Chemokine Like Receptor-1 (CMKLR-1) Receptor: A Potential Therapeutic Target in Management of Chemerin Induced Type 2 Diabetes Mellitus and Cancer

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Abstract: Background: Chemerin is an adipokine that induces insulin resistance by the mechanism of inflammation in adipose tissue but these are still unclear. A high level of chemerin in humans is considered as a marker of inflammation in insulin resistance and obesity as well as in type 2 diabetes mellitus. Despite the role of chemerin in insulin resistance progression, chemerin as one of the novel adipokines is proposed to be involved in high cancer risk and mortality.

Aim: The aim of this paper was to review the role of CMKLR-1 receptor and the potential therapeutic target in the management of chemerin induced type 2 diabetes mellitus and cancer.

Pathophysiology: Increased chemerin secretion activates an inflammatory response. The inflammatory response will increase the oxidative stress in adipose tissue and consequently results in an insulin-resistant state. The occurrence of inflammation, oxidative stress and insulin resistance leads to the progression of cancers.

Conclusion: Chemerin is one of the markers that may involve in development of both cancer and insulin resistance. Chemokine like receptor-1 (CMKLR-1) receptor that regulates chemerin levels exhibits a potential therapeutic target for insulin resistance, type 2 diabetes and cancer treatment.

Keywords: Chemerin, insulin resistance, type 2 diabetes mellitus, cancer, chemokine-like receptor 1, therapeutic target, obesity, inflammation.

1. INTRODUCTION

Chemerin, also called as retinoic acid receptor responder protein 2 (RARRES2), RAR-responsive protein TIG2, or tazarotene-induced gene 2 protein (TIG2), is a 14-kDa protein secreted as pro-chemerin, an inactive form of chemerin, and is activated through the C-terminus split off by inflammatory and coagulation serine proteases. It is coded by RARRES2 [1, 2]. Chemerin is a chemotactrant protein that acts as a ligand for a G-protein-coupled receptor, chemokine-like receptor 1 (CMKLR1) (also known as ChemR23) [3].

Beside CMKLR-1, there are two other chemerin receptors: chemokine receptor-like 2 (CCRL2) and G-protein-coupled receptor 1 (GPR1). It is believed that through these receptors, chemerin expresses its chimeric nature. Consequently, this promotes the mechanism by which chemerin increases insulin resistance and cancer-related inflammation [4]. The CMKLR1 and GPR1 are able to stimulate or inhibit MAPK ERK1/2, Akt, and AMPK signalling pathways to regulate different biological mechanisms such as angiogenesis and inflammation. On the other hand, CCRL2 is not a signalling receptor but it can internalize CCL19 or present chemerin to CMKLR1, and plays an anti-inflammatory role [5].

Epidemiologically, the incidence rates of people with diabetes increased by 74% from 1980 to 2014 [6]. The number of people with obesity worldwide has reached 2.1 billion, leading to an explosion in obesity-related health risk associated with increased comorbid conditions and mortality [7, 8]. In 2012, there were 14.1 million people diagnosed with cancer and the death rate reached 8.2 million [9].

Insulin resistance is a hallmark of obesity and generally appears early in metabolic syndrome. It is closely associated with increased visceral adipose tissue mass [10]. The incidence of type 2 diabetes mellitus (T2DM) is majorly due to increased body mass and insulin resistance [11]. Increased adipose tissue mass can result in the release of adipokines. Chemerin is one of the adipokines found to be associated with obesity-related insulin resistance and therefore, T2DM [12]. The association between high serum levels of chemerin and components of metabolic syndrome and T2DM indicates that chemerin may be a novel marker of these diseases and may be a metabolic risk factor leading to insulin resistance in T2DM as well as metabolic syndrome [13].

The risk for cancers has been linked to high levels of circulating chemerin in humans [14]. The progression and proliferation of cancers associated with chemerin have been explored in various pathways including the inflammatory response and anti-apoptosis [15]. Gastric cancer is one type of cancer that has been well studied for its relationship with plasma levels of chemerin [16]. Other types of cancers that have been studied for their associations with chemerin include ovarian cancer, liver cancer, lung cancer, esophageal cancer, and colorectal cancer [17-21].

Changes in paracrine and endocrine activities of adipose tissue are associated with insulin resistance and obesity. Increased adipose tissue mass can result in decreased blood supply to adipocytes and induce the release reactive oxygen species (ROS), mediated by the decreased bioavailability of nitric oxide (NO). As a result, oxidative stress in adipocytes increases, macrophages are recruited, and adipokines are released [22, 23].
Obesity-induced inflammation is reported to play a determining role in the secretion of many adipokines including chemerin and leptin, various types of cytokines such as tumor necrosis factor (TNF) and interleukin (IL), and free fatty acids (FFA) [24]. These molecules may promote insulin resistance through multiple pathways [25, 26] and eventually lead to hyperglycemia and T2DM. With hyperglycemic progression, oxidative stress increases and results in DNA damage [27]. Decreased apoptosis and cell proliferation may also be implicated under hyperglycemic conditions [28, 29]. Taken together, it is possible that these mechanisms may promote the initiation of cancer processes. So, the aim of this paper is to review the role of CMKLR1 receptor and the potential therapeutic target in the management of chemerin induced type 2 diabetes mellitus and cancer.

2. CHEMERIN AND THE ETIOLOGY OF INSULIN RESISTANCE AND T2DM

Insulin resistance is one of the major pathophysiological events contributing to the development of T2DM [30]. Insulin resistance is defined clinically as the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and its use in an individual by as much as it does in a normal population [31]. Insulin resistance is one of the main metabolic syndromes associated with increased body weight. Generally, people with obesity develop insulin resistance and T2DM compared with non-obese individuals [32]. A person is classified as being obese if his/her body mass index (BMI) is more than 30.0 kg/m² or if his/her waist circumference is more than 40 inches for men and more than 35 inches for women [33].

One mechanism that induces obesity-related insulin resistance is inflammation in adipose tissue [34]. Adipose tissue is made up of various cell types, such as adipocytes, pre-adipocytes, fibroblasts, macrophages, and blood vessels [35]. The human body has two types of adipose tissue, white adipose tissue and brown adipose tissue, and both can be found together throughout adipose tissue sites. White adipose tissue is involved in fat storage and is considered the largest endocrine system in the body. It has autocrine, paracrine, and endocrine functions on the human brain, muscle, liver, vessels, kidney, and bone [36]. The plasticity of white adipose tissue is associated with weight gain in humans [37]. Brown adipose tissue plays a role in dissipating energy through the regulation of thermogenesis in response to food intake and cold, and also in sympathetic activation. A decrease in brown adipose tissue is thought to be associated with insulin resistance and hyperglycemia but the pathogenesis is unclear [36].

Inflammation in adipose tissue is mediated by the activation of adipocytokines. Adipocytokines are key players in the pathogenesis of obesity-related insulin resistance. Adipocytokines are highly lipolytic [36]. In adipocytes, NO is produced by endothelial nitric oxide synthase and inducible nitric oxide synthase. NO is the signaling molecule that regulates energy homeostasis in adipose tissue. Adipogenic differentiation and obesity increase inducible nitric oxide synthase expression, resulting in increased generation of NO. Therefore, increased insulin secretion by β-cells with insulin resistance increases NO generation in human pre-adipocytes and increases ROS [38]. Adipocytokines are the signaling molecules that signal inflammatory pathways.

Several adipokines synthesized by adipocytes may induce insulin resistance [24]. The production of most adipokines is upregulated in obesity [39]. With obesity and progressive adipocyte enlargement, the blood supply to adipocytes may decrease, with consequent hypoxia. Hypoxia has been proposed to be an initiating etiology of necrosis and macrophage infiltration into adipose tissue that leads to overproduction of adipokines [36]. Adipokines can be classified as pro-inflammatory adipokines and anti-inflammatory adipokines. Overexpression of pro-inflammatory adipokines induces insulin resistance. Some pro-inflammatory adipokines that mediate inflammation and insulin resistance are TNF-α, IL-6, plasminogen activator inhibitor-1, C-reactive protein (CRP), and IL-1β. Some other recently discovered pro-inflammatory adipokines are thought to be associated with insulin resistance [24].

Chemerin is a recently discovered adipokine that promotes obesity-linked metabolic diseases, in particular, insulin resistance [40]. Chemerin is a multifunctional protein that affects adipogenesis and glucose homeostasis in adipocytes [41]. Chemerin is expressed in many tissues such as the liver, kidneys, and white adipose tissue [42]. Chemerin and CMKLR1 are important for adipogenesis in adipocytes (sell). An increased level of chemerin in humans is considered a marker of inflammation, metabolic syndrome, and obesity [43].

Chemerin is released from adipose tissue. Chemerin plays a crucial role in adipocyte differentiation and it modulates adipocyte genes expression in glucose and lipid homeostasis, for instance, glucose transporter-4, fatty acid synthase, via CMKLR1. Increased numbers of pre-adipocytes result in an increase in body weight and are associated with insulin resistance and T2DM [44]. Pre-adipocytes reside in white adipose tissue and give rise to adipocytes [45]. Adipose tissue macrophages can be divided into M1 macrophages and M2 macrophages. The proportion of activated M1 macrophages to M2 macrophages is higher in the obese state. The degree of adipose tissue macrophage infiltration is associated with the progression of insulin resistance [46].

In the obesity-related hyperglycemic and insulin-resistant state, cells of the adipose tissue actively participate in tumor cell progression through the action of the adipokine chemerin. Hyperglycemia is defined as a state of excess glucose concentration in the circulation, a hallmark for both type 1 and type 2 diabetes [24]. In response to hyperglycemia, oxidative stress increases in obese people with T2DM [47]. The pathway begins when adipocytes induce the release of ROS such as superoxide radicals and lipid peroxide and increase ER stress. ROS is a group of free radical molecules derived from diatomic oxygen. ROS is generated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and exhibits a spectrum of reactivity. Increased ROS increases oxidative stress in accumulated fat. NADPH oxidase activity is stimulated by angiotensin II which is secreted by adipose tissue. Oxidative stress is associated with the irregular production of chemerin. Increased oxidative stress decreases the release of anti-oxidative enzymes including superoxide dismutase, glutathione peroxidase, and chloramphenicol acetyltransferase. Therefore, the reduced levels of anti-oxidative enzymes are unable to compete with the increased levels of ROS and are unable to stabilize or deactivate the free radicals before they attack cellular components [48]. At the same time, the bioavailability of NO diminishes in the higher oxidative stress state [49].

ER is the principal intracellular organelle responsible for protein folding, translocation, and post-translation alteration. ER stress is induced under various situations and triggers the unfolded protein response. The unfolded protein response is involved in the progression of cancer [50].

The increase in ROS, oxidative stress, and ER stress eventually initiates inflammatory processes by activating inflammatory signaling pathways [23]. The chronic inflammation that connects obesity to the development of insulin resistance is known as metabolic inflammation or meta-inflammation [51]. In the inflamed state, adipose tissue enlarges and becomes adipocytes from blood vessels and consequently becomes poorly oxygenated. Hypoxia-inducible factor (HIF)-1α is activated in this hypoxic state. HIF-1α is the key regulator of oxygen homeostasis and may elevate the inflammatory response in adipose tissue by mediating the recruitment of macrophages into adipose tissue. HIF-1α also plays an important role in the development, growth, and metastasis of a variety of cancer
types. Hypoxia and inflammation in people with obesity-related insulin resistance may modulate tumor angiogenic processes [38].

Obesity-induced inflammation is believed to contribute to increased plasma concentrations of insulin and insulin-like growth factor 1 [12]. Insulin-like growth factor 1 is a 70-amino acid polypeptide hormone produced mainly by the liver in response to endocrine growth hormone stimulus, but also has paracrine and autocrine effects [52]. Accumulation of both molecules can lead to elevated secretion of cytokines (called adipokines when released by adipose tissue). The resulting increase in adipokines such as chemerin is modulated by some inflammatory cells [12]. Adipocytes in adipose tissue undergo a process called hypertrophy, which is an increase in the size of the adipocyte due to accumulation and deposition of excess lipids. Together with various immune cells, hypertrophic adipocytes release non-esterified fatty acids, also called FFA, adipokines (chemerin) and various pro-inflammatory cytokines [24]. In most people with obesity, elevated plasma FFA, cytokines, and adipokine levels inhibit the anti-lipolytic action of insulin, which further leads to abnormal insulin signaling [36].

Many studies have reported the role of circulating FFA and pro-inflammatory cytokines in insulin resistance progression and the link with obesity. One study investigated the mechanisms by which FFA cause hepatic insulin resistance by insulin receptor signalling and hepatic hyperinsulinemic clamping with and without infusion of lipid/peparin (to raise or to lower plasma FFA) in alert male rats. The results showed that FFA-induced hepatic insulin resistance was associated with increased hepatic diacylglycerol content, increased expression of inflammatory cytokines, increased activation of the pro-inflammatory nuclear factor-xB pathway, and increased activities of two serine/threonine kinases (protein kinase C-δ and inhibitor of κB kinase-β). The researchers concluded that hepatic insulin resistance is caused by FFA, which can produce overproduction of glucose and hyperglycemia [24]. The increased plasma FFA level in people with obesity and T2DM contributes to insulin resistance by activating inflammatory cytokines such as TNF-α and IL-6 [53].

Studies have reported that knockdown of the expression of chemerin and CMKLR1 in pre-adipocytes reduces the expression of genes involved in glucose and lipid metabolism [11]. Although studies describe the effects of chemerin on glucose homeostasis, the exact mechanism is unclear [54].

A number of studies have sought to identify the effect of chemerin on insulin resistance as well as T2DM. A study by Lee et al. (2013) concluded that chemerin levels were associated with insulin resistance at baseline and also after lifestyle intervention [54]. Another study found that plasma levels of chemerin in patients with T2DM were higher than the control group, with the researchers concluding that there is a potential link between chemerin and the pathogenesis of insulin resistance, obesity, and metabolic syndrome [55]. Chemerin concentrations were found to be elevated in elderly T2DM patients and appeared independent of the term of the disease and BMI, suggesting that adipocyte dysfunction increases with age [56].

A study by Weigert et al. (2010) reported that circulating chemerin levels were similar in T2DM and people with obesity but significantly elevated in both cohorts compared with normal-weight individuals [57]. A study by Sell et al. (2013) reported that insulin resistance at adipocyte lipogenesis and insulin-stimulated antilipolysis secretion correlated with increased chemerin secretion. In a study, CMKLR1 and chemerin were highly expressed in mouse and human adipocytes [5]. A recent study reported that acute administration of recombinant human chemerin aggravated glucose intolerance, lowered serum insulin levels, and decreased tissue glucose uptake in ob/ob, db/db, and diet-induced obese mice but not in normoglycemic wild-type mice [17]. These findings are consistent with those of Becker et al. (2010), who demonstrated that the glucose intolerance is promoted by expression of chemerin via induction of insulin resistance in the skeletal muscle of low-density lipoprotein receptor knockout mice on a high-fat diet [26].

In another study, a higher level expression of CMKLR1 was found in obese and T2DM Psammomys obesus’ adipose tissue than in lean normoglycemic Psammomys obesus’ adipose tissue. In vitro, chemerin protein which was secreted by cultured 3T3-L1 adipocytes, induced CMKLR1 autocrine signaling in adipocytes. The process of 3T3-L1 cells’ differentiation into adipocytes was impaired, expression of adipocyte genes that participated in glucose and lipid homeostasis reduced, and the mature adipocytes’ metabolic functions altered as a result of adenoviral small hairpin RNA targeted knockdown of chemerin [58]. From these studies, we can conclude that, chemerin and CMKLR1 interaction results in a novel mechanism that manages adiogenesis and these findings altogether suggest that chemerin is associated with hyperglycemia and obesity-induced insulin resistance. Table 1 summarizes some of the studies that have found an association between chemerin and obesity, insulin resistance, and T2DM [11].

Besides insulin resistance and T2DM, chemerin may also be associated with other diseases that are related in some way with inflammation, such as cancer. It is suggested that cancers have the same inflammatory pathway as obesity-related insulin resistance and T2DM. The tumorigenesis process in cancer involves the release of ROS and increased oxidative stress, as in obesity-related insulin resistance.

3. CHEMERIN AND THE ETIOLOGY OF CANCER

Over the years, the pathogenesis of cancer has been studied, and, recently, studies have investigated the causative relationship between chemerin and cancer risk. The mechanism behind chemerin and the development of cancer are thought to be through multiple pathways. Evidence suggests that circulating chemerin induces progression of cancer cells through inflammation, anti-apoptosis, increased cell proliferation and migration pathways, and metastasis [15]. Some cancers that have been reported to show a relationship between circulating chemerin levels and cancer risk include gastric cancer, esophageal cancer, lung cancer, colorectal cancer, liver cancer, and cancer of the nerves (Table 2).

3.1. Gastric Cancer

Wang et al. (2014) reported a novel action of chemerin in gastric carcinogenesis. They investigated serum levels of chemerin in 36 gastric cancer patients and 40 healthy participants using enzyme-linked immunosorbent assay (ELISA) to see what effect it had on gastric cancer cells. They found that the serum chemerin level was significantly higher in gastric cancer patients compared with healthy controls (P<0.01), and increases were associated with advances in clinical stages and non-intestinal types of gastric cancer. With in vitro studies, the researchers observed that chemerin increased the invasiveness but not the development of gastric cancer cells and which later induced phosphorylation of p38 and ERK1/2 mitogen-activated protein kinases (MAPK) and upregulated vascular endothelial growth factor (VEGF), matrix metalloproteinase-7 (MMP-7), and IL-6. Inhibition of ERK1/2 phosphorylation abolished the upregulation of VEGF, MMP-7, and IL-6 and the pro-invasive effect of chemerin [16]. A similar finding was reported by Zhang et al. (2014). In their study, the researchers evaluated the relationship between preoperative plasma chemerin levels and the prognosis of gastric cancer in a study of 196 patients and 196 age and gender-matched healthy participants. Using ELISA, they also found that plasma chemerin levels increased in gastric cancer. In addition, chemerin was identified as an independent predictor of 5-year mortality and adverse events of gastric cancer as well as a predictor of overall survival and disease-free survival. On the whole, the study suggested that high plasma chemerin levels may play a role as a prognostic biomarker in gastric cancer survival as...
3.2. Esophageal Cancer

Higher serum concentrations of chemerin may be a possible contributor to squamous esophageal cancer. A recent study found overexpression of chemerin in esophageal squamous cancer-associated myofibroblasts (CAM) compared with adjacent tissue myofibroblasts. The researchers proposed that chemerin secreted from esophageal CAM is a potential chemoattractant for mesenchymal stromal cells and its inhibition may delay tumor progression [20]. The researchers extended their study by investigating the mechanisms of stromal cells in cancer progression, and found that chemerin can stimulate esophageal cancer cell invasion [20].

3.3. Lung Cancer

The contribution of chemerin in the genesis and development of lung cancer has been studied in a Chinese population in which the expression of chemerin in the peripheral blood of patients was detected using ELISA. This study examined samples from 42 lung cancer patients and 31 healthy controls. Findings showed that concentrations of chemerin in the peripheral blood of patients with lung cancer were significantly higher than that of the healthy controls [63]. A study by Zhao et al. (2011) examined the expression of chemerin and the relationship between chemerin expression and prognosis in patients with non-small cell lung cancer. Non-small cell lung cancer cells and corresponding normal tissue were collected from 108 random patients (80 males and 28 females). Similar to Qu et al., the level of chemerin protein expression in lung cancer tissue was significantly higher than that of normal lung tissue. Importantly, there was a close correlation between chemerin expression and recruitment numbers of natural killer cells. In contrast to Qu et al. (2009), low expression levels of chemerin correlated with a poor prognosis in non-small cell lung cancer patients [19].

3.4. Liver Cancer

Evidence suggests that the levels of chemerin in serum and adipose tissue are significantly increased in metabolic syndrome patients compared with healthy people [64, 65]. Chemerin also plays a critical role in inflammation and is associated with various inflammatory diseases [66]. Imai et al. (2014) studied the impact of chemerin on liver functional reserves in hepatocellular carcinoma (HCC) patients and on the recurrence and prognosis of HCC. A total of 44 patients with any stage of HCC were involved in the study. The researchers found that serum albumin levels, platelet counts, and prothrombin times significantly correlated with serum chemerin levels in HCC patients. No significant correlation was found between serum chemerin levels and recurrence-free survival or overall survival. The researchers concluded that in HCC patients, serum chemerin levels correlated with liver functional reserves and platelet counts, but not with recurrence or prognosis [18]. This is consistent with the study by Kukla et al. (2010) who found that serum chemerin is markedly elevated in chronic hepatitis C patients, as chronic hepatitis C is an underlying risk factor for HCC [67]. Conversely, a recent clinical trial by Lin et al. (2011), reported that protein expression of chemerin protein significantly decreased in HCC tissues from 72 patients compared with noncancerous liver tissue [68]. In addition, the lower expression of chemerin was associated with a poor prognosis. Similar to these findings, expression levels of chemerin did not significantly correlate with its receptor (CMKLR1) in chronic hepatitis C patients [67].

3.5. Colorectal Cancer

Few studies have studied the association between chemerin and colorectal cancer. One study examined 41 patients with colon cancer and a control sample of 27 patients with benign conditions diagnosed by colonoscopy for the association between colorectal cancer, inflammation, and adipokines including chemerin. Median chemerin levels were significantly higher in patients with colon cancer compared with the control group. CRP, fibrinogen, and erythrocyte sedimentation rates were also significantly higher in patients with colon cancer, suggesting that higher levels of circulating chemerin, CRP, fibrinogen, and a higher erythrocyte sedimentation rate are risk factors for the development of colorectal cancer [21].

3.6. Ovarian Cancer

Studies have reported elevated ovarian and circulating chemerin levels in a chronically androgenized rat model and suppression of follicle stimulating hormone-induced steroidogenesis by chemerin. Results suggested that expression of chemerin and CMKLR1 is elevated by chronic androgen administration and is associated with suppressed antral follicle development. The latter effect was characterized by dysregulated interaction between survival and pro-apoptotic modulators in a cell-specific manner, marked changes in follicle structure, apoptotic deletion of granulosa cells and oocytes.
Table 2. Relative risk for the association between chemerin and different types of cancer based on previous studies.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Study design</th>
<th>Sample size (n)</th>
<th>Population</th>
<th>Observations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>Case control</td>
<td>36 cases &amp; 40 controls</td>
<td>Chinese</td>
<td>1. Increment of serum chemerin level in gastric cancer patients and was associated with advanced clinical stages and non-intestinal type of gastric cancer. 2. Chemerin enhanced gastric cancer cell invasiveness by activating ERK1/2 and p38 MAPKs and promoting the expression of pro-invasive genes (e.g. VEGF, MMP-7, and IL-6).</td>
<td>[16]</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Case control</td>
<td>36 cases &amp; 40 controls</td>
<td>Chinese</td>
<td>1. Plasma chemerin levels are elevated in gastric cancer 2. Chemerin is associated with poor prognosis of gastric cancer and long-term survival of gastric cancer</td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td>In vitro</td>
<td>4 cases</td>
<td>Hungarian</td>
<td>1. Chemerin overexpressed in esophageal squamous CAMs compared with ATMs 2. Inhibit of chemerin may delay tumor progression</td>
<td>[20]</td>
</tr>
<tr>
<td>Lung</td>
<td>Case series</td>
<td>108 cases</td>
<td>Chinese</td>
<td>1. Level of chemerin protein expression in lung cancer tissues was significantly higher than that of normal lung tissues. 2. In contrast, a low expression of chemerin correlated with a poor prognosis in NSCLC patients has been found.</td>
<td>[19]</td>
</tr>
<tr>
<td>Liver</td>
<td>Case control</td>
<td>42 cases &amp; 31 controls</td>
<td>Chinese</td>
<td>1. Concentration of chemerin in peripheral blood of patients with lung cancer was significantly higher than the normal individuals.</td>
<td>[63]</td>
</tr>
<tr>
<td></td>
<td>Case series</td>
<td>44 cases</td>
<td>Japanese</td>
<td>1. Serum chemerin concentrations correlated with liver functional reserves and platelet counts, but not with recurrence or prognosis in HCC patients</td>
<td>[18]</td>
</tr>
<tr>
<td></td>
<td>Case control</td>
<td>40 cases &amp; 20 controls</td>
<td>Polish</td>
<td>1. Serum chemerin is also markedly elevated in CHC patients</td>
<td>[67]</td>
</tr>
<tr>
<td>Colon</td>
<td>Case control</td>
<td>41 cases &amp; 27 controls</td>
<td>Turkish</td>
<td>1. Higher levels of chemerin, CRP, fibrinogen, and ESRin patients with colorectal cancer than the control group.</td>
<td>[21]</td>
</tr>
<tr>
<td>Ovary</td>
<td>In vivo and in vitro</td>
<td>12 cases &amp; 10 controls</td>
<td>Mice</td>
<td>1. Ovarian and circulating chemerin levels increase in a chronically androgenized rat model. 2. Chemerin suppresses FSH-induced steroidogenesis</td>
<td>[17]</td>
</tr>
<tr>
<td>Tongue</td>
<td>Case series</td>
<td>147 cases</td>
<td>Chinese</td>
<td>1. Chemerin in SCCOT was overexpressed 2. Overexpression of chemerin correlated with tumor angiogenesis and poor clinical outcomes of SCCOT patients</td>
<td>[16]</td>
</tr>
</tbody>
</table>

Abbreviations: CAM, cancer-associated myofibroblasts; ATM, adjacent tissue myofibroblasts; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; CHC, chronic hepatitis C; SCCOT, squamous cell carcinoma of the oral tongue; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

and the survival and retention of theca cells. Based on the results, the researchers suggested that their rat model has implications for female reproductive disorders with hyperandrogenism [17].

3.7. Tongue Cancer

A recent study examined the expression and clinical significance of chemerin in squamous cell carcinoma of the oral tongue (SCCOT). Specimens from 147 cases of primary SCCOT and corresponding peritumoral noncancerous tissues were used to evaluate chemerin protein expression with immunohistochemistry. To quantify mRNA expression of chemerin, only 19 pairs of fresh SCCOT samples matched with peritumoral mucosa tissues were used. The relationship between chemerin expression and clinicopathologic parameters, angiogenesis, and cancer-related survival of patients was investigated. Results showed an overexpression of chemerin in SCCOT compared with peritumoral noncancerous tissues (P<0.01). SCCOT patients with overexpressed chemerin also had a shorter cancer-related survival rate. The researchers concluded that overexpression of chemerin in SCCOT correlated with tumor angiogenesis and a poor clinical outcome for SCCOT patients [16].

4. CHEMERIN AND THE ETIOLOGY OF THE DEVELOPMENT OF CANCERS, INSULIN RESISTANCE, AND T2DM

There is substantial evidence that chemerin is associated with obesity, insulin resistance, T2DM, and cancer risk. Obesity can be caused by genetic susceptibility or environmental factors such as an excess calorie intake, stress, and a sedentary lifestyle [16].

As mentioned earlier, the progression of inflammation caused by obesity may contribute to metabolic disorders, especially insulin resistance and the development of T2DM, through several pathways and may consequently lead to the development of several types of cancers, such as breast, prostate, hepatic, colorectal, gastric, lung,
nerve, pancreatic, bladder, and ovarian cancers. Therefore, obesity and insulin resistance are independent risk factors for various types of cancers [69].

The cancer risks increase in insulin resistance. There are evidences that support the association between insulin resistance, T2DM and cancer. An increased incidence of colorectal, hepatic, pancreatic, breast, endometrial and urinary tract malignancies has been recorded and medical researches provided evidence of involvement of insulin resistance in cancers [70, 71]. The carcinogenesis mechanism of insulin is hypothesized to be associated with insulin receptors as well as with the metabolism of endogenous hormone. Insulin plays a role in producing insulin-like growth factor 1 (IGF1). IGF1 involves in cell proliferation in an over-nutrition state. In an animal study, removal of IGF1 receptor or decrease of IGF1 concentration resulted in reduced cancer growth. Effect of hyperinsulinemia on sex hormones may result in cancer growth [72].

Previous studies have described the relationship among insulin resistance, T2DM, and cancer. In a prospective study of 1.3 million Koreans, Jee et al. (2005) concluded that fasting blood glucose levels higher than 140 mg/dL increased the risk for all types of cancer by up to 1.29 times. They found that higher blood glucose levels were associated with an increased risk for esophagus, liver, and colorectal cancer among men. In women, higher blood glucose levels were associated with cervical and liver cancer. Higher blood sugar levels were associated with the risk for pancreatic cancer in both men and women [73]. A study by Wolf et al. (2005) concluded that T2DM may contribute an increase of 10-20% to breast cancer risk [74]. In a study of 7 619 Japanese-Americans, the researchers found that a high BMI increased the risk of colon cancer [75].

There have also been studies on the association between chemerin and metabolic syndromes and on the association between chemerin and cancers. A study of Pakistani men by Fatima et al. (2013) indicated that circulating chemerin levels were significantly higher in people with obesity and the sustained reduction of chemerin serum levels was associated with improvement in metabolic parameters and weight loss in morbidly obese patients undergoing bariatric surgery [76]. A study by Wang et al. (2014) on a population of Chinese people indicated that serum chemerin levels were significantly higher in gastric cancer patients compared with the control group. The median serum chemerin level was 42 ng/mL in the gastric cancer patients and 28 ng/mL in the control group. From these studies, it may be hypothesized that chemerin is associated with obesity-related insulin resistance and cancers [16].

Recently, Huang and Xie (2015) explored the insulin resistance-inducing effect of chemerin on murine C2C12 myoblasts and the underlying molecular mechanism. It was proposed that chemerin might induce insulin resistance in C2C12 cells through a nuclear factor-xB pathway-mediated inflammatory reaction by inhibiting glucose uptake of C2C12 cells in a dose-dependent manner. It is therefore suggested that high levels of chemerin may contribute to hyperglycemia and T2DM through inflammation-mediated insulin resistance [25].

Recently, Spindel et al. (2012) suggested that hyperglycemia promotes oxidative stress through inhibition of thioredoxin function by thioredoxin-interacting protein (TXnip). Through p38 MAPK-mediated induction of TXnip, hyperglycemia inhibits the thioredoxin ROS-scavenging function. Overexpression of TXnip increases oxidative stress, while TXnip gene silencing restores thioredoxin activity in hyperglycemia [77]. Follis et al. (2011) suggested that hyperglycemia contributes to mitochondrial superoxide overproduction in endothelial cells of large and small vessels as well as the myocardium through increased production of ROS and the inactivation of two critical anti-atherosclerotic enzymes: endothelial nitric oxide synthase and prostacyclin synthase. Hyperglycemia-induced oxidative stress induces endothelial dysfunction and consequently plays a determining role in the pathogenesis of micro and macrovascular diseases [78]. Oxidative stress also induces several phenotypic alterations in vascular smooth muscle cells. Klaunig et al. (2011) observed that in exogenous oxidative stress, spontaneous and unrepaired DNA damage interferes with the normal cellular response [79]. Oxidative damage results in toxic and/or mutagenic single-strand and double-strand breaks, DNA base modifications, and the formation of apurinic/apyrimidinic lesions [80]. This DNA damage and oncogenic mutation can lead to genetic lesions that initiate tumorigenicity and subsequent cancer progression. However, the etiology of obesity-related cancers through DNA damage and oncogenic mutations is not well explored. A recent study compared DNA damage lesions and chromosome mutations in peripheral lymphocytes from overweight and obese children in an Italian population. The researchers concluded that a constitutively high frequency of DNA lesions and unrepaired DNA damage in micronuclei can lead to an elevated cancer risk later in life for children [27]. It is therefore suggested that inflammation-induced hyperglycemia in T2DM plays a role in cancer initiation and promotion.

It is thought that hyperglycemia can induce the risk for cancer through direct impact on cancer cell proliferation, apoptosis, and metastasis [81]. In the context of cell proliferation, a high sugar intake is suggested to be associated with elevated cancer cell proliferation [29]. In this respect, a high glucose level because of hyperglycemia could be a fuel source for cancer cells, supporting rapid proliferation. This is supported by the Warburg effect, a process involving enhanced glucose metabolism in cancer cells comprising aerobic glycolysis increments [82]. Several studies have suggested that increased levels of circulating glucose in humans can be an independent risk factor to predict poor survival in patients with cancer [83]. Interestingly, several proteins are involved as mediators of hyperglycemia and cancer cell proliferation. An in vitro study conducted by Hartman et al. (1998) reported that hyperglycemic condition regulates the glucose-transport system of clonal choriocarcinoma cells through expression of GLUT1 and GLUT3 isoforms [84]. The hyperglycemic condition also promotes pancreatic cancer cell proliferation via the induction of endoplasmic growth factor expression and transactivation of endoplasmic growth factor receptor [85]. Protein kinase C and pexoxime proliferator-activated receptor levels are also stimulated during hyperglycemia, and their overexpression can accelerate cell proliferation [86]. Taken together, these findings strongly suggest hyperglycemia as a causal factor leading to enhanced cell proliferation and promotion of the initiation of cancer.

Low levels of apoptosis have also been suggested as a mediator of hyperglycemia and cancer risk. Apoptosis is a genetically regulated process of programmed cell death that is essential for multicellular organisms to maintain individual homeostasis. Uncontrolled cellular growth can be caused by the dysregulation of apoptosis, one of the distinctive hallmarks of cancer cells [87]. In an in vivo study, the requirement of glucose for thymocyte survival was investigated. As expected, glucose resulted in the expression of anti-apoptotic genes and both mouse and human thymocytes demonstrated increased survival under hyperglycemic conditions. The researchers reported that there is a decrease in apoptosis of thymocytes under hyperglycemic conditions in vivo, allowing for the survival of potentially self-reactive thymocytes [28].

Another possible explanation for the connection between hyperglycemia and cancer cell apoptosis is hypoxia. During rapid anabolic cell proliferation, many cancers are exposed to hypoxic conditions because of the limited oxygen supply, and this is regulated by hypoxia-inducible factor-1α (HIF1α). HIF1α is stabilized at the protein level and is then translocated into the nucleus. The stability and function of HIF1α are regulated in the hyperglycemic condition through interfering with the degradation of HIF1α by prolyl hydroxylase enzymes. As a result, expression of genes asso-
In its active form, chemerin by proteolytic cleavage of six ammatory stokines are released and act as signaling molecules in the inflamatory response. Adipose tissue increases in size in obese people. As a result, markers of, or potential target in, insulin resistance and diabetes as well as colorectal cancers are associated with obesity and type 2 diabetes mellitus (T2DM). With obesity, adipocytes cause elevation of reactive oxygen species (ROS) and endoplasmic reticulum (ER) stress. Elevated ROS leads to DNA damage resulting in oncogenic mutation and cancer risk. Together with ER stress, increased ROS also contributes to inflammation, which further increases the levels of circulating free fatty acids (FFA), cytokines, and chemerin. Such an increase results in insulin resistance, followed by hyperglycemia and T2DM (interconnected with elevated oxidative stress), lowered apoptosis, and increased cell proliferation. The end result of these pathways in an increase in the risk for cancer.

There is a correlation between obesity and T2DM. High levels of chemerin in the body are associated with obesity-related insulin resistance and therefore T2DM [12]. High chemerin levels are also associated with the risk for gastric, ovarian, liver, lung, esophageal, and colorectal cancers [16-21]. Therefore, chemerin may be used as a marker of, or potential target in, insulin resistance and diabetes as well as various cancers.

Reduction in NO bioavailability and the release of ROS occur as adipose tissue increases in size in obese people. As a result, adipokines are released and act as signaling molecules in the inflammatory state.

Prochemerin, an inactive 18-kDa precursor protein, is activated by proteolytic cleavage of six amino acids from the C-terminal end [89]. In its active form, chemerin binds to the G-protein-coupled receptor ChemR23 (also called CMKLR-1).

Adipocyte differentiation increases chemerin synthesis, and activation of CMKLR-1 promotes adipogenesis [90]. However, the mechanism by which chemerin enhances inflammation is poorly understood. A study has suggested that circulating chemerin is associated with inflammation through its receptors [21].

Acting through CMKLR-1, chemerin has been reported to have both pro- and anti-inflammatory properties [57]. According to Zabel et al. (2005), CMKLR-1 binds to its ligands and presents to signaling receptors expressed on signaling cells. This suggests that chemerin is capable of stimulating and inhibiting inflammatory processes. Cell-bound chemerin sends stimulatory signals by bridging pro-inflammatory cells that express the silent receptor with those expressing the CMKLR-1 receptor [41].

A strong relationship was found between chemerin and several key aspects of metabolic syndrome in an animal model of obesity and T2DM [91]. Several experiments with mouse models support the influence of CMKLR-1 on glucose homeostasis by affecting glucose-stimulated pancreatic insulin release. A study by Ernst et al. (2010) used mice to investigate the effects of exogenous chemerin on glucose uptake and serum insulin levels in vivo between normal mice compared with hyperglycemic mice. In normal mice, they found that exogenous chemerin had no effect on tissue glucose uptake. In contrast, three different murine models of obesity (db/db, ob/ob, and diet-induced obesity) showed an exacerbation in glucose intolerance and a decrease in serum insulin levels after recombinant chemerin administration [92]. In another study, the relationship between CMKLR-1 knockout mice and T2DM was investigated. The researchers found that the serum chemerin level increased in CMKLR-1 knockout mice and subsequently reduced glucose-stimulated insulin secretion. This was attributed to reduction in glucose transporter 2 expression, which is regulated by CMKLR-1 [93].

Cancer progression in stromal cells, including CAM, is linked to the role of chemerin and CMKLR-1. In cancer cells, chemerin is...
upregulated compared with adjacent tissue myofibroblasts [20]. CMKLR-1 overexpression has been identified in breast, pancreatic, and esophageal cancers. A study by Erdmann et al. (2016) found strong CMKLR-1-specific uptake of targeted breast cancer peptide tracers in positive tissue using optical and magnetic resonance imaging. The researchers suggested that CMKLR-1-targeted peptide tracers could be promising candidates for potential clinical translation [94].

It is suggested that CMKLR-1 could be a therapeutic target in the treatment of cancer and insulin resistance as it is hypothesized that chemerin is associated with cancer and insulin resistance progression (Fig. 1). Pachynski et al. (2012) suggested tumor inhibition required CMKLR-1 host expression and was abrogated by natural killer cell depletion [14]. In another study, Kumar et al. (2016) found that expression of CMKLR-1 stimulated esophageal squamous cancer cell invasion using immunohistochemistry. With this method, the researchers identified the expression of CMKLR-1 in esophageal squamous cancer cells. CMKLR-1 is also expressed in the esophageal squamous cancer cell line OE21. The data showed that OE21 cell migration and invasion were stimulated by chemerin in Boyden chambers, and OE21 cell invasion was stimulated by conditioned medium from esophageal squamous cell CAM. This was inhibited by chemerin immuno-neutralization, pre-treatment of cancer-associated myofibroblast siRNA, and the CMKLR-1 antagonist CCX832. These findings indicate that cancer cell invasion is stimulated by chemerin released from myofibroblasts. It will be therapeutically useful to find a treatment directed at inhibiting chemerin-CMKLR-1 to delay the progression of cancer [20].

Chemerin and CMKLR-1 targeting may also hold therapeutic potential to improve insulin signaling in T2DM. Neves et al. (2016) investigated the role of CMKLR-1 on vascular insulin signaling in db/db mice and found that vascular insulin signaling was impaired by chemerin via P13K/Akt. The researchers hypothesized that CMKLR-1 antagonism will improve insulin signaling in db/db mice, with the results showing that CMKLR-1 antagonism by CCX832 decreased body weight, the inflammatory profile of adipocytes, and vascular oxidative stress in db/db/mice. CMKLR-1 antagonism also improved insulin signaling from the aorta and partially restored vascular function in db/db mice [95].

Several drugs have been developed to treat various inflammatory diseases by modulating CMKLR-1. Although aspirin is used in coronary artery disease, studies suggest that a dose as low as 75 mg of enteric-coated aspirin is effective for treating diabetes (ADA, 2004), and evidence suggests that a low dose of aspirin (81 mg daily) may prevent the development of many types of cancer, such as colorectal and prostate cancers [96].

**CONCLUSION**

Chemerin is a newly discovered adipokine that may have an effect on obesity-related metabolic diseases including insulin resistance. An increased level of chemerin in humans is considered a marker of inflammation, metabolic syndrome, and obesity. Numerous studies have described the causative association between chemerin and cancer risk. Etiologically, the association between chemerin and insulin resistance, obesity, and cancer risk is through the inflammatory response. The underlying mechanism is regulated by a chemerin receptor, CMKLR-1. Targeting CMKLR-1 may have potential as a promising therapeutic tool for T2DM and cancers. Chemerin and CMKLR-1 might be associated with inflammation, insulin resistance, and cancer risk. This review suggests CMKLR-1 as a new potential therapeutic target to limit insulin resistance and cancer-related inflammation in T2DM.

**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>C2C12</td>
<td>A mouse myoblast cell line</td>
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Chemokine Like Receptor 1 (CMKLR1) Receptor

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