-terminus amino acid.[24-26] This approach thus serves as a central regulatory mechanism for determining locally and systemically active chemistry concentrations, which are responsible for various biological actions, including immunology, insulin sensitivity, adipose tissue functions, metabolic homeostasis, growth, blood pressure, and lipid profile.[27-29]

Chemerin is widely expressed in the male reproductive system, Leydig cells.[30] It helps to control the female reproductive system and functions as well. Functional receptors were discovered in human granulosa cells and the human uterus.[31-33] The concentration of chemerin is relatively high in the liver, adipose tissue and the placenta, and is present in the skin, gut, pancreas, airways, adrenal gland, and kidney as well.[23, 34, 35] Chemerin synthesis is regulated by nuclear receptor agonists (retinoids, vitamin D, glucocorticoids), stimuli primarily attributable to metabolic pathways (insulin, lipid, glucose) and mediators of immunomodulation (TNF-α, interleukin, liposaccharide).[36-40]

Chemokine-like receptor 1 (CMKLR1)[23,41,42], chemokine (C-C motif) receptor-like 2 (CCRL2)[43] and G protein-coupled receptor 1 (GPR1)[44] are all heptahelical receptors that have been shown to bind chemerin. In 1996, the CMKLR1, chemerin-receptor, was found and Chemerin Receptor 23 (ChemR23) was identified in 1998. Zabel *et al.* had put forth several mechanisms of chemerin and its receptor expression and functions in immune regulation.[41,45-47] The mitogen-activated protein kinase extracellular signal-regulated kinase 1 and 2 (MAPK/ERK1/2), Akt, and AMPK can be stimulated or inhibited by CMKLR1 and GPR1 to control various biological processes. Chemerin-CMKLR1 binding promotes chemotaxis of CMKLR1-expressing leukocyte populations. The activation leads to intracellular calcium release, cAMP aggregation inhibition, and phosphorylation of MAPK/ ERK1/2 or the phosphatidylinositol 3-kinase/Akt pathway.[48-51]

GPR1 is the nearest CMKLR1 homologue, sharing a sequence identity of more than 40% with CMKLR1. In Leydig cells, CMKLR1 and GPR1 are indeed likely to facilitate chemerin binding and steer the subsequent signalling pathways.[30] The central nervous system, epidermal keratinocytes, granulosa cells, and fat tissue were shown to have expression of GPR1.[30, 35, 52, 53] GPR1 and chemerin relationships remain uncertain in their physiological significance. Chemerin binding to GPR1 activates internalization of receptors. However, it is unclear whether any physiological functions result from this change.[44]

CCRL2 was first discovered in humans in 1998[54], the protein displays a changed amino acid sequence (QGYRVFS) instead of the preserved motif DRYLAIV in the intracellular extension of the third transmembrane segment, which is essential to initiate the G protein-mediated response. While an earlier report revealed that CCRL2 can be expressed through MAPK activation and facilitate cell migration, another study also found that CCRL2

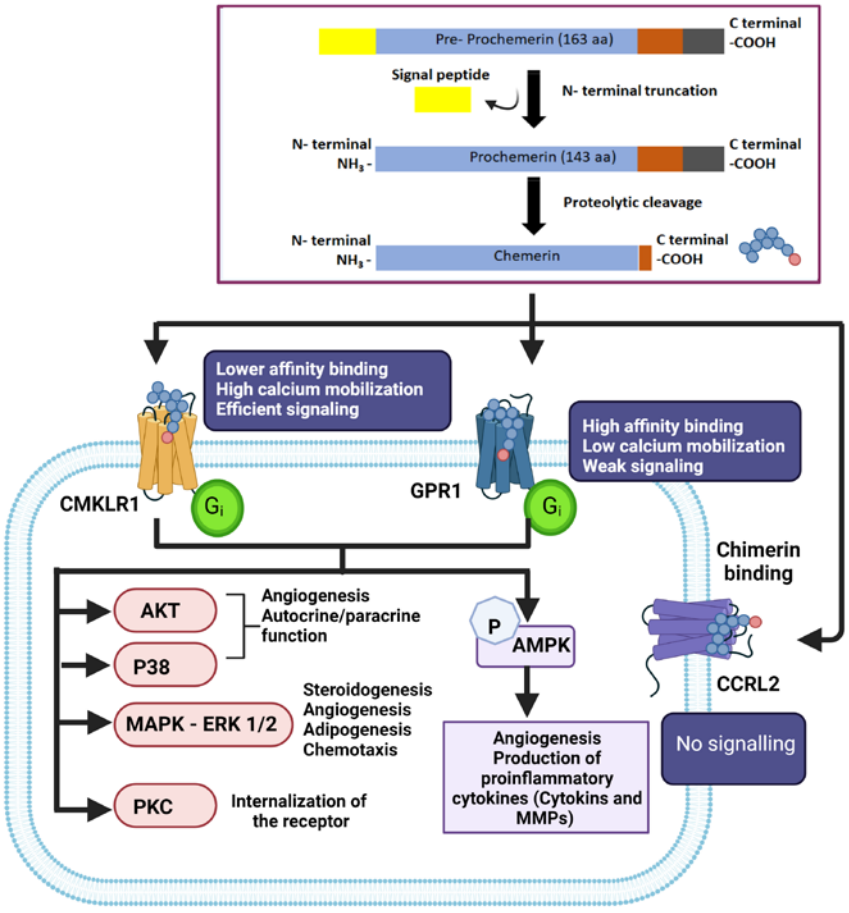

Figure 1. Chemerin synthesis, its signalling pathways and mode of action.

does not activate ERK1/2.[55-57] As a result, CCRL2 neither initiates nor mediates conventional G protein-mediated signalling or cell migration.[55-57] Leukocytes and non-hematopoietic cells both express CCRL2, a non-chemokine chemotactic.[58]

Indeed, the biological relevance of CCRL2 as well as its scavenging and recycling characteristics are currently being disputed. The N-terminus of CCRL2 binds chemerin while leaving the C-terminus exposed for potential interaction with cells expressing the functional receptor. As a result, it is hypothesized that CCRL2 acts as a chemerin exhibiting molecule on the surface of barrier cells. Nonetheless, it has been proposed that in the pre-B cell line, human CCRL2 undergoes membrane endocytosis of a potential ligand.[43, 59-61]

Adipokines in chemerin expression

Tissue adipose consists of adult adipocytes, preadipocytes, endothelial cells, fibroblems, mast cells, and cells of the immune system.[40] Adipokines are hormones secreted by adipose tissues.[39] Currently known adipokines include adiponectin, apelin, chemerin, resistin, vaspin, and visfatin. They are found in the brain, gut, kidneys, pancreas, liver, and capillaries. They play a significant role and participate in the regulation of many facets of the metabolism of biomolecules, neuroendocrine activity, reproduction, and cardiovascular features across a network of autocrine, paracrine, and endocrine pathways.[62-64] Owing to their participation in these regulations, adipokines could be considered prospective candidates for novel therapeutic treatments in a variety of medical disorders.

Apparently, elevated chemerin mRNA expression in obese animals' adipose tissue, as well as elevated plasma chemerin levels, has shown the presence of a connection between this unique adipokine and metabolic syndrome.[2] These adipokines are critical for the progression of obesity-related illnesses and inflammatory diseases. In various animals, a surplus or shortage of white adipose tissue impacts puberty, sexual development, and fertility.[64] Adipokine receptors are present in human reproductive organs, implying that adipokines have direct effects on these tissues.[65]

Obesity is linked to infertility in both men and women, as well as unfavorable reproductive outcomes. Obesity and being overweight appear to have a detrimental impact on male reproductive capacity, not simply by lowering the total number of sperm, and also by changing the physical and molecular composition of germ cells in the testes, affecting the functional as well as growth of sperm cells. A significant increase of excess fat tissue is seen in the majority of polycystic ovarian syndrome (PCOS). Obesity has a detrimental influence on oocyte maturation, implantation, growth of the embryo, placental health, and uterine condition.[66, 67]

Chemerin signalling pathways

Chemerin is a small chemotactic protein, relatively new adipokine has a biological function by binding to its receptor and G protein-coupled receptors. The role of chemerin in inflammation is dual. It mainly regulates leukocyte recruitment to inflammatory sites. It can also interestingly inhibit proinflammatory mediators' synthesis and thus play an essential role in anti-inflammatory roles. The opposite effects of chemerin have different influences on various phases of inflammatory reactions and are often associated with the organism's internal and external environment.

Chemerin activates multiple immune cells, the protein levels are strongly linked to body mass index, visceral fat, and blood pressure.[44, 48-51, 68] GPR1 is found mostly in the liver, stomach, kidneys, and adipose tissues. CCRL2 is highly expressed in lung endothelial cells and has a lower expression in liver endothelial cells, but it does not promote chemerin signalling.[43, 44, 48, 69] The affinity toward CMKLR1 and GPR1 is almost the same, however, with lower affinity to CCRL2. Still, these receptors have shown cell-specific expression profiles, which contribute to challenges in evaluating the activation of receptors in the same tissue.[55,70]

Chemerin binding to CMKLR1 promotes phospholipase C activation, extracellular signal-regulated kinase phosphorylation, calcium mobilization, and inhibits cAMP production. This Gi/o-protein-coupled receptor activates intracellular signalling molecules, participating in angiogenesis metabolic and inflammatory reactions, MAPK, ERK, and phosphatidylinositol 3-kinase. It is thought that it also causes arrestin2 to be recruited to CMKLR1,[48-51] and has a crucial function in male steroidogenesis.

The synchronization of multiple reproductive phases, including sexual development, growth, and maturation, is dependent on gonadal steroidogenesis. Chemerin and resistin are reported to lower IGF-1 (Insulin Like Growth Factor 1)-induced steroidogenesis, whereas visfatin and apelin stimulate steroidogenesis in human granulosa cells via MAPK/ERK1/2 activation.[71]

Chemerin had reduced testosterone synthesis generated by hCG (human chorionic gonadotropin) in rat primary Leydig cell cultures. Chemerin has also been found in lower amounts in seminal plasma than in human blood plasma. In general, this is linked to the suppression of the 3-beta hydroxysteroid dehydrogenase (3βHSD), steroidogenic acute regulatory protein (StAR), and the production of MAPK/ERK1/2 phosphorylation. The plasma testosterone level in mice lacking CMKLR1 (CMKLR1/) is lower than in wild-type (WT) animals. Furthermore, gene expression of 3βHSD, StAR, P450scc, Sf1, Gata4, and Insl3 was significantly reduced in cultured Leydig cells isolated from CMKLR1/ mice compared to WT mice. Obesity is significantly linked with lower sperm motility and serum testosterone, as well as elevated chemerin among obese patients, indicating a detrimental direct effect on epididymal motility/ripidation or indirect effects during the epididymis maturation.[72-74]

Across most testis cells, chemerin and CMKLR1 are present, *in vitro* testis studies revealed that recombinant chicken chemerin inhibits hCG-induced testosterone synthesis, which was linked to lower 3βHSD, StAR expression, and MAPK/ERK2 (Mitogen-Activated Protein Kinase Extracellular signal-regulated kinase 2) phosphorylation. Chemerin levels in seminal plasma were shown to be lower than in blood plasma, but it was found to be negatively associated with the percentage of motility and spermatozoa production *in vivo* in roosters. Recombinant chicken

chemerin had a lower total sperm count and reduced motility in roosters *in vitro*, but this effect was successfully reversed with sperm pre-incubation with presence of an anti-CMKLR1 antibody. Furthermore, fresh chicken sperm had been treated with chemerin and utilized for artificial insemination (AI) in hens exhibited decreased egg reproductive productivity throughout the first four days following AI. Identified chemerin concentration was adversely linked with rooster fertility, and chemerin produced locally by the testis or male tract contributed a detrimental influence on sperm quality and testosterone production via CMKLR1.[22]

Chemerin, which regulates proinflammatory factors in endothelial cells, regulates the formation of new blood vessels through a variety of mechanisms. In addition, chemerin isomers also facilitate additional cell recruitment and possibly neutrophils, exacerbating inflammation. Both dendritic cells and macrophages are recruited at the beginning of the immediate response in response to chemerin activations that bind innate and adaptive immunity, and the basis of this occurrence is that CMKLR1 is expressed on dendritic cells although it is related to the maturation state of dendritic cells. Chemerin also encourages dendritic cells to be transported from the bloodstream to reactive lymph nodes. Fully developed dendritic cells gain cell phenotypes such as antigenic presence and upright major costimulatory cell classes I and II, as well as T histocompatibility molecules, which promote cell activation of CD^{4+} and CD^{7+} T cells even if their surface loses CMKLR1 expression. Biochemistry modulation thus plays a key role not only in controlling the recruitment of dendritic cells in inflammatory areas, but also in the development of innate immunity.[2,36,75,76] Elevation of chemerin expression has a strong correlation with C-reactive protein (CRP), interleukin-6 (IL6), and calprotectin. Furthermore, if inflammatory factors such as CRP, IL-6, and TNF are elevated in the serum of elderly patients with iron deficiency anemia, chemerin, defensive, and hepcidin expression is also elevated.[77, 78] Chemerin binding to GPR1 has also been demonstrated to cause modest calcium mobilization in recombinant cell lines, but it is uncertain if GPR1 begins signalling cascades in natural settings. Chemerin binding induces GPR1 downregulation, indicating that it is a scavenger receptor that controls extracellular chemerin levels.[35, 52, 53, 79] GPR1 has a role in the regulation of inflammation through an adenylate cyclase-activating G protein-coupled receptor signalling pathway.[80]

While most studies on chemerin concentrate on its anti-inflammatory effects, some evidence suggests that chemerin can also have anti-inflammatory properties. Adrych *et al.* noted chemerin delays pancreatic development by inducing macrophage penetration, platelet-derived growth factor (PDGF), and transforming growth factor β1 (TGFβ1) by platelets.[81] The effects are particularly noticeable during the inflammatory regression phase. Chemerin, can be transformed by other serine or cysteine proteases into inactive, nonchemotactic, or anti-inflammatory peptides such as chemerin-155 or chemerin-154. Mast cell tryptase, for example, transforms prochemerin to chemerin-158 and chemerin-155, while mast cell chymase converts active chemerin-157 and chemerin-156 to inactive chemerin-154.[82] Since chemerin binding to CCRL2 will not activate downstream signalling channels, it is therefore categorized as an atypical chemokine receptor. Still, the protein binding appears to enhance *in situ* chemerin concentration for CMKLR1 and GPR1 interaction.[43,55]

In summary, chemerin is linked to physiological activities and inflammatory, its dysregulation in human pathophysiology is critical. Chemerin has been linked to gonadal steroidogenesis, reproductive health, obesity, diabetes, hypertension, cardiovascular disease, psoriasis, respiratory disease, renal failure, arthrosis, and gastrointestinal illness.

CHEMERIN ON HOST DEFENCE

The host's protection against pathogens is structured as a series of layered barriers with increasing precision. Skin keratinocytes release antimicrobial peptides such as chemerin, which function as an epithelial chemical barrier against infections. It also plays a crucial role as a secondary role in host defense by acting as a leukocyte attractant.[83] Chemerin could directly kill or inhibit cell development in a wide range of microorganisms, including fungus and bacteria.

Chemerin, a multifunctional innate immunocyte chemoattractant with adipokine properties. Chemerin receptors are present on various immune cells. This endogenous immunocyte chemoattractant has been demonstrated to promote and upregulate phosphatase and tensin homolog (PTEN) expression in human prostate and sarcoma tumor lines while supressing programmed death-ligand 1 (PD-L1) expression. Due to its varied expression and involvement with inflammatory and metabolic processes, it is expected to be a component of local and systemic gene expression programs which are essential in immunity and metabolism. This protein is said to belong to the protein class of structural cathelicidins/cystatins. Catholicidin peptides are one of the families of antimicrobial peptides found as components of the early host defenses of mammals against infection in neutrophils and epithelia. After being cleaved off the holoprotein, the C-terminal peptides exhibit anti-inflammatory or antibacterial characteristics, contributing to host defense through both direct pathogen destruction and additional biological actions. These enzymes include coagulation (factor VII) and fibrinolytic (plasmin) cascade enzymes, as well as those originating from post-neutrophil degranulation (elastase and cathepsin G).[23, 37, 41, 82, 84-86]

C15 (AGEDPHGYFLPGQFA) is a 15-amino acid chemerin-derived peptide that inhibits macrophage activation in picomolar concentrations. In terms of the acute inflammatory response, C15 reduces proinflammatory cytokine (TNF, IL-1, IL-12 p40, and IL-6), and chemokine recruitment. Importantly, C15 promotes the non-phlogistic clearance of apoptotic neutrophils and microbial particles from the inflammatory environment, aiding in inflammation resolution[87]. The fast proteolytic activation of chemerin at mechanical barrier breach locations (bleeding, cell injury) may encourage these early responder ‘immunointerpreters' to assess local circumstances (sterile bruise vs. microbial infiltration) and activate an efficient immune

response. In most cases, the chemotactic effects of chemerin are mediated through CMKLR1. These cells respond to chemerin with integrin activation, calcium signaling, and chemotaxis.[83]

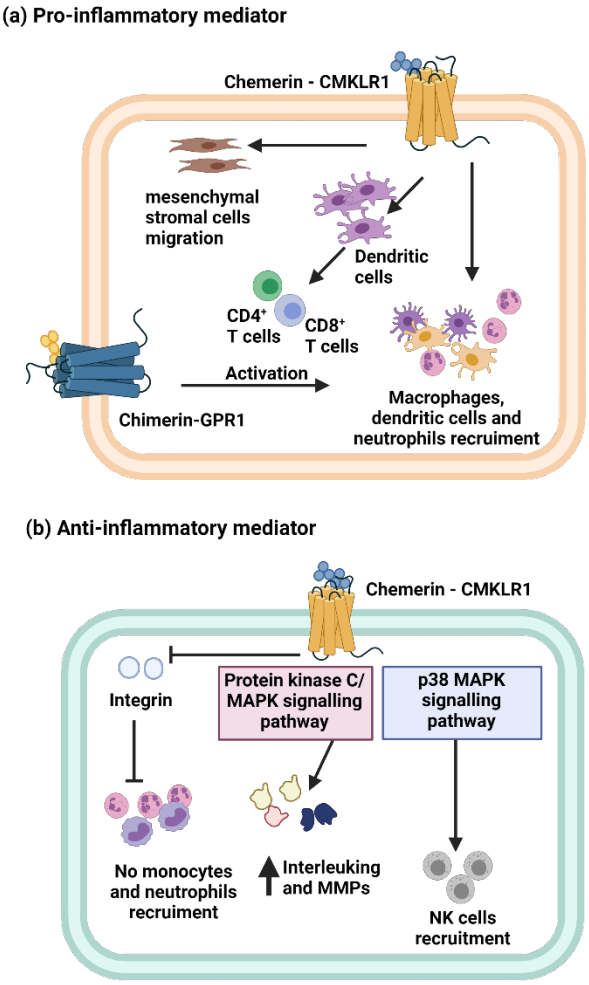

Figure 2. Mechanism of action of chemerin as (a) pro-inflammatory and (b) anti-inflammatory mediator.

Chemerin has been shown to be 20-fold more potent than CXCL8 (IL-8), one of the most important effective chemical agents in humans, for inducing the migration of NK (natural killer) cells. *In vivo* studies demonstrate that NK cell stimulation is linked with CMKLR1 downregulation, but only with short-term cell stimulation. In long-term stimulation of CMCLR1 active cells, there was no indication that chemerin/cmclr1 signals were linked with NK cells mobilization during the initial point of infection/inflammation. The immunoregulatory function of chemerin is not restricted exclusively to NK cells but is essential in the inflammatory phase of lichen planes for NK cells and DCs (dendritic cells). Both NK cells and DCs have CMKLR1 and have been identified presence of co-locations in active lichen planus. Chemerin expression was also documented as a potential function for the chemical in NK cells and DCs recruitment during skin inflammation in the cell lining of the endothelial blood vessels in active lichen planus tissues.[86, 88]

Vermi *et al.* have reported that CMKLR1 on circulating myeloid and plasmacytoid DCs is expressed by various membrane markers and flow cytometry. In addition, it has been estimated that chemerin promotes migration of DCs through the monolayer of endothelial cells with around 100-fold greater power and very same efficiency compared with CXCL12. Furthermore, chemerin chemotactic activity has been totally blocked by the CMKLR1 monoclonal antibody. Zabel *et al.* showed, instead, the CMKLR1 is expressed on human myeloid DCs but is only expressed on plasmaticytoid DCs in the population of peripheral mononuclear blood cells (PBMC). The variations between the two groupings may be due to approach differences in the separation and maintenance of PBMCs *in vitro*. More notably, both studies found that chemerin promoted plasmacytoid DCs migration through human umbilical vein endothelial cells.[41, 75]

Due to the recruitment of chemotherin-dependent CMKLR1+ macrophages, adipose tissue can produce persistent low-level systemic inflammation associated with obesity and the accompanying consequences. Depending on their phenotype, macrophages may stimulate both pro- and anti-inflammatory activity. The phenotype of macrophages changes depending on the form of stimulus. The synthesis of chemerin abounds in adipose tissue, and the development of adipose chemerin increases with the separation of the adipocyte and obesity. Obese patients had a significant increase in adipose tissue macrophage infiltration.[1, 89] When chemerin-deficient mice were compared to WT mice, the concentration of macrophages in epididymal adipose tissue was much lower. The effect, however, could not be replicated in CMKLR1 knockout mice since there was no change in the percentage of macrophages between white adipose tissue and WT. Other chemerin receptors may be able to compensate for CMKLR1 loss in coordinating macrophage entrance into adipose tissue.[90, 91]

Both CMKLR1 and CCRL2 appear to have been involved in the recruitment of immune cells during inflammation. Regan-Komito *et al.* observed over-expression of CCRL2 in recruited peritoneal neutrophils during acute inflammation. Furthermore, *ex situ* tests of lipopolysaccharide, interferon-β (IFN-α) or polyI:C bone marrow-derived macrophages (BMMs) have shown greater CCRL2 expression in comparison to untreated BMMs. In the case of Ccrl2 deficient mice, the induction of acute inflammation was not only manifested by higher peritoneal monocytes or neutrophils but also by an elevated number of blood neutrophils. The suggested method through which CCRL2 includes immune cell movement appears to be related to chemerin modulation, which leads to an increase in chemokine ligand 1 levels (motif C-X-C).[92]

Utilizing CCRL2 KO mice, it was noticed that the receptor needed in passive cutaneous anaphylaxis (PCA), a model of *in vivo* allergy that retains the highest ear swelling and leukocyte infiltration. In particular, it was shown that mast-cell-discarded animal CCRL2 was needed for optimal induction of PCA in mice sensitized to a low dose of antigen-specific IgE with either WT- or CCRL2-KO bone marrow-posited mast cells (high levels of sensitizing antigen abrogated this difference). CCRL2 KO mice

were protected from lung inflammation in a model of ovalbumin mediated airways. These defects were linked to a trafficking defect for antigen-laden lung DC to mediastinal lymphatic nodes.[93]

CHEMERIN IN ENERGY METABOLISM

Whole body metabolism

Numerous adipokines linked to metabolic syndrome and their impact on metabolism have been discovered and are being investigated since the discovery of leptin. Various reports have demonstrated that the adipokine chemerin is important in adipogenesis, as well as in the control of glucose homeostasis and the prevalence of obesity.

Particularly, the data on the involvement of chemerin in whole-body metabolism and its relationship with obesity and insulin resistance has been contradictory. Earlier studies found that expression of the chemerin gene and plasma levels of chemerin are linked to higher BMI (Body Mass Index) and obesity-related biomarkers.[2, 38, 94] Obese mice on a high-fat diet exhibited increased plasma chemerin levels, which are reduced by fasting overnight. This finding is independent of the mouse species (FVB or C57BL/6) used in research.[95] In contrast, plasma chemerin levels in mice fed with high-lipid or cafeteria diet did not alter.[96] This disparity might be explained by the fact that certain mouse strains are more vulnerable to obesity caused by a meal intake than others. In genetically obese (ob/ob) mice, plasma chemerin levels were increased,[1] while leptin receptor-deficient animals (db/db mice) exhibited lower blood chemerin levels and increased insulin signalling.[97] In rats on a limited diet, a decrease in the quantity of chemerin (Rarres2) mRNA in the white adipose tissue (WAT) was related to a drop in serum chemerin concentration. When these rats were re-fed after a dietary restriction, both chemerin expression in WAT and serum chemerin levels increased.[98] Chemerin intraperitoneal injections resulted in a decreased body weight in rats, which was surprising.[29] This appears to refute the idea that increased plasma chemerin levels cause obesity. The approach with site injections into the brain, found a bimodal response to body weight and food intake. Whereas chemerin acute intracerebroventricular bolus injections reduced body weight, continuous chemerin infusions raised it.[3] Thus, chemerin might have a variety of biological effects.

Considering that higher chemerin levels are linked to increased body weight in most studies, a protracted proinflammatory impact could be related to insulin resistance among the obese population. Glucose tolerance was not affected by intraperitoneal injections of chemerin in normal mice, but glucose intolerance was enhanced in ob/ob mice and db/db mice.[49] Studies on mice missing the GPR1 receptor revealed more evidence connecting chemerin to glucose homeostasis. In comparison to wild-type mice, Gpr1-KO animals on a high-lipid diet exhibited higher glucose intolerance, but without changes in body mass, body composition, or energy expenditure.[99]

Similarly, metabolic abnormalities in Cmkrl1-KO mice have been described inconsistently. When fed a low-lipid or high-lipid meal, Cmklr1-KO mice exhibited lower calorie intake and body mass[90] while other reports negated the impact on body composition and glucose homeostasis.[100,101] The reported discrepancies might be related to the age and sex of the animal model, as well as the various durations and diets employed in these experiments. Wargent *et al.* recently sought to explain the problem and discovered that on a high-lipid diet, male and female Cmklr1-KO mice have modestly gained body fat and acquired a dysfunction in glucose homeostasis, though this is age dependent.[95] Hence, it's uncertain if elevated chemerin levels cause obesity, and additional research is needed to address this question definitively.

Effects on adiposity

Adiposity points towards being morbidly overweight. Adiposity indices that incorporate the waist circumference, which do not use body weight, reflect the quantity of WAT, which is a significant predictor of metabolic disease in humans.[102] White fat tissue produces a variety of adipokines, that influence adipose tissue homeostasis, adipocyte metabolism, and fat tissue inflammation. Chemerin and Cmklr1 are highly expressed in WAT but have moderate expression in brown adipose tissue (BAT).[34] Since BAT is linked to thermogenesis, it is possible that chemerin affects weight through controlling adipogenesis rather than thermogenesis. However, it has recently been discovered that in WAT and BAT, the deletion of CMKLR1 inhibits the expression of thermogenesis-related genes.[103] Due to its capability to produce heat energy and hence result in weight reduction, BAT was shown to be a viable target for obesity therapy. Retinoic acid is an important regulator of BAT thermogenesis.[104] Since chemerin is the downstream signalling agent of retinoic acid, chemerin may improve BAT or WAT activity.

Adiposity is defined by an elevation in size (hypertrophic obesity) and total amount (hyperplastic obesity), as well as an excessive expansion of WAT.[105] Chemerin and CMKLR1 expression are substantially enhanced during the differentiation of human preadipocytes into adipocytes.[106] The Chemerin-CMKLR1 axis promotes preadipocyte proliferation and differentiation by stimulating the AKT-mTOR and ERK signalling pathways.[107] Surprisingly, chemerin-CMKLR1 signalling, which is controlled by the peroxisome proliferator-activated receptor (PPAR), predisposes bone marrow mesenchymal stem cells (BMSCs) to differentiate into adipocytes instead of osteoblasts.[108] Inactivation of chemerin-CMKLR1 signalling can be achieved by genetic alteration or antibody neutralization modifications. The progression of BMSC clonal growth from adipogenic to osteoblastogenic.[108, 109] Chemerin administration also causes myoblast cells to switch from myogenesis to adipogenesis. In mice, disrupting the Cmklr1 gene reduces food consumption, body mass, and fat accumulation, which is consistent with these findings.[90] In contrast, Cmklr1-KO mice had moderate obesity but normal adipocyte differentiation, according to recent research.[110] The quantity of adipocytes in Cmklr1-null mice does not change, but there is an increase in fat deposition in each of the adipocytes. Surprisingly, the deletion of CMKLR1 had no impact on the development of preadipocytes into adipocytes *in vitro*.[110] The

contradictory evidence confounds our knowledge and understanding associated with involvement role of chemerin in controlling mechanisms in adipogenesis. It would be interesting to see if diet, genetic constitution, sex, and sanitary status affect body mass and adipose deposition in Cmklr1-knockout mice, as well as if cell type and culture media influence cell development.

Glucose metabolism

Metabolic syndrome is a global public health issue that predisposes people to various metabolic diseases. Even though the underlying processes are still unknown, growing findings suggest that adipokines play an important part. The adipokine chemerin is vitally important in adipogenesis and is significantly linked to the regulation of fat tissue in terms of glucose homeostasis regulation and the progression of obesity. Recent reports also show a connection between chemerin and metabolic syndrome and inflammation markers.[3, 111, 112]

Chemerin is required for proper adipogenesis and contributes to insulin resistance in peripheral tissues such as skeletal muscle. Chemerin inhibits skeletal muscle cell glucose uptake directly, but has the reverse effect on 3T3 adipocytes, boosting insulin-stimulated glucose uptake. As a result, chemerin could have distinct actions in the endocrine and paracrine/autocrine systems. Other chemokines, such as monocyte chemoattractant protein-1 (MCP-1), are believed to cause insulin resistance in skeletal muscle cells by activating ERK1/2 in a manner analogous to chemerin. However, their modes of action vary, since MCP-1 does not stimulate the NF-κB pathway, while chemerin does.[38, 97, 113]

Type 2 diabetes mellitus (T2DM) is recognized by insulin resistance and high levels of sugar in the blood profile. The preliminary chemerin analysis in humans showed that BMI was independent of the glucose tolerance in chemical blood concentrations. Obesity contributed to a rise in serum chemerin levels, which is closely associated with chemerin expression in the T2DM population. The truth is that chemerin regulates glucose homeostasis, but its role in regulating glucose tolerance is unclear. There is a lot of contradictory evidence from a range of laboratory experiment examinations. Moreover, the insulin signalling pathway is another principal hub for maintaining glucose homeostasis by increasing glucose absorption into fat and muscle while decreasing glucose synthesis in the liver and having a crucial function in regulating insulin secretion and sensitivity.[2, 63, 112, 114, 115]

Chemerin secretion was shown to be negatively linked with adipocyte insulin sensitivity as higher chemerin secretion was closely related to poorer insulin sensitivity of lipogenesis and decreased insulin-stimulated anti-lipolysis. Chemerin was released from fat tissue, and its levels were elevated in the obese population. Chemerin has been linked to fat cell insulin sensitivity, which may contribute to obesity-related local insulin resistance. As a result, chemerin may be used as a biological indicator for body composition. Its potential role as a marker for metabolic regulation and homeostasis should be researched further.[38] Skeletal muscle isolated from T2DM patients has lower levels of diacylglycerol kinase-delta (DGK), a crucial enzyme in triglyceride biosynthesis necessary for proper AMPK action. DGKs regulate diacylglycerol (DAG) expression by catalyzing its conversion to phosphatidic acid with ATP. In obese models, elevated plasma free fatty acid (FFA) levels from swollen adipose tissue force intramyocellular DAG accumulation. In an obese population, increased DAG aggregation as a result of decreased DGK or increased circulating FFA inhibits both glucose absorption and glycogen synthesis. This aggravates insulin resistance even further, as depicted.[116, 117] Multiple proinflammatory factors are produced, all of which are known to be protein catabolic and release circulating FFA, resulting in further liver damage. Some hepatokines, such as fetuin-A, selenoprotein P (SeP), chemerin, and leukocyte cell-derived chemotaxin 2 (LECT2), promote hepatic fat storage and inflammatory signalling. They also impair hepatic glucose metabolism and insulin signalling.[118]

Metabolic syndrome

High circulating chemerin is an important metabolic component. Chemerin is thought to have a multifaceted role in the development of metabolic syndrome in humans by modulating metainflammation, adipocyte plasticity, and glucose metabolism. Chemerin appears to have a well-established connection with obesity, diabetes, and hypertension. Chemerin has also been related to a number of other ailments.[68, 76, 81, 100, 119]

Various reported studies have found that systemic chemerin concentration are higher in obese people. Chemerin levels have a strong and positive association with BMI, waist-hip ratio, waist size, or visceral adipose tissue mass, indicating that visceral fat tissue is the primary contributor of circulating chemerin.[120, 121] A subsequent research found that the secretion of chemerin from adipose tissue explants of obese people is greater than that of normal-weight controls, and that the quantity of secretion is directly linked to BMI, waist-hip ratio, and fat cell volume.[38] According to these findings, systemic chemerin levels are lower in obese individuals who have lost weight by diet or bariatric surgery.[94, 122] Interestingly, exercise-induced weight reduction reduces plasma chemerin levels further, indicating that chemerin is a significant biomarker of change in insulin resistance in obese individuals.[94, 123] Research shows that exercise alone has a positive impact on chemerin levels in the elderly, regardless of weight loss.[124]

Obesity does not affect the expression of CMKLR1 in fat tissue, but it does increase the expression of RARRES2 in both visceral and subcutaneous adipose tissue.[94] Chemerin expression in omental fat tissue, but not subcutaneous fat tissue, contributes to increased circulating chemerin. With the introduction of ELISAs targeting the four distinct isoforms of chemerin, it was shown that greater C-terminal processing of chemerin occurred in obese individuals' adipose tissue, resulting in a higher quantity of bioactive chemerin in local tissue and the circulating system.[125] Obese patients are more likely to acquire a variety of comorbid illnesses, and elevated chemerin levels have been related to several of these diseases.

Novel adipokines such as vaspin, omentin, retinal-binding protein-4, fibroblast growth factor 21, adipocyte fatty acid-binding protein, and dipeptidyl peptidase 4 have recently been shown to be associated with insulin resistance and T2DM in

humans.[102, 126] A number of investigations have also looked into the relationship between chemerin levels and diabetes, plasma chemerin levels in T2DM patients were substantially higher than in normal-weight Caucasian controls.[112] The Caucasian control group showed no differences or even decreased when compared to Asian T2DM patients who met the inclusion criteria of having no other metabolic complications.[31, 91] An important finding from a prospective research is that an increase in systemic chemerin precedes the development of T2DM,[127] implying that chemerin might be used as a biomarker for early T2DM detection. Regardless of ethnicity, linear regression studies indicate a cross-sectional association between systemic chemerin in T2DM volunteers and chronological age, BMI, waist-hip ratio, triglyceride profile, HOMA-IR, HbA1c, 2 hours plasma glucose or blood pressure.[112,127] Obese people with T2DM have significantly higher levels of circulatory and local chemerin in their adipose tissue.[2,94,122] The connection between circulating chemerin and gestational diabetes mellitus, on the other hand, has been hotly disputed for a long time.[2, 31]

CHEMERIN AND MALE REPRODUCTION

Topography in male genital tract

Chemerin, and particularly its involvement in reproductive function, has been the subject of a small amount of research. Chemerin and its receptors (CMKLR1, GPR1, and CCRL2) are expressed in the male reproductive tract of different species, including humans, mice, and rats, indicating that chemerin and its receptors have an endocrine and/or paracrine function in testicular activity.[79, 91, 128] However, their specific molecular mechanisms that contribute to male reproductive function have received very little attention. Chemerin, CMKLR1, CCRL2, and GPR1 immunoreactivity have been found in testicular sections of adult rodents and humans, by the study of Li and colleagues. Chemerin and its receptors were shown to be developmentally regulated in the rat testis. Chemerin protein immunolocalization was found predominantly in the cytoplasm of interstitial Leydig cells and was scarce in developing germ cells in seminiferous tubules.[30,79]

Effects on male reproduction

Adipokines have been discovered to influence sex steroid production and function, as well as to have a pleiotropic effect on tissue homeostasis. Although there is no evidence that blood levels of the recently discovered chemokine chemerin are connected to male subfertility, it is considered to influence testosterone production in males.

There are only a handful of studies that have reported the impact of chemerin on male fertility. A study conducted on 96 males having no spermatogenic problems detected chemerin in the semen of all subjects and this adipokine was shown to negatively correlate with sperm motility while having a positive correlation with sperm concentration. Thomas *et al.*[129] exhibited higher chemerin concentrations in control participants' sperm compared to a group of vasectomized patients ($p<0.001$). This evidence shows that chemerin is secreted locally in the male genital tract, notably at the testicular level. Based on findings in 3T3-L1 adipocytes, another study hypothesized that chemerin is produced by adipocytes from the epididymal fat pad.[97] As a result, obesity may enhance chemerin production from epididymal adipose tissue, lowering the quality of sperm. Chemerin levels in vasectomized males were found to be considerably lower than in non-vasectomized men, indicating that this theory may be correct. The study showed that seminal plasma contains many adipokines that are linked to sperm functions and that BMI and waist circumference, both regarded as surrogate measures of visceral fat mass, had no effect on the modulation of these adipokines in the seminal plasma.[129] Seminal plasma adiponectin levels are substantially lower in obese men than in lean men, probably due to the increased visceral and epididymal adipose tissue deposition as found in studies using obese mouse model.[130] Despite this, there was no link between adiponectin semen levels and BMI or waist circumference. Chemerin showed a negative correlation with progressive sperm motility, after adjusting for age, waist circumference, BMI, and trophic hormone levels.[129] This may imply that the association of chemerin with sperm functions is independent of either body weight or reproductive hormones, and this adipokine may possess a unique role in male reproductive functions. Bobjer *et al.*, 2018, have reported via a case control study, that chemerin negatively correlates with luteinizing hormone (LH), sex hormone binding globulin (SHBG) and estradiol, while chemerin level is inversely linked with subfertility.[20] Brzoskwinia *et al.*, have shown that androgen signaling disruption in rat testis using non-steroidal anti-androgen (flutamide), has a significant impact on the chemerin level and its functioning in the testis.[21] Estienne *et al.*, has investigated the impact of chemerin on male reproductive functions in chicken.[22] The study demonstrated that chemerin operating via its CMKLR1 inhibited HCG-induced testosterone synthesis, and was negatively associated with the expression of 3βHSD and StAR. It also inhibited MAP/ERK2 phosphorylation, inversely associated with sperm concentration, sperm motility, as well as the fertilizing capacity of the sperm. Thus, chemerin has been shown to have a negative impact on sperm quality and testosterone level.[22]

Long-term treatment of human cultured Sertoli cells with chemerin, resistin or visfatin at high concentrations (as seen in obese men) inhibits follicle-stimulating hormone receptor expression and enhances cytochrome P450 CYP26A1 expression, resulting in a pre-pubertal phenotype.[131] These adipokines are thought to inhibit Sertoli cell development, perhaps leading to testis dysfunction and reproductive issues associated with obesity. *In vitro* studies have also demonstrated the inhibitory impact of chemerin upon steroidogenesis.[132] However, further investigations are needed to reveal the exact role played by this novel adipokine in human male reproduction.

CHEMERIN AND MALE REPRODUCTION: A CONNECTING LINK OF METABOLISM AND INFLAMMATION

Obesity is a public health concern in Western countries due to the various effects it causes, including sleep apnea, atherosclerosis, depressive disorder, orthopaedic diseases, diabetes mellitus, and infertility. Obesity and male infertility

have lately received much attention.[11, 133] Although not all studies have verified such relationships, normal weight men had greater sperm count and sperm concentrations,[11,134,135] higher percentage of motile spermatozoa,[136] and a lesser sperm DNA fragmentation index (DFI)[136] as compared to obese men.[137] The hypothalamo-pituitary gonadal (HPG) axis is the main regulator of male reproductive functions, while its crosstalk with other hormones may modulate this process.[133,138-142] During obesity, adipokines, proteins mostly produced by fat tissue, potentially play an essential role in the underlying processes behind obesity-associated male infertility.[143,144]

Adipokines are released into the peripheral circulation by adipocytes, leucocytes,[145] lymphocytes,[146] fibroblasts[147] and trophoblasts,[148] and impact glucose metabolism, hunger, satiation, and subclinical inflammation.[14,17,18,149,150] Within the past few decades, leptin, ghrelin adiponectin, visfatin, progranulin, resistin, chemerin, and vaspin have all been identified as key adipose tissue-derived mediators in central and peripheral functions[151-153] including modulation of male fertility.[139,154,155]

Chemerin has emerged as an inhibitor of insulin signalling and the metabolism of glucose. As discussed earlier, its involvement in reproductive functions has been suggested. The direct influence of chemerin on numerous reproductive parameters has been studied and it is shown to exert antigonadal actions, but there is inadequate *in vivo* data, which provides a more comprehensive view of chemerin's regulatory mechanism in relation to male and female reproductive activities. A high chemerin/low adiponectin ratio, plays a significant role in the development of dyslipidemia and metabolic diseases in patients. Due to the extreme altered ratio of adiponectin to chemerin in many metabolic disorders, it is highly useful in diagnostic applications. Obesity and a sedentary lifestyle are two of the most important risk factors for hypertension, insulin resistance, and dyslipidemia. Chemerin has been linked to inflammatory responses as well as metabolic instability, as observed in the metabolic syndrome.[111] Chemerin levels were shown to be higher in obesity and T2DM, and were associated with an increased level of the high-sensitivity inflammatory marker CRP. Chemerin was also found to have a positive correlation with leptin, resistin, and the 'homeostatic model assessment for insulin resistance' (HOMA-IR) as well as the baseline insulin levels.[102] Thus, chemerin provides a fascinating link between obesity, inflammation, and pathophysiological alterations associated with obesity in humans. Chemerin levels were significantly linked to a variety of metabolic syndrome characteristics.[111] These findings imply that chemerin might be a useful tool for detecting obesity-related problems. Because there has been so little research, the role of chemerin and its corresponding receptor in metabolism-related male reproductive disorders remains unknown.

Chemerin expression has been found to be sex dimorphic, with greater levels in males than in women,[156] however this has not been confirmed.[157] The above-mentioned metabolic roles, as well as the negative impact of chemerin on Leydig cell steroidogenesis,[119] sperm functions and overall semen quality,[20-22, 71] may suggest that chemerin might be a promising biomarker in the connection between sex steroid regulation, male reproductive functions, obesity, and inflammation.

In general, a rise in LH is thought to be a sign of poor androgenicity or a risk factor for future hypogonadism.[158] Secondary hypogonadism, defined by low/normal LH levels and subnormal testosterone levels, can occur in obese men.[159] This is thought to be related either to leptin's suppression of Leydig cell testosterone synthesis[160] or negative feedback upon hypothalamo-pituitary hormones mediated by excess estrogen synthesized by the adipose tissue.[161] The discovery of the relationship between chemerin and BMI does not rule out the potential that the protein is involved in a similar process in overweight males by decreasing LH secretion. However, given that chemerin was shown to be significantly related to infertility, it is reasonable to conclude that the negative connection observed between chemerin and LH is, at least in part, a result of low chemerin levels in infertile males. Chemerin was found to be inversely associated with levels of SHBG.[20] It is well known that SHBG level decreases in obesity[162], and therefore the negative association of chemerin with SHBG suggests the association of obesity with compromised testicular functions. Moreover, the inverse association of chemerin with estradiol has been shown in both men and women with varying body weight.[157] Whether prostaglandin E2 inhibits expression of chemerin or vice versa is unknown. However, *in vitro* studies show that chemerin has an inhibiting impact both on steroidogenesis in granulosa cells in the female and on aromatase activity, which supports the latter idea.[53,163]

Li *et al.* indicated that chemerin has an inhibitory impact upon hCG-induced Leydig cell steroidogenesis[30]. If so, the testicular cells would be resistant to LH and, in the presence of chemerin, the greater LH levels would correlate with reduced testosterone production. As per the report of another study, serum chemerin levels were not linked to sperm parameters, whereas the seminal plasma chemerin levels had a positive association with sperm count and was inversely related to sperm motility[129]. This data may show a detrimental effect of chemerin on sperm functions.

It is well discussed that chemerin functions via its CMKLR1 to aid chemotaxis of dendritic cells and macrophages,[23] while its receptor expression is also found in numerous immune cells, including leukocytes and natural killer (NK) cells.[86] Moreover, chemerin levels in the serum increase proportionately with the rise in proinflammatory mediators, mainly those of TNFα, IL-6 and CRP.[111,112] With substantial evidences towards proinflammatory functions for chemerin, there is evidence suggesting that chemerin signalling pathway might mediate anti-inflammatory functions.[164] It is plausible that in the case of metabolic syndrome, such as obesity, chemerin/CMKLR1 signalling may be linked with inflammation of adipose tissue. Activation of CMKLR1 by chemerin thus induces immune cells recruitment to the lymphoid organs and affected tissues[41, 75] possibly to the dying adipocytes in obese adipose tissue.[165, 166] Furthermore, the white adipose tissue is a critical location for chemerin expression, and production would rise with increased adipose tissue accumulation in obesity, exacerbating obesity-

related systemic inflammation. Obesity-induced adipose tissue-derived substances are now known to cause systemic inflammation, which leads to an increase in reactive oxygen species and oxidative stress (OS).[17, 18] These can alter the HPG axis both centrally and peripherally leading to hypogonadotropic, hyperestrogenic, and hypogonadism.[19] Moreover, obesity-mediated inflammation and OS can directly affect testicular cells, [18] impair spermatogenesis, steroidogenesis, induce germ cell apoptosis, cause sperm DNA fragmentation and disrupt sperm functions.[17,167,168]

CONCLUSION AND FUTURE PERSPECTIVES

Chemerin is an adipokine with versatile functions. It can inhibit insulin signalling and downregulate glucose catabolism. Moreover, this protein is a chemoattractant and also has been linked to the regulation of inflammatory reactions. However, it is still unclear under what conditions chemerin exhibits pro-inflammatory properties and under what conditions it exhibits anti-inflammatory properties. Chemerin levels increase in obesity and other metabolic syndromes, suggesting its role in metabolic disorder-induced systemic inflammation. Interestingly, chemerin reportedly plays a role in male reproduction whereby it downregulates trophic hormones, testosterone secretion, as well as impairs sperm functions. It may be suggested that the adverse impact of chemerin upon male reproduction might be mediated through its elevation in obesity and other metabolic syndrome followed by induction of inflammatory and OS pathways.

In the past few years, various research focuses on investigating the mechanism of the dual effect of chemerin on inflammation, the pathophysiological process of atherosclerosis, hypertension, and the development of chronic obstructive pulmonary disease (COPD), and elucidating the anti-tumoral and tumor-promoting effects of the protein in different cancers. Research on the direct effect of chemerin on the various organs, including the male reproductive tissues, is crucial to understand the outcome of the interaction between chemerin and the receptors in various pathologies. On the other hand, it would be fascinating to know the extent to which systemic and paracrine prochemerin processing and metabolite distribution affect chemerin receptor activation. Thus, further investigations to reveal the exact position of chemerin in inflammatory responses and the mechanisms underlying its actions on male fertility will be intriguing.

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