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Biological Role of Chemerin in Inflammatory Skin Disease: Review Article

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ABSTRACT

Background: Chemerin is a novel adipokine that has been found to function in both autocrine and paracrine pathways. It draws in both innate and adaptive immune cells as a chemoattractant. There are several roles for this pro-inflammatory chemokine. Also called retinoic acid receptor responder 2 (RAR2) and tazarotene-induced gene 2 (TIG2). The protein chemerin is involved in a variety of processes, including metabolism, inflammation, and adipogenesis, as well as vascular dysregulation. Chemerin was evaluated among different inflammatory skin diseases and showed significant correlations.
Objective: Review of the biological role of chemerin in inflammatory skin disease.
Methods: We looked for data on Chemerin, Biological role and Inflammatory skin disease in medical journals and databases like PubMed, Google Scholar, and Science Direct. However, only the most recent or extensive study was taken into account between February 2015 and January 2023. References from related works were also evaluated by the authors. There are not enough resources to translate documents into languages other than English, hence those documents have been ignored. It was generally agreed that documents such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations did not qualify as legitimate scientific study.**Conclusion:**
Psoriatic individuals had increased chemerin levels in their skin biopsies. Also serum chemerin levels were found to increase with acne vulgaris disease severity. Recent research has found a correlation between obesity and atopic dermatitis, an inflammatory skin condition. Adipokines can be used as a marker for the degree to which eczema is present.
Keywords: Chemerin, Inflammatory skin diseases.

INTRODUCTION

Psoriasis is a genetically and environmentally influenced multisystemic inflammatory skin disorder. Like other erythematous-squamous illnesses, it can affect the skin and the joints. There is mounting evidence linking it to metabolic syndrome, cardiovascular illness, and other psychological disorders that contribute significantly to morbidity and mortality, hence the condition is being labelled a "global burden" [(1)].

Over the past 30 years, psoriasis has become increasingly common over the world. Psoriasis is estimated to affect 3–4% of the population. There are about 100 million people throughout the world who are affected. Its prevalence is highest in industrialised nations, where 5.32% of the population, split fairly evenly between sexes and age groups, is affected by it [(2)]. Reports of the frequency among Egypt's Caucasian population vary from 0.19 to 3% [(3)].

Atopic dermatitis (AD) is a chronic recurrent inflammatory skin illness. Asthma of the bronchi and allergic rhinitis/conjunctivitis may coexist in what is known as an allergic triad. Atopic eczema is another name for it. It can first be seen in newborns or children and persists throughout maturity. The development of the illness is influenced by genetic and immunological abnormalities. Infected people have a lower quality of life because of their illness. It has not been totally healed, and future efforts to rein it in will be fraught with difficulty. As a result of its rapid expansion into a major public health issue, atopic dermatitis has recently experienced a dramatic increase in its prevalence. It is estimated that between 7 and 20% of children and 7 to 14% of adults are affected by this globally. 80% of individuals develop symptoms within the first five years of life, and 60% of them suffer a recurrence in maturity [(4)].

Itching is the most prominent sign of AD. Initial symptoms of the condition include scratching, followed by the appearance of excoriation marks. Weeping, eczematous, and erythematous lesions covered the flexural areas of the skin. Persistent scratching leads to a chronic phase characterized by lichenification and prurigo nodules [(5)].

One of the most prevalent chronic inflammatory skin illnesses affecting humans is acne vulgaris. Acne is one of the most common medical conditions treated by dermatologists. The hair follicles and sebaceous glands are both impacted. Acne vulgaris had the second-highest incidence of disability-adjusted life years (DALYs) among all skin disorders included in 2013 Global Burden of Disease (GBD) Study, behind only dermatitis. The quality of life for both patients and their relatives suffers as a result [(6)]. Over 85% of young people globally suffer from acne vulgaris, with the prevalence being higher in industrialised countries than in developing ones. The onset of puberty and the subsequent increase in BMI are both factors in the earlier onset of acne in developed-world females [(7)].

About 9% and a half of all people have acne. Puberty, when sex hormones are at their peak, is when it first manifests in teenagers and young people. The incidence of this, however, declines with age. Infants are hardly ever impacted. Acne affects 40% of

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adolescents by age of 12, and nearly all guys by age of 16 years. Girls also experience similar increases in prevalence, from 61% to 83%. Intensity increases with puberty, making it more common in males than females [8].

New to the adipokine family, chemerin is noteworthy for its both autocrine and paracrine functions. It draws in both innate and adaptive immune cells as a chemoattractant. Inflammatory chemokine with multiple roles in the body. Tazarotene-induced gene 2 (TIG2) is also known as retinoic acid receptor responder 2. (RARRES2). Adipogenesis, inflammation, metabolic dysfunction, and vascular dysregulation are all impacted by chemerin [9]. Besides adipose tissue, the protein chemerin is also present in the following organs and tissues: liver, skin, adrenal glands, lungs, fibroblasts, chondrocytes, pancreas, kidney, epithelial cells, and platelets. This marker has been employed as a unique prognostic indicator of chronic heart failure, and its importance has been proven in a large number of studies [10, 11].

Structure and processing:

Chemerin is initially expressed as a pre-proprotein consisting of 163 amino acids, which is then cleaved by proteases into a proprotein consisting of 143 amino acids (18 KDa). Additional C-terminal activation of this proprotein is required for its clotting, fibrinolytic, and inflammatory functions by plasmin, carboxypeptidases, or serine proteases in the extracellular environment [12]. Intricate structures of chemerin. Pro-chemerin has little effect on human biology, its C-terminal portion undergoes proteolytic degradation to generate six isoforms as illustrated in **(figure 1)** [13].

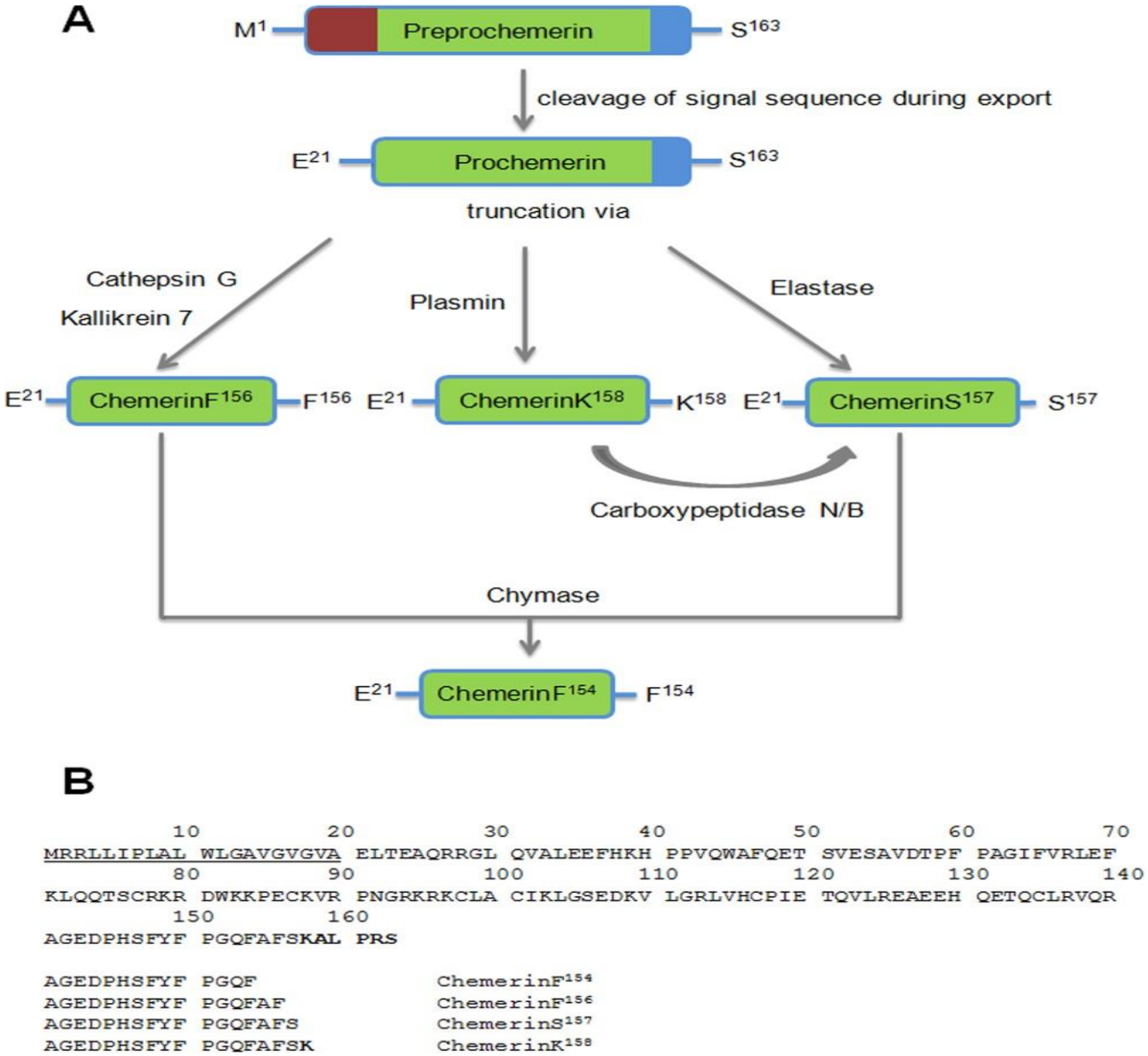

Figure (1): Proteolytic processing of chemerin [13].

Proteolytic processing is hypothesised to render chemerin inactive. In addition, angiotensin-converting enzymes, mast cell-derived serine protease, and neutrophil-derived serine protease all convert chemerin's bioactive forms into inactive derivatives. As a result, chemerin proteolytic cleavage is a crucial process that regulates both the systemic and local levels of active chemerin [(14)].

As shown below, chemerin interacts to three different G protein-coupled receptors (GPCRs): Chemokine receptor 23, or chemokine-like receptor 1 (CMKLR1), and C-C motif chemokine receptor-like 2 (CCR2) are all types of the same receptor (CCRL2). Despite GPR1's high affinity, CMKLR1 is responsible for the majority of its effects, such as those shown in adipocyte differentiation, vasoconstriction, and neutrophil chemotaxis in inflammatory responses [(15)].

Biological role of chemerin:

Chemerin and inflammation:

The orphan chemokine receptor chemerin was first discovered to facilitate the chemotaxis of immature macrophages and dendritic cells (DCs) (CMKLR1). CMKLR1-expressing immune cells include immature plasmacytoid DCs, myeloid DCs, macrophages, and NK cells. TNF-alpha, IL-6, and C-reactive protein concentrations, as well as CMKLR1 serum levels, are all indicators of inflammation [(15)].

According to many research, chemerin contributes to the inflammatory process in addition to its primary roles in healthy skin. TNF-α, IL-1, 6 and 12 are all pro-inflammatory cytokines that have been linked to chemerin's pro-inflammatory function. Vascular endothelial cell activation, an increase in intercellular adhesion molecule 1, E-selectin, and chemerin provide evidence for the link between endothelial dysfunction and chemerin's inflammatory activity in obese patients [(16)].

Chemerin and obesity:

There has been a worldwide uptick in the prevalence of conditions like obesity and metabolic syndrome (MetS), both of which may have their origins in early life. To put it simply, obesity is a disorder characterised by an abnormally large amount of fat storage in the body, which has numerous negative effects on various bodily systems. The Body Mass Index (BMI) has become the gold standard for determining obesity. Body mass index (BMI) is determined by dividing one's weight in kilograms by one's height in meters squared (kg/m^2). Individuals are classified as normal, overweight, or obese based on their BMI [(17)].

Having visceral fat and high blood sugar, high blood pressure, and abnormal lipid profiles are the hallmarks of metabolic syndrome. Poor health outcomes have been related to obesity and MetS, which are characterised by chronic low-grade inflammation and immune response failure**.** The rate at which people are becoming overweight has increased threefold in recent decades. It's become a worldwide pandemic and a financial drain. Low-grade systemic inflammation is linked to obesity in many cases. Lymphocytes such as macrophages, NK cells, and T cells can be found in the stromal vascular component of adipose tissue. As a person gains weight and their adipocytes enlarge, there are corresponding molecular and cellular changes in the adipose tissue that influence the body's metabolism and inflammation. Levels of inflammatory markers in the blood are increased in obese people. It appears that a significant amount of these cytokines originate from adipose tissue [(18)].

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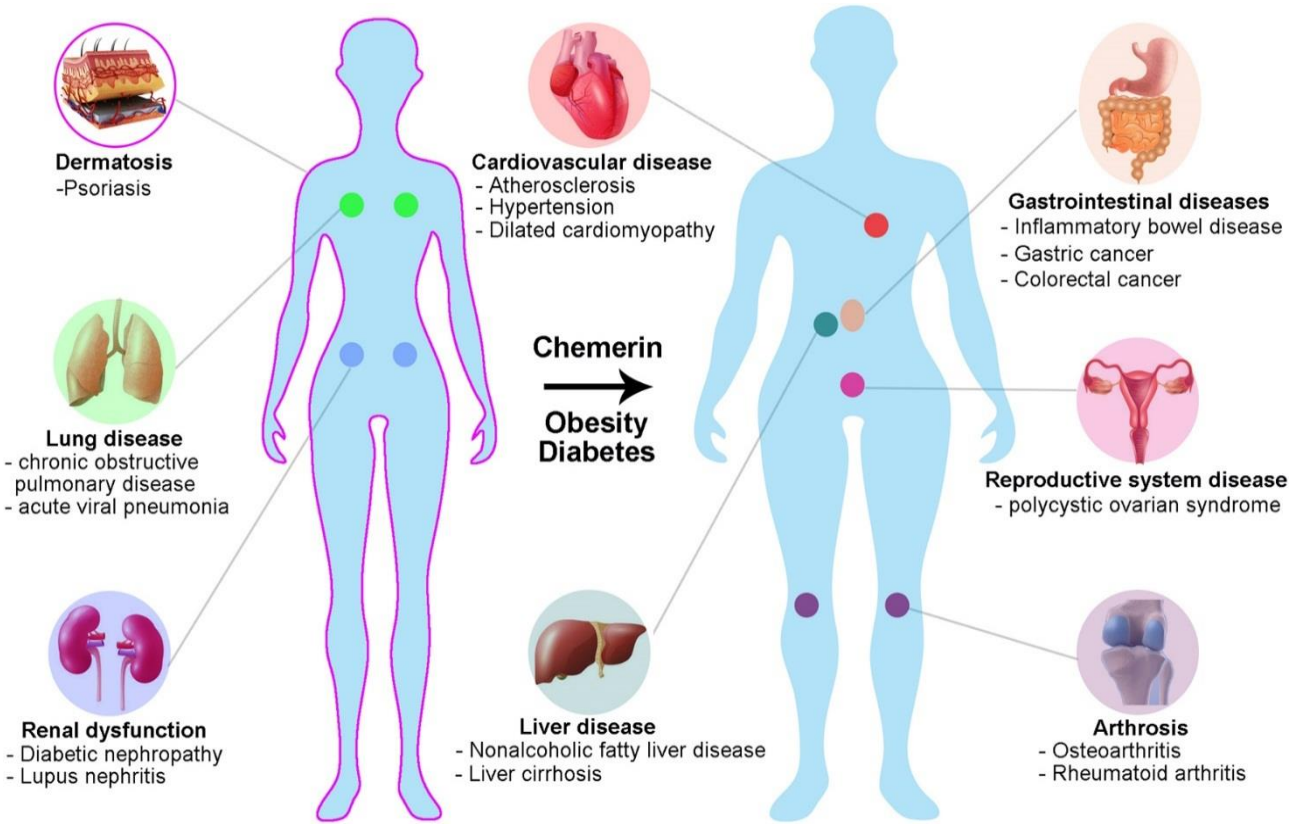

Figure (2): Chemerin association among obesity and different systems [20].

Serum chemerin levels are connected to a number of factors associated with obesity, including body mass index, blood pressure, serum lipids, insulin, and cholesterol. Serum chemerin levels fall down as a result of losing weight, whether from cutting calories or working out, and this is a positive reaction to insulin resistance [20].

To this day, metabolic syndrome remains one of the world's leading health concerns. It's a long-term inflammatory disease. It has been found that the adipocytokines chemerin, IL-8, and IL-1 beta play a crucial role in the link between Met S and inflammation and could serve as useful diagnostic and monitoring markers for the condition [21].

Chemerin and glucose homeostasis:

Type II diabetes mellitus is a metabolic disorder characterised by decreased insulin production and elevated blood glucose levels (hyperglycemia). The development of type 2 diabetes mellitus is strongly associated with serum chemerin increases, which are correlated with obesity [21].

Both pancreatic insulin secretion and glucose uptake by peripheral tissues contribute to maintaining a healthy range of glucose tolerance. Since chemerin and its receptor CMKLR1 are both expressed in pancreatic beta cells, it is possible that they control insulin secretion [21].

Chemerin and inflammatory skin disease:

Chemerin and psoriasis:

Psoriasis is a common metabolic illness that causes chronic inflammation throughout the body. There is a correlation between the existence of an aberrant lipid profile, the expression of a number of inflammatory cytokines, and adipokine. These mediators can have a role in the pathophysiology of illnesses, including immune-mediated inflammatory disorders [22].

Researchers have found that people with metabolic syndrome have a higher incidence of psoriasis and more severe symptoms. Patients with psoriasis have been shown to have substantial shifts in serum adipokine levels in recent investigations. Researchers discovered a link between high serum chemerin levels and metabolic syndrome. It was shown that patients with psoriatic arthritis expressed chemerin at higher levels than those with only psoriasis. Acute-phase mediators such as oncostatin M and interleukin-1 beta may promote mRNA and protein expression in human keratinocytes [23].

The patient with psoriatic arthritis had higher chemerin levels in his skin biopsies. Extreme psoriasis instances benefited from chemerin's anti-inflammatory effects. Psoriatic patients who take chemerin can have their leukocytes removed from the inflamed area and their homeostasis restored [14].

Chemerin has been linked to the development of psoriasis and is expressed pathologically in psoriatic lesions, where it controls the activity of DCs, monocytes, macrophages, and NK cells. The

expression of chemerin is thought to facilitate the migration and activation of plasma DCs, making it a marker for preclinical lesions. This demonstrates that chemerin and CMKLR1 have a role in drawing unique types of immune cells to the lesion, which may affect the relationships between cell types that control the development of psoriatic inflammation [(24)].

Chyl-Surdacka *et al.* [(25)] study on individuals with psoriasis and 40 healthy participants were evaluated. Serum chemerin concentrations and chosen components of the metabolic syndrome, such as cholesterol and glucose levels, were measured in all individuals. The PASI and BSA indices were used to measure the severity of the psoriasis. In psoriatic individuals, increasing low-density lipoprotein (LDL) cholesterol levels were associated with significantly higher chemerin concentrations compared to those with normal LDL values ($p = 0.032$). Patients with psoriasis and high glucose levels had greater chemerin concentrations than those with normal glucose levels ($p = 0.043$).

Chemerin and acne Vulgaris:

A recent study found that serum chemerin has been connected to acne vulgaris' pathogenesis. Serum chemerin levels were found to increase with illness severity. Acne sufferers' lipid levels were linked to the development of acne. Additionally, the GAGS score revealed a correlation between serum chemerin and acne vulgaris severity. Proinflammatory cytokines including tumor necrosis factor alpha and interleukin (IL)-6 are released in response to chemerin, proving its role in acne [(26)]. Triglyceride levels, high-density lipoprotein levels, and fasting blood sugar were all found to be more common among acne sufferers. This led to the discovery that MetS is associated with an increased risk of acne and demonstrating the value of risk assessment and early intervention in preventing chronic diseases like diabetes and cardiovascular disease [(27)].

Chemerin and atopic dermatitis:

Recent research has found a connection between obesity and both skin inflammation and AD. Scientists found that obese kids and adults have a greater chance of developing AD than their leaner counterparts. Obesity impacts skin health because of the interplay of adipocytokines, hormones, fatty acids, and mechanical factors. The levels of adipokines in the blood are correlated with how bad eczema is. Evidence from the studies showed that there is a favourable relationship between BMI and SCORAD [(28)].

CONCLUSION

In the skin biopsies of psoriatic patients, chemerin levels were significantly higher than in healthy controls. Also, serum chemerin levels were found to increase with acne vulgaris severity. Recent studies have shown that being overweight is associated with skin inflammation and atopic dermatitis. Adipokines can be utilized as a marker for the severity and intensity of eczema.

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