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REVIEW

Chemerin: a potential endocrine link between obesity and type 2 diabetes

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Abstract Obesity and type 2 diabetes have reached epidemic levels and account for a substantial portion of the annual health expenditures of developed nations. While there is an abundance of epidemiological evidence demonstrating that obesity is a primary risk factor for developing type 2 diabetes, the mechanism(s) underlying this linkage are not completely understood. Given the enormous impact of these disorders on global health, considerable research effort has been devoted to elucidate the pathophysiological relationship between these two disorders. Two factors believed to contribute to the causal link between obesity and type 2 diabetes are chronic inflammation and altered secretion of adipose-derived signaling molecules (adipokines). Independent lines of investigation have implicated the novel adipokine chemerin as a regulator of adipogenesis, inflammation, and glucose metabolism through interactions with the cognate cell surface receptor chemokine-like receptor 1. Increased levels of chemerin that occur with obesity are hypothesized to be a causal factor in the development of type 2 diabetes as a consequence of dysregulation of the key physiological processes regulated by this adipokine. This review summarizes current research on the biological roles of chemerin and chemokine-like receptor 1, and highlights key questions to guide future research on the role of this adipokine in mediating obesity and the development of type 2 diabetes.

Keywords Chemerin · CMKLR1 · Obesity · Diabetes · Inflammation · Insulin resistance · Adipokine

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Introduction

Obesity, a condition of excess adipose tissue, develops from a complex interplay of modifiable (e.g., diet, behavior, environment) and non-modifiable (genetic) factors. Over the past 50 years, the global rate of obesity has increased dramatically; in the United States alone it is estimated that one-third of adults and 17 % of children are obese [1, 2]. This rise in obesity has been paralleled by a reduction in life expectancy and an increase in various obesity-related comorbidities, most significantly type 2 diabetes mellitus (T2DM) [1]. T2DM is a metabolic disorder characterized by elevated blood glucose secondary to insulin resistance that puts an individual at elevated risk for a number of long-term complications including stroke, myocardial infarction, kidney failure, and blindness [3]. Similar to obesity, T2DM has reached epidemic proportions with over 25 million children and adults in the United States alone suffering from this disease accounting for 175 billion dollars in annual healthcare costs [2]. Given the combined health and economic burdens of obesity and T2DM, considerable research has been devoted to defining the pathophysiological relationship between these conditions. Among the possible links between obesity and the development of T2DM, inflammation and altered secretion of adipose-derived signaling molecules have received particular attention [4, 5].

It is now generally recognized that white adipose tissue, in addition to serving as a long-term energy store, is also an active endocrine organ that secretes a number of bioactive molecules, collectively termed adipokines (as reviewed by [6, 7]). Adipokines are important regulators of adipose tissue development and function, have a significant influence on glucose metabolism in various tissues and influence overall energy balance at the systemic level [5, 8–12].

The circulating levels of many adipokines are known to change with adiposity and this has been proposed as a contributing factor to the deleterious metabolic changes that often accompany obesity and ultimately lead to the development of T2DM [13–18]. One mechanism by which these altered levels of adipokines may contribute to T2DM is through inflammation mediated insulin resistance. For example, high levels of pro-inflammatory cytokines with obesity contribute to the development of chronic state of inflammation that impairs normal adipose tissue function. Although the mechanism whereby this adipose dysfunction affects insulin sensitivity is not fully understood, activation of serine/threonine kinases that phosphorylate and thereby regulate various effectors of the insulin signaling pathway (e.g., insulin receptor, insulin receptor substrate-1) has been implicated in numerous studies [19–21]. A large body of experimental evidence also supports the proposition that altered synthesis and secretion of adipokines that directly affect insulin sensitivity and glucose metabolism in various tissues, similarly contributes to the development of insulin resistance and T2DM in obesity [15, 22–26].

Chemerin (also known as tazarotene-induced gene 2 and retinoic acid receptor responder 2) is a recently identified adipokine that has attracted considerable interest due to an increasing body of evidence supporting roles for this adipokine in adipogenesis, energy metabolism, and inflammation. In particular, chemerin has been hypothesized as a possible link between obesity and the development of T2DM [27]. This proposal has been fueled by a surge of clinical data demonstrating increased levels of serum chemerin in patients with obesity, T2DM and/or with components of the metabolic syndrome when compared to lean, healthy subjects [18, 28–35]. Circulating chemerin levels have also been reported to correlate positively with established markers of inflammation including tumor necrosis factor-alpha, interleukin-6, and C-reactive protein [29, 36]. In one of the earliest studies investigating the relationship of chemerin to obesity, plasma chemerin levels were reported to be higher in a group of obese and overweight Mexican–American patients compared with lean controls [37]. Moreover, those patients with T2DM also have higher serum chemerin levels as compared to normoglycemic counterparts. This study also reported that plasma chemerin levels positively correlated with body mass index (BMI), fasting serum insulin, fasting glucose, plasma triglycerides, and total serum cholesterol, and negatively correlated with high-density lipoprotein. Similar studies in a Mauritian and Caucasian population corroborated the relationship between serum chemerin with adiposity and various aspects of the metabolic syndrome [28]. In further support of a relationship between adiposity and serum chemerin levels, patients who underwent various weight loss methods including caloric restriction or bariatric surgery, have significantly reduced serum chemerin levels compared to obese individuals who did not undergo a weight loss intervention [32, 38, 39]. In another study, examining patients with polycystic ovary syndrome, a condition associated with insulin resistance, T2DM, visceral adiposity, and dyslipidemia, patients were found to have elevated levels of chemerin in subcutaneous and omental adipose depots [40]. Overall, these findings suggest that circulating chemerin levels are associated with adiposity and the metabolic syndrome and that visceral adipose is a modifiable source of chemerin in obese individuals. In this review, we highlight the role of chemerin in inflammation and glucose metabolism and pose unanswered questions that may guide future research concerning chemerin as a possible link between obesity and the development of T2DM.

Chemerin identification and processing

Chemerin was initially identified in 1997 using differential display, as a retinoid responsive gene present in psoriatic skin lesions [41]. However, it wasn't until 6 years later that experimental evidence provided the first clues to the biological function of the protein. A key early finding was the detection of chemerin in human inflammatory fluids such as ascites from patients with ovarian cancer and synovial fluid from patients with rheumatoid arthritis [42]. Functional analysis revealed that chemerin was as a ligand activator for the orphan G-protein coupled receptor chemokine-like receptor 1 (CMKLR1, also known as ChemR23 and DEZ) and served as a chemotactic signal for cells expressing CMKLR1 [41, 42]. Chemerin is expressed at the highest levels in liver and white adipose tissue, at moderate levels in lung and brown adipose tissue, and at lower levels in tissues such as heart, ovary and kidney [37, 43]. By comparison, CMKLR1 is expressed at the highest levels in macrophages, immature dendritic cells and white adipose and at lower levels in developing bone, lung, brain, heart, and placenta [42, 43]. Among the tissues of the body, white adipose is unique in that it expresses high levels of both chemerin and CMKLR1, prompting the original hypothesis by Goralski et al. [43] that this tissue was both a source of chemerin and target for the biological actions of this protein. Consistent with this proposal, in 2007 chemerin was identified as a novel adipokine that regulates adipogenesis and adipocyte metabolism as evidenced by experimental data showing that loss of chemerin or CMKLR1 abrogates adipocyte differentiation and modifies the expression of genes critical in glucose and lipid metabolism. Subsequent studies confirmed these findings and have provided experimental evidence for additional roles of chemerin in diverse biological processes including

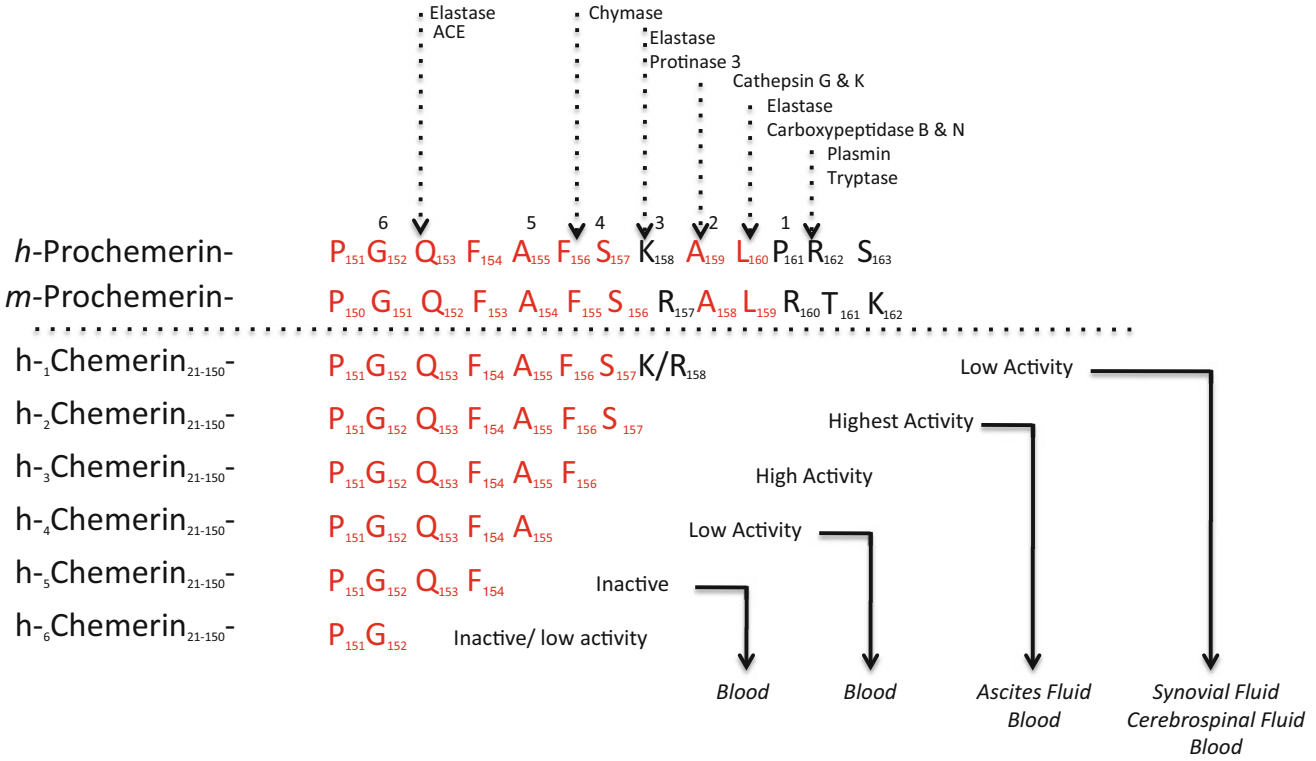

Fig. 1 Pro-chemerin Processing. In vitro recombinant h-pro-chemerin studies identified h-pro-chemerin is cleaved by immune cell and serum-associated enzymes into 6 chemerin products that differ in their C-terminal amino acid and potency for CMKLR1 activation. Given the sequence homology between human and mouse chemerin C-terminus (conserved amino acids are indicated in *red*), similar *m*-pro-chemerin protease cleavage is predicted. Only the C-terminal amino acids of the full-length protein are identified within this figure

cell proliferation and differentiation, angiogenesis, renal function and energy metabolism [27, 44, 45]. Moreover, two additional chemerin receptors have been identified, chemokine receptor like 2 (CCRL2) and G-protein coupled receptor 1 (GPR1) [46, 47]. While chemerin is known to bind CCRL2 and GPR1, all of the biological actions currently ascribed to chemerin are elicited through activation of CMKLR1.

Chemerin is initially translated as prepro-chemerin, a 163 amino acid protein that undergoes N-terminal cleavage of a signal peptide sequence prior to secretion as an inactive 18-kDa precursor, pro-chemerin [42]. Pro-chemerin undergoes C-terminal processing by extracellular proteases of the coagulation, fibrinolytic, or inflammatory cascade to produce the active 16-kDa form of chemerin [42, 43, 46, 48]. A number of enzymes capable of cleaving pro-chemerin into an active form have been identified (Fig. 1); these enzymes produce different length products each with varying degrees of activity toward CMKLR1. Elastase and cathepsin G, two neutrophil proteases, were the first enzymes shown to activate pro-chemerin [49]. Whereas elastase cleaves the 6, 8 or 11 C-terminal amino acids of pro-chemerin cathepsin G removes 7 C-terminal amino acids to generate a less active chemerin form (chemerin-156). While plasmin and mast cell tryptase cleave pro-chemerin into a form with relatively low bioactivity (chemerin-158), further processing by plasma carboxypeptidase N or B can generate a highly active form (chemerin-157) [48, 50]. In addition to the proteases that generate active chemerin forms, others have been shown to inactivate bioactive chemerin or produce relatively inactive forms of chemerin from pro-chemerin. For example, mast cell chymase and angiotensin converting enzyme can cleave bioactive forms of chemerin to produce relatively inactive forms (e.g., chemerin-154, -152) [50, 51]. While much of the information regarding chemerin processing is derived from in vitro or ex vivo studies, the presence of most of the predicted forms of chemerin have been verified in human blood (chemerin-158, -157 and -155), hemofiltrate (chemerin-154), ascites (chemerin-157), synovial fluid (chemerin-158) and cerebrospinal fluid (chemerin-158) indicating that alternative processing of chemerin does occur in vivo [52–56]. Taken together, these data indicate that in addition to the circulating and local concentrations of total chemerin protein, the degree of chemerin bioactivity at any particular anatomical site is determined by the relative expression and activity of proteases with the ability to activate/deactivate chemerin.

Chemerin and inflammation

Chemerin, acting through CMKLR1 has been reported to have both pro- and anti-inflammatory properties. One of the first pro-inflammatory roles postulated for chemerin was as a chemoattractant for leukocytes to sites of inflammation. This idea was based on early data demonstrating expression of CMKLR1 on macrophages and immature dendritic cells [42, 53]. In vitro experiments confirmed that recombinant human serum and plasma chemerin promote the migration of various CMKLR1-expressing effector cells of the immune system including, preB lymphocytes, macrophages, immature plasmacytoid dendritic cells, and natural killer cells [42, 57–59]. In addition to a role in chemotaxis, it has more recently been demonstrated that chemerin promotes linkage of macrophages to extracellular matrix proteins and adhesion molecules, therefore facilitating adhesion of macrophages to tissue endothelium [60]. Interestingly, CMKLR1 expression is lost in mature dendritic and natural killer cells, suggesting a role for chemerin in the initial phases of leukocyte recruitment. This idea is supported by data showing that neutrophils, generally the first cells recruited to sites of inflammation, secrete serine proteases that activate human pro-chemerin into two highly active mature forms of chemerin [49]. Support for a pro-inflammatory role of chemerin in humans derives from data in which serum chemerin levels positively correlate with serum levels of a number of pro-inflammatory cytokines including IL-6, C-reactive protein, and TNFα [29, 36]. Furthermore, studies of pathological tissue show that CMKLR1-expressing natural killer and dendritic cells are found in inflammatory skin lesions and in kidneys of patients suffering from systemic lupus erythematosus [58, 59], and that increased chemerin and CMKLR1 levels are found in plasma and tissue lesions of patients suffering from chronic inflammatory disorders including oral lichen planus, psoriasis, osteoarthritis, inflammatory bowel disease, and chronic hepatitis C [61, 62]. Taken collectively, these data support a pro-inflammatory role for chemerin acting through CMKLR1 involving both the chemotaxis and adhesion of leukocytes in inflamed tissue.

Experimental evidence has also been reported in support of anti-inflammatory properties for CMKLR1 signaling. This has been proposed to involve resolvins, anti-inflammatory mediators derived from omega-3 polyunsaturated fatty acids, rather than chemerin as the receptor ligand. Resolvins are generated during the resolution phase of inflammation where they act as potent inhibitors of leukocyte infiltration. Resolvin E1 (RvE1) has been proposed to signal through CMKLR1 resulting in reduced TNF alpha-mediated signaling and production of the potent pro-inflammatory cytokine IL-12 by dendritic cells [63]. However, it is important to note that these findings have yet to be independently verified and subsequent studies indicated that the actions of RvE1 are elicited through interaction with receptors other than CMKLR1 [64, 65]. Both chemerin and a synthetic polypeptide derived from the last 15 C-terminal amino acids of chemerin (chemerin15) were reported to protect mice from the development of zymosan-induced peritonitis by decreasing the production of pro-inflammatory cytokines and reducing the number of neutrophils and monocytes present in peritoneal fluid [66]. The authors reported that CMKLR1 knockout mice were not protected from peritonitis by chemerin15 administration, suggesting that the anti-inflammatory actions of this peptide were dependent on CMKLR1 signaling. The same group subsequently reported that Chemerin15, but not chemerin, might also function in the resolution of inflammation by promoting the phagocytosis of microbial particles and apoptotic cells by macrophages both in vitro and in vivo [67]. These findings are intriguing as they hint at the possibility of selective CMKLR1 modulator peptides that can elicit different functional effects through interaction with the same receptor. However, as with RvE1, it is important to note that while other research groups have studied this peptide [68, 69], the efficacy of Chemerin15 toward CMKLR1 has not yet been independently verified. An anti-inflammatory role for chemerin/CMKLR1 signaling has also been described in a mouse model of LPS-induced lung inflammation. In this study [68], administration of recombinant chemerin decreased lung tissue inflammation and alveolar infiltration by neutrophils compared to vehicle treated mice. CMKLR1-knockout mice were both unresponsive to the beneficial effects of chemerin and exhibited elevated LPS-induced neutrophil accumulation, suggesting a central role for chemerin/CMKLR1 signaling as a mediator of inflammation in this model.

At present, experimental data derived from animal and cell-based models supports both pro- and anti-inflammatory roles for chemerin/CMKLR1 in immune processes. In humans, this research is supported by correlational data between inflammatory states and elevated chemerin levels. Although it is not clear whether chemerin contributes more to the propagation of inflammation or the resolution, it is likely that different isoforms of chemerin have different roles in the various stages of inflammation. Which of these is most important in any particular context is likely to be dependent upon the nature of the immune stimulus as well as a complex interplay with other signaling molecules and effector cells of the immune system. A recent study of CMKLR1-knockout mice revealed substantially less white adipose tissue infiltration of CD3+ T-cells and increased numbers of natural killer cells when compared to wild type mice in a diet-induced obesity model [70]. As described in the next section, the knockout mice also exhibit metabolic

derangements primarily characterized by impaired glucose tolerance. While this suggests a linkage between adipose inflammation and glucose homeostasis that is mediated by CMKLR1 in these mice, it is important to recognize that at present there is no direct evidence linking the immune function of chemerin/CMKLR1 with the development of T2DM. However, this possibility is attracting increasing attention given the parallel investigations of chemerin in immune function and numerous reports of elevated circulating levels of this adipokine in obese versus lean individuals.

Chemerin and glucose homeostasis

Although evidence exists demonstrating an influence of chemerin on glucose homeostasis, at present the precise role and significance is unclear due to conflicting results derived from various in vivo and in vitro studies. For example, experiments with cultured 3Tl-1 derived adipocytes have provided evidence for both inhibitory [71] and stimulatory [72] effects of chemerin on glucose uptake. Inhibition of glucose uptake and reduction of insulin sensitivity in response to exposure of skeletal muscle cells to chemerin has also been reported [40, 73]. In some measure, the discrepancies among these studies reflect differences in experimental models as well as differences in chemerin dosage and treatment duration. Similarly, while experiments with mouse models generally support an influence of chemerin/CMKLR1 on glucose homeostasis, apparent discrepancies have emerged. In part, this may reflect differences in experimental models but also the influence of physiological context on the actions of chemerin. For example, recent studies in mice have revealed that the effect of exogenous chemerin on glucose uptake and serum insulin levels in vivo is different in normo- versus hyperglycemic animals. Specifically, while there was no effect on tissue glucose uptake in normal lean mice, recombinant chemerin administration exacerbated glucose intolerance and decreased serum insulin levels in three different murine models of obesity/diabetes (db/db, ob/ob and diet-induced obesity) [74]. Moreover, in the obese/diabetic mice, but not lean healthy controls, chemerin decreased hepatic glucose uptake, but not that of adipose or skeletal muscle suggesting that the effect of chemerin was elicited primarily through modulation of GLUT2 expression and/or activity.

Studies of chemerin and CMKLR1 knockout mice have revealed that reduced glucose-stimulated insulin secretion is a phenotype common to both models [70, 75]. GLUT2 is a facilitative glucose transporter that is highly expressed in pancreatic beta-cells and promotes insulin secretion by increasing the intracellular concentration of glucose. Consistent with the reduction of glucose-evoked insulin secretion, GLUT2 expression and glucose-stimulated insulin release was reported to be decreased in pancreatic islets prepared from chemerin knockout mice [75]. While the precise mechanism of this effect remains to be fully elucidated, experimental evidence suggests that chemerin/CMKLR1 signaling positively regulates the expression of MafA, a transcription factor expressed in pancreatic beta-cells that positively regulates GLUT2 expression [75]. As GLUT2 serves as a principle sensor of blood glucose levels, reduction of pancreatic MafA and consequently GLUT2 expression may explain the reduction of glucose-evoked insulin release in chemerin knockout mice. However, it is important to note that while the authors also reported a modest reduction of glucose-stimulated insulin secretion in response to chemerin siRNA knockdown in the pancreatic beta cell line Min6, independent verification of these findings was not successful [70]. At present it can only be concluded that independent findings support that chemerin/CMKLR1 signaling affects glucose-stimulated pancreatic insulin release, but further study is clearly required to validate these results and precisely define the mechanism(s) involved.

As previously discussed, administration of recombinant chemerin exacerbates glucose intolerance in mouse models of obesity/diabetes. However, in CMKLR1 knockout mice, loss of chemerin signaling through this receptor resulted in impaired glucose intolerance and reduced glucose uptake in skeletal muscle and adipose tissue [70]. These deleterious metabolic outcomes were accompanied by an apparent beneficial reduction in adiposity and resistance to diet-induced obesity, a finding consistent with both reduced food consumption in the knockout mice and the autocrine/paracrine role of chemerin/CMKLR1 to promote adipocyte formation [43]. In contrast, chemerin knockout mice were reported to have increased insulin sensitivity of skeletal muscle but reduced adipose and hepatic insulin sensitivity, increased hepatic glucose production and no substantial differences in adiposity compared to wild-type mice [75]. Reconciliation of the findings from these animal studies is confounded by numerous factors including but not limited to: potential interactions with other signaling pathways (e.g., deficient leptin signaling in the ob/ob and db/db models), the complex phenotype of the existing knockout mouse models (coincident tissue-dependent beneficial and detrimental effects on glucose metabolism), differences in experimental approaches (e.g., simple blood glucose measures in [27, 74] versus more sophisticated euglycemic clamp techniques in [75]), the existence of multiple chemerin receptors (CMKLR1, GPR1, and CCRL2), the potential existence of multiple chemerin receptor ligands (e.g., RvE1) and the increasing realization that chemerin influences numerous physiological processes (e.g.,

Table 1 Key research questions to guide future chemerin research

Key research questions
What isoform(s) of chemerin are increased in obesity and T2DM and what are the physiological functions of these different isoforms?
What is the physiological significance of chemerin binding at GPR1 and CCRL2?
What signaling pathways are activated by chemerin binding to CMKLR1?
In obesity, does chemerin act to promote leukocyte infiltration to adipose tissue or does chemerin contribute to the resolution by increasing pro-inflammatory cytokines?
How do other ligands of CMKLR1 affect glucose metabolism?
How does chemerin impact glucose metabolism in diabetic versus non-diabetic adipose and other tissue?
How do current pharmacotherapies for T2DM impact chemerin levels/signaling?

inflammation, metabolism, cell proliferation, and differentiation). Thus, at present the role(s) of chemerin and the cognate receptors in glucose homeostasis remains to be clarified; however, the balance of cell-based, animal and human studies support a role for this adipokine as a regulator of this fundamental aspect of metabolism.

Conclusion

While an abundance of experimental data suggests that the elevated chemerin levels with obesity are associated metabolic dysfunction characteristic of metabolic syndrome, further studies are necessary to define the precise role of chemerin in inflammation and glucose homeostasis. These studies will help to discern whether the increase in circulating chemerin levels with obesity is solely due to an increase in adipose tissue mass or if it is also related to changes in inflammation and/or insulin resistance. Although at this time, it is not possible to assign direct causality between altered chemerin levels and deleterious changes in metabolic function, the reported impact of chemerin/CMKR1 signaling on glucose homeostasis in various cell- and animal-based models is compelling and driving this exciting area of endocrine research. In particular, it will be important to resolve whether chemerin is elevated in obesity in response to inflammation, or if it directly contributes to the development/maintenance of inflammation in adipose and other tissues in the obese states. This is relevant not only to the development of T2DM, but also to the potential role of this adipokine in the development of other prevalent disorders, such as coronary artery disease, that are related to the metabolic derangements associated with obesity [76].

Among the numerous clinical reports regarding circulating chemerin levels, adiposity and metabolic dysfunction, the most intriguing have demonstrated that white adipose tissue is the major modifiable source of circulating chemerin [32, 38, 39]. These findings suggest that if chemerin is established as a causal link between obesity and the development of T2DM, modification of chemerin release from white adipose or the actions of this adipokine at cognate receptors may offer a future pharmacological target that can influence the development of T2DM and/or metabolic syndrome in obese patients. However, a more imminent clinical utility may derive from the use of circulating chemerin levels as marker for the diagnosis of the metabolic syndrome. This is supported by the findings of Stejskal et al. [28] who were able to use a 240 μg/L serum chemerin threshold to diagnose metabolic syndrome with a sensitivity and specificity of 67 and 75 %, respectively. Uncovering the answer to critical questions (Table 1) will help define the relationship between chemerin, inflammation, and glucose metabolism—not only in a physiological context but also in the pathophsyiological obesity and obesity-related disorders.

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