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Meeting Review

Chemerin in immunity

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Abstract

Chemerin is a distant member of the cystatin protein family, initially discovered as a chemotactic factor and subsequently also reported to act as adipokine and angiogenetic factor. The biological activity of chemerin is regulated at different levels, such as gene expression, protein processing, and interaction with both signaling and nonsignaling receptors. Chemerin is mostly produced by stromal cells, such as adipocytes, fibroblasts, and epithelial and endothelial cells, and circulates in almost all human tissues as a zymogen that needs to be proteolytically activated to exert its biological functions. At the receptor level, chemerin binds a G protein-coupled 7-transmembrane domain receptor $Chemerin_1$ (also named ChemR23 and CMKLR1), mostly expressed by innate immune cells, such as macrophages, dendritic cells, and natural killer cells, and by border cells. In addition, chemerin may bind GPR1, a weak signaling receptor, and CCRL2, a nonsignaling receptor expressed by barrier cells, such as endothelial and epithelial cells, able to regulate leukocytes' migration by multiple mechanisms. The aim of this review is to summarize the contribution of chemerin in the regulation of immune responses.

Keywords: cancer, CCRL2, chemerin, CMKLR1, inflammation

1. Introduction

Chemerin is a chemotactic protein unrelated to chemokines and characterized by the absence of close sequence homology to other chemotactic factors.[1] It is classified as a distant member of the antimicrobial cathelicidin/cystatin protein family.[2,3] No experimentally resolved crystal structure is available to date, except for a Nuclear Magnetic Resonance preliminary and uncomplete structure,[4] which matches with an in silico predicted structure of human chemerin recently generated by the AlphaFold2 system.[5,6] As shown in Fig. 1A, chemerin protein does not fold as any known chemotactic factor. Instead, chemerin adopts a tertiary structure that mirrors the soluble members of the cystatin family (Fig. 1B and C).[1] Human chemerin is encoded by the *RARRES2* gene (retinoic acid receptor responder 2), also named *TIG2* (tazarotene-induced gene 2) that maps into Chr7.p14.[2,10,11] Its genomic region shows additional similarities to the cystatin protein family, and the number and distribution of introns across the *RARRES2* gene further support their evolutionary relationship.[1]

2. Proteolytic maturation of chemerin

Human chemerin is constitutively secreted in the circulation at nanomolar concentrations (6 to 12 nM/100 to 200 ng/mL) by hepatocytes, adipocytes, and fibroblasts upon truncation of its N-terminal signal peptide (20 amino acids) as an inactive form named prochemerin (143 amino acids).[12–14] Prochemerin needs to be further cleaved at the C-terminus to produce the active chemerin (Fig. 1A).[2,15] The proteolytic processing of prochemerin consists of the removal of the last 6 or 7 amino acids by both elastase (ELANE) and cathepsin G (CTSG).[15] Depending on the protease and the site of cleavage, several isoforms with different biological activity are produced (Fig. 1A).[2,16] Indeed, chemerin 21-157, which is the most active form, is generated by ELANE through the removal of 6 amino acids, while CTSG removes 7 amino acids, producing a slightly less active chemerin form (21-156) (Fig. 1A).[17,18] Other serine proteases involved in the coagulation and fibrinolytic cascades, like urokinase, tissue plasminogen activator, factor VIIa, and factor XIIa, can process prochemerin to the bioactive chemerin form as well.[16] Finally, active chemerin can be inactivated by further cleavage at its C-terminus via serine proteases like proteinase 3 and chymase.[1]

Prochemerin is the most abundant form present in the bloodstream; therefore, a pool of inactive circulating form of chemerin is constantly available for activation. Thus, the proteolytic processing represents a crucial mechanism of regulation of chemerin bioavailability at both systemic and local pathological sites. On the contrary, in adipose tissue, the active form of chemerin (21-157) is the predominant one, probably due to the simultaneous expression of elastase and tryptase with prochemerin during adipocyte maturation.[19]

While chemokines interact with their cognate chemokine receptors through the N-terminal peptide,[20] chemerin shows a different behavior. Indeed, several peptide fragments of the chemerin C-terminal possess strong binding ability for $Chemerin_1$ and GPR1, with the nonapeptide ^{149}YFPGQFAFS^{157} (chemerin 9)

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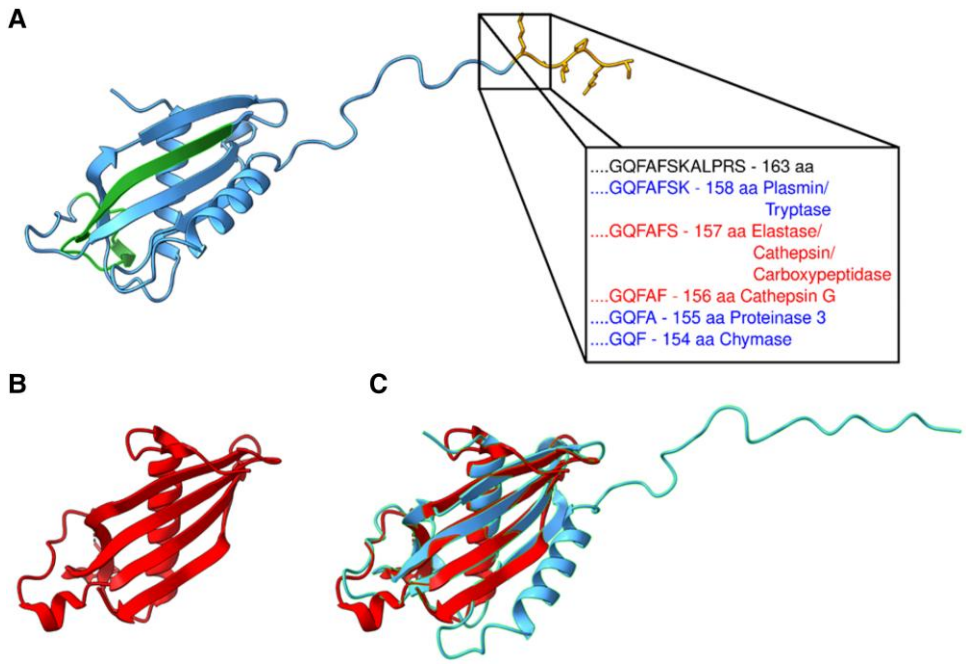

Fig. 1. Structure of human chemerin and its comparison with the human cystatin family. (A) The homology model of monomeric human prochemerin (RARRES2, 20-163 aa), devoid of its N-terminal signal peptide, was obtained from the AlphaFold Protein Structure Database (Jumper et al.[5]; Varadi et al.[7]). The p4 peptide (Val66-Pro85) is highlighted in green, and the C-terminal sequence that has to be removed to activate chemerin is marked in orange. The box shows the different chemerin proteoforms and the accountable serine proteases, where the blue-labeled sequences are inactive chemerin forms, and the red ones show active chemerin proteoforms. (B) The crystal structure of monomeric human cystatin C (PDB: 3GAX, Kolodziejczyk et al.[8]) is in red. (C) Merge between human prochemerin (cyan) and human cystatin C (red) shows a relevant overlapping between the 2 proteins, thus suggesting that chemerin is a distal member of the cystatin family. Molecular graphics and analyses were performed with UCSF ChimeraX (Pettersen et al.[9]).

showing a full-chemerin-like activity.[17] Likewise, in the mouse system, the corresponding nonapeptide ^{149}LFPGQFAFS^{157} displays similar properties.[21]

3. Chemerin expression across human and mouse tissues

Prochemerin is produced in almost all tissues, with the exception of hematopoietic cells (Table 1). Although the predominant cell types responsible for plasma prochemerin are considered the hepatocytes and the adipocytes,[19,37] mouse *Rarres2* transcripts were found also in the epithelial barriers of skin, uterus, testes, ovary, spleen, lung, and colon, as shown in Table 1.[21,38] Chemerin expression was also described in rat hypothalamus, suggesting a potential role in neuroendocrine regulation and hypothalamic remodeling.[32] Chemerin is widely distributed in human tissues, including lung, liver, pancreas, adipose, endocrine, and muscle tissues, where it may be involved in physiological and pathological processes.[39] For instance, human chemerin was detected in synovial fluids of inflamed joints, with elevated expression by articular chondrocytes.[40,41] Moreover, platelet granules can store chemerin, which is released upon activation by different signals, including thrombin, ADP, or collagen.[42]

4. The 3 chemerin receptors fulfill different biological roles

Chemerin can bind 3 different 7-transmembrane domain receptors—namely, CMKLR1 (chemokine-like receptor 1); GPR1 (G protein-coupled receptor 1), recently named chemerin receptor 1 (Chemerin$_1$) and chemerin receptor 2 (Chemerin$_2$), respectively; and CCRL2 (C-C chemokine receptor-like 2).[43] Each of these receptors displays distinct signaling properties and biological activity (Fig. 2).

CMKLR1 was the first identified in 1998,[44] and it is expressed by different types of immune cells, including monocytes, macrophages, dendritic cells (DCs), and natural killer (NK) cells, with very low transcript levels for lymphocytes.[2,44–46] Recently, by analysis of the CD8$^+$ T-cell transcriptome, an increased expression of CMKLR1 was observed in CD8$^+$CD27$^-$CD28$^-$ subpopulation in comparison with CD8$^+$CD27$^+$CD28$^+$ T cells.[47,48] In line with this observation, CMKLR1 was observed on CD27$^-$CD28$^-$ T cells from patients with Rheumatoid Arthritis (RA), and its surface level expression was reduced by anti-CD3 antibody or chemerin treatment.[49] CMKLR1 was also found by Ballet et al.[50] to be expressed on CD27$^-$CD28$^-$ CD8 and CD4 effector memory/effector memory RA (EM/EMRA) in blood and tumor tissues. Of note, it has been shown that CMKLR1-expressing CD28$^-$CD8$^+$ EMRA cells are a specialized CD8 subset with NK-cell features and potential antitumor activities that can be recruited by chemerin, together with α4-integrin, at the tumor sites.

Among leukocyte populations, CMKLR1 is expressed on immature DCs, with higher levels in plasmacytoid DCs (pDCs) compared to myeloid DCs (mDCs), and is downregulated during their maturation.[17,45] Due to its expression pattern and chemerin distribution, CMKLR1 represents one of the main functional chemotactic receptors driving the trafficking of pDCs in secondary lymphoid organs (across high endothelial venules [HEVs]) and in skin inflammatory conditions (i.e. lupus).[45] Langerhans cells were reported not to express CMKLR1.[45]

CMKLR1 expression in macrophages has been documented, but there are still many unknowns about the regulation in M1 and M2 phenotypes. In mouse macrophages, CMKLR1 is downregulated

Table 1. Expression of chemerin (*RARRES2*) across human and mouse tissues.

RARRES 2 mRNA expression	Chemerin protein expression	Tissue	Cell type	Species	References
X	X	Liver	Hepatocytes	Mouse/human	Wittamer et al.[2]
X	X	White adipose	Adypocites	Mouse/human	Goralski et al.[22]
X	X	Placenta	Trophoblastic cells, cytotrophoblasts, and Hofbauer's cells	Mouse/human	Wittamer et al.[2] Garces et al.[23] Tan et al.[24]
X	X	Testes	Leydig cells	Mouse/human	Li et al.[25]
X	X	Skin	Keratinocytes, fibroblasts	Mouse/human	Banas et al.[26] Haydont et al.[27]
X	X	Blood vessels	Endothelial cells	Mouse/human	Kennedy et al.[28]
X		Lung	Airway smooth muscle	Human	Wittamer et al.[2] Dileepan et al.[29]
X		Lymph nodes		Human	Wittamer et al.[2] Zabel et al.[30]
X		Spleen	Fibroblasts	Mouse	Bellomo et al.[31]
X	X	Pituitary gland		Human	Wittamer et al.[2]
X		Hypothalamus	Ependymal cells, tanycytes	Mouse	Helfer et al.[32]
X	X	Bone marrow		Mouse/human	Wittamer et al.[2] Li et al.[33]
X	X	Colon	Enterocytes	Mouse/human	Maheshwari et al.[34] Dranse et al.[35] Terzoudis et al.[36]
X	X	Muscle	Cardiac, smooth and skeletal muscle	Mouse/human	Kennedy et al.[28]

From a search in the literature as well as from data taken from the consortium "Human Protein Atlas," the tissues and cell type, if available, that were found positive for both chemerin mRNA and protein are listed.

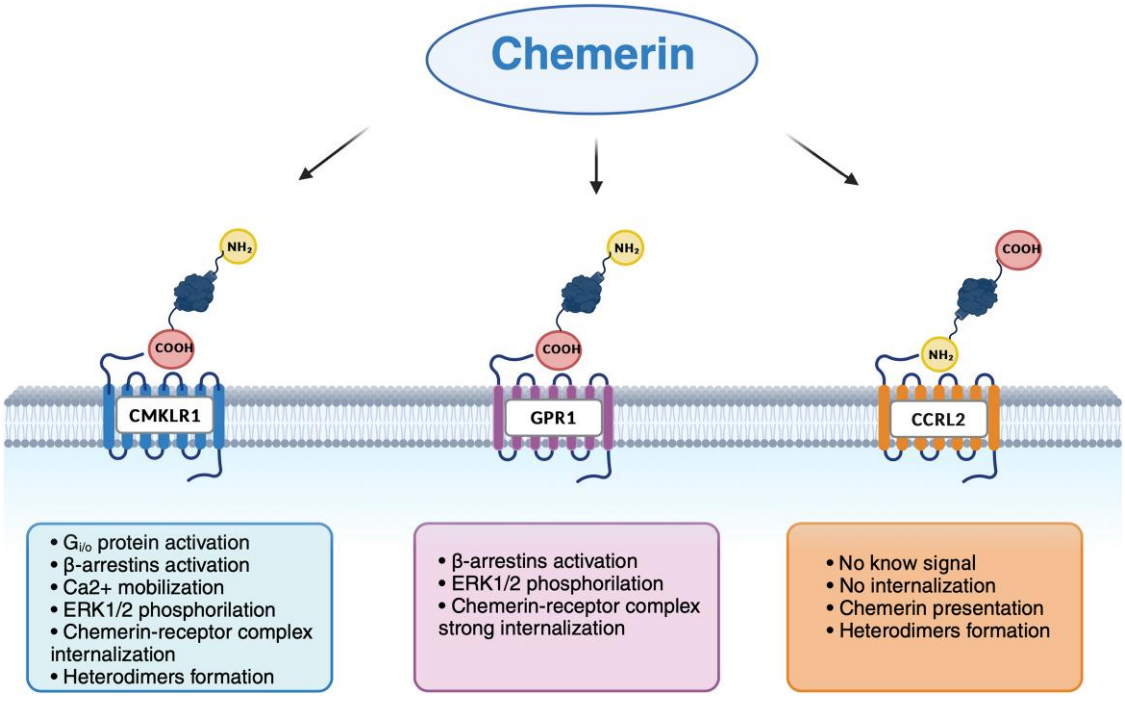

Fig. 2. Chemerin binds three 7-transmembrane domain receptors. The 3 receptors (CMKLR1, GPR1, and CCRL2) bind chemerin with distinct signaling properties and biological activities.

by inflammatory cytokines and Toll-Like Receptor ligands but upregulated by TGF-β, suggesting a potential involvement of chemerin in the recruitment of M2-polarized macrophages with an anti-inflammatory phenotype.[51] According to more recent works on human monocytes/macrophages, CMKLR1 is expressed and is functional on M1 but not M2 macrophages,[52] and high CMKLR1 expression is associated with excessive M1 macrophage infiltrates in inflammatory bowel disease (IBD).[53] However, CMKLR1 has been found to be expressed at higher levels in Tumor-associated macrophages (TAM) in human tumors and in TAM-like macrophages differentiated in vitro from monocytes in the presence of Macrophage Colony-Stimulating Factor instead of Granulocyte Colony-Stimulating Factor.[54] The discrepancies observed in CMKLR1 expression in macrophages could be due to the difference between mouse and human systems and to the macrophage phenotypic subpopulations with functional heterogeneity.

Moreover, CMKLR1 is also expressed by nonleukocyte cell populations, including adipocytes, osteoclasts, chondrocytes, skeletal muscle cells, cardiomyocytes, and endothelial, epithelial, and mesenchymal stem cells.[12,41,55–58] As a natural ligand of CMKLR1, chemerin binding to the receptor leads to the activation of Gi/o proteins and the recruitment of β-arrestins in particular, whereas phospholipase C activation, calcium mobilization, and Erk1/2 phosphorylation are G protein dependent, and the internalization of the chemerin/CMKLR1 complex is β-arrestin dependent.[59]

A second chemerin receptor, structurally closely related to CMKLR1, was discovered in 2008 and named GPR1 or Chemerin$_2$.[60,61] GPR1 expression has not been detected in immune cells, except for alveolar macrophages at the RNA level.[62] Elevated GPR1 expression levels were found in ovary, skeletal muscle, and adipose tissue, specifically in the stromal vascular fraction of white adipose tissue, where it might be involved in the regulation of glucose homeostasis,[63,64] and in the central nervous system.[65,66] Unlike CMKLR1, no ligand-induced G protein activation has been described for GPR1, despite the higher affinity for chemerin. Chemerin-induced GPR1 internalization requires β-arrestin but not G protein activation, whereas RhoA/ROCK requires G protein coupling but not β-arrestin.[59,64,67] Due to the unconventional signaling of GPR1, one possibility is that, at least in certain tissues, it may act as a decoy receptor for chemerin.[1]

CCRL2, also known as HCR or CRAM-A in humans and L-CCR or CRAM-B in mouse, was identified as the third chemerin receptor.[68] CCRL2 is closely related to the atypical chemokine receptor family due to the lack of the canonical conserved DRYLAIV motif involved in G protein-coupled signaling.[69,70] Among the hematopoietic compartment, CCRL2 is expressed by monocytes, macrophages, neutrophils, T and B lymphocytes, dendritic cells, and mast cells.[68,71–76] In several leukocytes, such as neutrophils and dendritic cells, CCRL2 expression is upregulated in response to proinflammatory stimuli such as lipopolysaccharides (LPSs), tumor necrosis factor α (TNF-α), and interferon-gamma (IFN-γ) alone or in combination with Granulocyte Macrophage Colony-Stimulating Factor.[70,74,76,77] High CCRL2 expression was detected in neutrophils isolated from inflamed joints of patients with arthritis.[71] Apart from a wide range of immune cells, CCRL2 expression has also been observed in inflamed bronchial epithelium,[78] adipocytes,[79] hepatic stellate cells,[80] skin,[26] murine lung endothelial cells, and human primary endothelial cells.[81–84] CCRL2 regulation was also reported in lymphatic endothelial cells stimulated with retinoid acid.[82] Moreover, microglia and astrocytes were shown to express CCRL2 both in vitro and in vivo under inflammatory conditions.[83,85] In contrast to the 2 other chemerin receptors, CCRL2 is supposed to interact with the N-terminus of the protein without inducing calcium mobilization, Erk1/2 phosphorylation, or ligand internalization.[59,68,86] In vitro and in vivo experimental evidence indicates that CCRL2, when expressed on barrier cells, acts as a presenting molecule able to regulate the local concentration of chemerin and to drive the recruitment of leukocytes expressing the functional chemerin receptor CMKLR1.[70,83] Our group identified a novel unconventional role for the atypical receptor CCRL2, namely, the capacity to regulate the expression and the activity of conventional chemokine receptors by forming heterocomplexes.[70,76] Indeed, by CCRL2 deletion and the use of an anti-CCRL2 monoclonal antibody, CCRL2 was shown to form heterodimers with CXCR2 and to regulate neutrophil migration.[76] However, CCRL2 neutralization on neutrophils with a different antibody did not inhibit the recruitment in vivo,[87] suggesting that differing responses can occur depending on the specific epitope-recognizing mechanism.

5. Proinflammatory role of chemerin

Since its discovery, experimental evidence has pointed out the relevant role of chemerin in shaping the immune responses (Fig. 3). As mentioned before, inactive prochemerin is constantly circulating in the bloodstream, and its activation is directly mediated by serine proteases.[88] These enzymes are produced upon tissue damage and/or inflammation in the extracellular milieu by stromal cells, neutrophils, and mast cells.[16,89] In several pathological conditions, the chemerin/CMKLR1 axis represents a crucial mechanism driving the recruitment of immune cells in the inflammatory sites. The system is not redundant, as demonstrated by the abrogation of the chemotactic activity of chemerin by blocking the functional chemotactic receptor CMKLR1 using genetic deletion or a specific monoclonal antibody.[21,90]

In lupus lesional skin, CMKLR1$^+$ DCs were found in close proximity to vascular endothelium immunoreactive for chemerin.[45] Chemerin expression was also selectively detected on the luminal side of HEVs, suggesting a role for chemerin in the recruitment of both pDCs and mDCs to secondary lymphoid organs and in the activation of adaptive immune responses.[45] In patients with lupus nephritis, CMKLR1$^+$ pDCs infiltrate the kidney parenchyma, and chemerin was detected in proximal tubular cells and renal lymphatic endothelium.[91] Prepsoriatic skin adjacent to active lesions and early lesions was characterized by the dermal infiltration of CMKLR1$^+$ pDCs, while chemerin expression was localized mainly in dermal vascular endothelium, fibroblasts, and mast cells.[14] Moreover, human chemerin has been implicated in the colocalization of NK cells with pDCs in oral lichen planus lesions, thus directly supporting the NK–DC cell crosstalk occurring in pathological peripheral tissues.[46] Chemerin is also expressed by normal keratinocytes, and its downregulation has been associated with increased neutrophil recruitment in human[14] and mouse.[92]

Intralesional cerebrovascular endothelial cells of patients with multiple sclerosis showed chemerin expression associated with infiltrating leukocytes, including pDCs.[93] Likewise, in a model of experimental autoimmune encephalomyelitis, CMKLR1$^+$ DCs and macrophages were shown to be recruited to the central nervous system in the acute phase of the disease, and CMKLR1 ablation induced protection with an attenuated clinical phenotype.[94] The chemerin/CMKLR1 was also implicated, in a genetic model of atherosclerosis, in plaque formation and progression by controlling the recruitment of pDCs and macrophage polarization in atherosclerotic lesions.[95] Accordingly, chemerin immunopositivity was

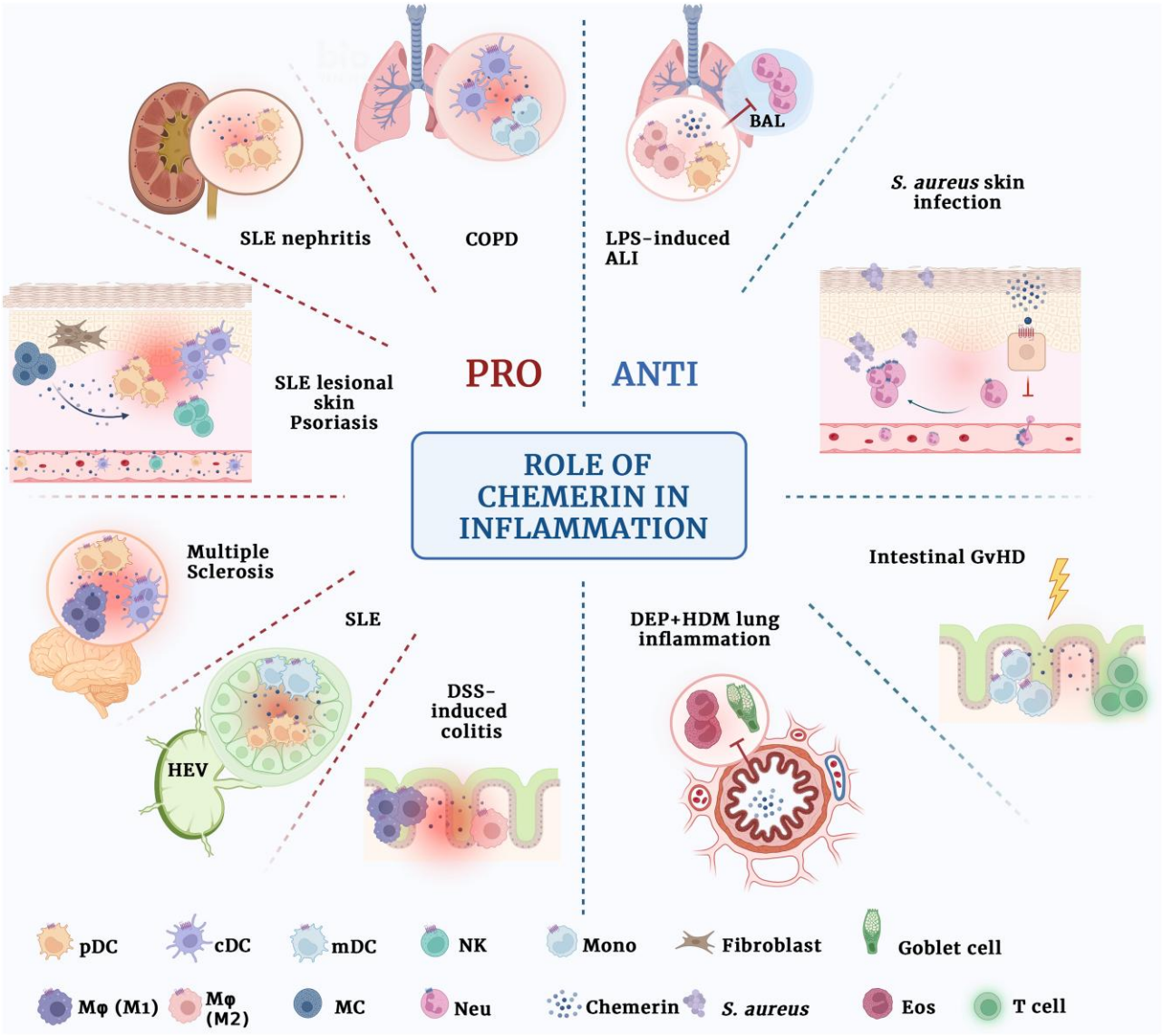

Fig. 3. Pro- and anti-inflammatory roles of chemerin. Chemerin is a multifaceted protein playing pro- and anti-inflammatory roles in different experimental models of human pathologies. ALI, acute lung injury; DSS, dextran sulfate sodium; HDM, house dust mite; SLE, systemic lupus erythematosus.

detected in both periadventitial fat depots, in vascular smooth muscle cells and foam cells of atherosclerotic lesions, and significantly correlated with the severity of atherosclerosis.[96]

In a mouse model of dextran sulfate sodium–induced colitis, chemerin treatment was described to exacerbate the colitis phenotype by promoting the local production of proinflammatory cytokines and by impairing the skewing of macrophages toward the anti-inflammatory M2 macrophages.[97] Chemerin-treated mice showed significant decreased expression of the M2-associated genes Ym1, FIZZ, Arg-1, and IL-10, and in vitro findings revealed that chemerin could directly suppress IL-4–dependent M2 polarization by suppressing STAT6 phosphorylation.[97] In accordance, elevated chemerin levels were found in patients with IBD and positively correlated with disease severity.[97,98]

In an acute model of lung inflammation induced by the exposition of mice to diesel exhaust particles (DEPs), chemerin was shown to be released by alveolar epithelial cells and to induce monocyte and DC recruitment, contributing to local inflammation.[99] Furthermore, increased plasma levels of chemerin, which positively correlated with inflammatory biomarkers, were found in patients with COVID-19.[100] Similarly, high circulating levels of chemerin were described in septic patients[101] and were proposed to be used to discriminate patients with sepsis from patients with septic shock.[102] However, other research groups reported decreased chemerin levels during COVID-19 infection[103] that were associated with a bad prognosis.[104] A proinflammatory role for chemerin was shown in a model of chronic obstructive pulmonary disease, where subacute and chronic exposure to tobacco smoke induced in *Cmklr1*-deficient mice was associated with reduced secretion of chemokines and decreased immune cell recruitment.[105]

6. Anti-inflammatory role of chemerin

The anti-inflammatory role of chemerin was first revealed in a mouse model of LPS-induced acute lung injury[21] (Fig. 3). The addition of chemerin to LPS impaired the pulmonary immune responses, with defective neutrophil recruitment in bronchoalveolar lavage (BAL), and in the lung and decreased proinflammatory

cytokines in a CMKLR1-dependent manner.[21] This protective effect of chemerin was related to increased mobilization of alveolar macrophages able to modulate local immunological homeostasis by their suppressive activity based on nitric oxide and prostaglandin E2 production.[21] The chemerin/CMKLR1 axis played a protective role in a mouse model of viral pneumonia partially through the recruitment of pDCs, which contributed to the activation of adaptive immune responses and viral clearance by secreting a large amount of type I IFNs.[90] Moreover, chemerin can dampen the inflammatory response induced by the viral infection by acting on CMKLR1-espressing nonhematopoietic cells.[90]

The dual role of the chemerin/CMKLR1 axis in the modulation of lung inflammation seems to be related to the specific conditions of airway inflammation. While exposure to DEP alone was functional for the generation of a proinflammatory phenotype,[99] the combined exposure of DEP with house dust mite as a model of allergic respiratory inflammation in *Cmklr1*-deficient mice induced increased peribronchial eosinophilic infiltrate, goblet cell metaplasia, and Th2 cytokine production compared to control animals, suggesting an anti-inflammatory role of chemerin in allergic lung disease.[99,106] These findings confirmed previous observations of an ovalbumin-induced asthma model, where the addition of recombinant chemerin impaired the recruitment of immune cells, such as inflammatory DCs, eosinophils, and T cells in the BAL, associated with a decrease of Th2 cytokines.[106] However, the mechanism underlying the chemerin-mediated protection was not ascribed to its direct effect on immune cells but to the capacity of chemerin to inhibit the secretion by lung epithelial cells of CCL2, a potent chemoattract for inflammatory DCs.[106]

Chemerin is abundantly expressed in the skin, and the chemerin/CMKLR1 axis was recently shown to play fundamental immunomodulatory effects in skin defense in a model of *Staphylococcus aureus* infection.[107] Chen et al.[107] demonstrated that *S. aureus* can hijack the chemerin/CMKLR1 pathway to facilitate bacterial immune invasion by restricting skin neutrophilia. *S. aureus* infection of keratinocytes leads to the simultaneous secretion of chemerin and IL-33, known to promote neutrophil influx. In turn, chemerin acts on keratinocytes via CMKLR1 to inhibit IL-33 expression with the consequent impairment of neutrophil infiltration to the site of infection and bacterial clearance.[107] These findings open a more complex scenario for the functions of chemerin in skin antimicrobial defense. Chemerin shares a similar tertiary structure with antibacterial cathelicidins and acts as an antimicrobial agent in human epidermis, causing direct bacterial lysis.[108] It can be hypothesized that chemerin antimicrobial activity prevails in the context of superficial skin infection and/or low bacterial load, while in invasive *S. aureus* skin infection, the chemerin/CMKLR1 axis promotes immune evasion by suppressing IL-33–dependent neutrophilia. In these conditions, the anti-inflammatory role played by chemerin is exploited by bacteria through the impairment of efficient innate responses.[92]

Finaly, in graft vs host disease (GvHD), chemerin plasma levels were increased in an allogenic-bone marrow-transplanted mouse model, and in patients, higher circulating levels of chemerin were predictive of GvHD.[109] Wild-type (WT) mice transplanted with an allogeneic graft from *Cmklr1*-deficient (t-KO) donors showed an exacerbated phenotype, with reduced survival and more severe gut GvHD. Interestingly, when CMKLR1 competent WT monocytes were adoptively transferred into t-KO mice, the phenotype was partially reverted, with reduced intestinal inflammation and T-cell activation, suggesting that the chemerin/CMKLR1 axis might play a protective role in the GvHD tissue damage by modulating local immune responses.[109]

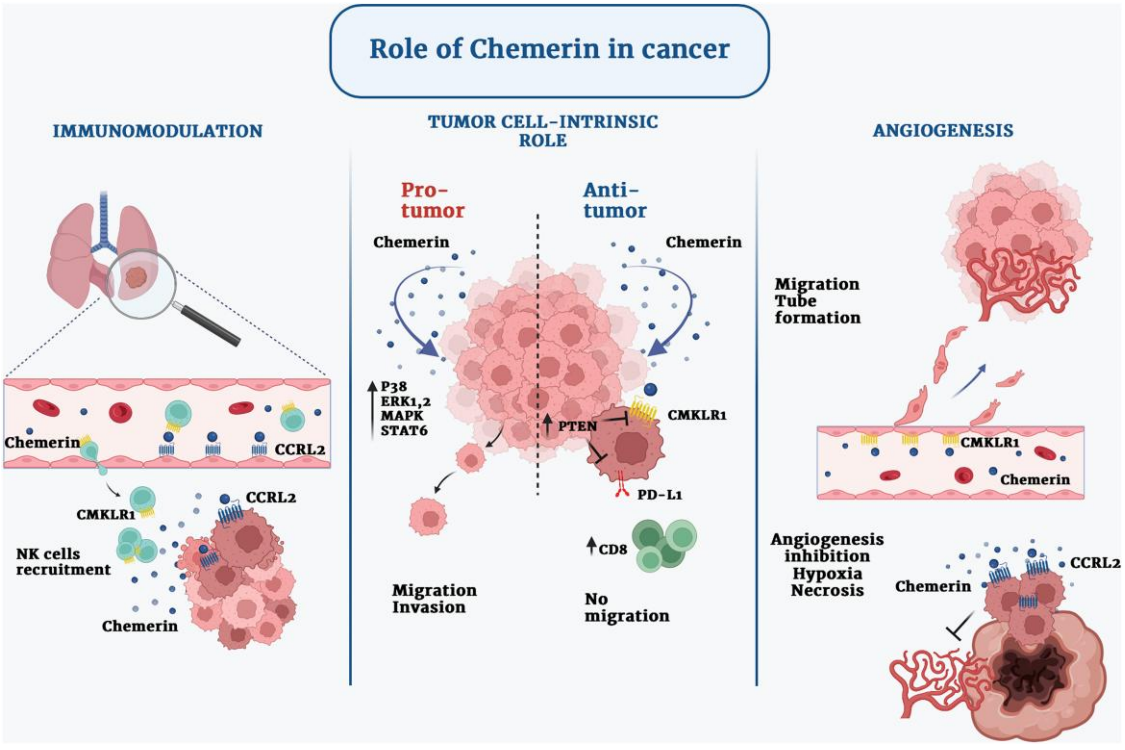

Fig. 4. Role of chemerin in cancer. The main mechanisms underlying the role played by chemerin in tumorigenesis and immunosurveillance are illustrated. Immunomodulation; tumor cell-intrinsic role; regulation of angiogenesis.

7. Chemerin in cancer

Chemerin is a multiplayer protein acting as both a proinflammatory and an anti-inflammatory mediator depending on the specific cellular context. Recently, growing evidence suggests that chemerin can play several potential roles in tumorigenesis and immunosurveillance[110] (Fig. 4). Depending on the tumor type, chemerin can exert both antitumor and tumor-promoting effects.[110,111] In some tumors, such as glioblastoma, mesothelioma, neuroblastoma, squamous cell carcinoma of the tongue and esophagus, and colorectal cancer,[18,112–116] chemerin is upregulated. On the contrary, in most cancer types, including breast cancer, melanoma, hepatocellular carcinoma, non–small cell lung cancer, Ewing sarcoma, acute myeloid leukemia, adrenocortical carcinoma, and prostate cancer, chemerin is downregulated.[117–122]

7.1 Immunomodulatory role of chemerin in cancer

One of the molecular mechanisms underlying the potential role of chemerin in the control of tumor growth and progression is related to the capacity to shape the tumor microenvironment by regulating the recruitment of immune cells through the binding of its receptors. In melanoma, chemerin-expressing tumors were shown to inhibit tumor growth by increasing the recruitment of antitumor effector cells, such as NK and T cells, in tumor lesions.[117] In particular, chemerin induced a shift toward an antitumor environment by affecting the ratio of immune balance toward the inhibition of immunosuppressive pDCs and myeloid-derived suppressor cells.[117] NK cell depletion as well as the deletion of CMKLR1 expression abrogated chemerin antitumor effects, indicating that they were mediated by CMKLR1-dependent NK cell recruitment into a tumor microenvironment.[117] As previously mentioned, a new subset of CMKLR1-expressing (human) CD8 effector memory T cells, which share genetic and functional features of NK cells, has been described.[50] This population was scarcely infiltrated in a prostate cancer mouse model in association with chemerin downregulation in the tumor microenvironment; chemerin overexpression in prostate tumor cells triggered the recruitment and activation of the NK-like CD8 T cells. This effect was abolished in the presence of anti-α4β1 neutralizing mAb, indicating that chemerin-dependent recruitment also involves α4β1 integrin.

A chemerin-dependent integrin activation has been shown for the adhesion/migration of other cell types. Notably, disturbed flow-induced endothelial expression of CCRL2 increased local chemerin concentration, thus contributing to monocyte adhesion by activating β2 integrin.[123] Moreover, activated endothelial cells promoted CMKLR1$^+$ DC transmigration across endothelial cell monolayers through the endogenous production of chemerin, the upregulation of CCRL2, and the activation of DC β1 integrin affinity.[82]

The chemerin/CCLR2/CMKLR1 axis was recently shown by our group to be indispensable in shaping the lung cancer tumor microenvironment.[83,84] Publicly available DNA microarray data revealed that chemerin expression was significantly downregulated in lung cancer tissues compared with normal lung.[111] Moreover, we found that CCRL2 expression was significantly decreased in Lung Adenocarcinoma tumors compared with paired-normal samples and that a higher CCRL2 expression correlated with a better clinical outcome, especially at early observational times.[83] In preclinical models of lung cancer—namely, urethane-induced lung carcinogenesis and the genetic model of Kras/TP53-driven ($Kras^{G12D/+}/p53^{LoxP}$) lung tumors—CCRL2 deficiency was associated with increased tumor growth. This exacerbated tumor phenotype was related to a decrease of some myeloid cell subsets, such as monocytes, macrophages, and neutrophils, and a consistent reduction of lung NK cell frequency, the most affected being the more mature CD27$^-$CD11b$^+$ mature NK cell subset.[83] Since CCRL2 is not expressed by mouse NK cells but by CD31$^+$ cells in the lung of tumor-bearing mice, these results further support the role of CCRL2 expressed by endothelial cells as a chemerin-presenting molecule regulating the recruitment of CMKLR1$^+$ NK cells in the lung tumor microenvironment. These findings were further confirmed in a model of orthotopic growth of lung tumor cells KP10.21, generated by primary $Kras^{G12D/+}$; $p53^{LoxP}$ lung tumors, injected in mice in which CCRL2 was conditionally deleted in vascular endothelium, which showed increased tumor burden associated with a decreased frequency of CMKLR1$^+$ lung-infiltrating NK cells.[84] Single-cell RNA sequencing analysis identified CCRL2 as the hallmark of general alveolar lung capillary endothelial cells, and CCRL2 expression was epigenetically regulated in lung endothelium, as demonstrated by the treatment with the demethylating agent 5-aza-2'-deoxycytidine in both in vitro and in vivo experiments.[84] Also, in a model of breast cancer, the forced overexpression of chemerin by a syngeneic orthotopic EMT6 breast tumor cells resulted in tumor suppression by the increased recruitment of effector NK cells and T cells.[124] Taken together, these findings provide strong evidence supporting the essential involvement of chemerin in modulating the tumor microenvironment, highlighting its potential as a promising target for immunotherapeutic approaches.

7.2 Cancer cell-intrinsic role of chemerin

Chemerin can influence tumor development and progression through immune-independent tumor cell-intrinsic mechanisms. By enhancing or suppressing the activity of Wnt/β catenin and Mitogen-Activated Protein (MAP) kinase pathways, chemerin can play antitumor or tumor-promoting effects.[111] For instance, the in vitro treatment with chemerin of gastric tumor cells stimulated invasiveness through upregulation of vascular endothelial growth factor, MMP7, and IL-6 mediated by p38 and ERK1/2 MAP kinase activation. Likewise, in oral squamous carcinoma cells, chemerin induced tumor cell migration and invasion through the promoted secretion of IL-6 and TNF-α via STAT6 activation.[125] However, in a different cellular context, namely in adrenocortical carcinoma, opposing results were observed by chemerin overexpression, which induced β-catenin phosphorylation/degradation and inhibited p38 mitogen-activated protein kinase (MAPK) activation, thus mediating tumor suppression, as shown in in vivo xenograft models.[122]

In hepatocellular carcinoma (HCC), chemerin suppressed tumor metastasis through the upregulated expression and activity of PTEN phosphatase, which interfered with PTEN–CMKLR1 interactions, inducing p-Akt decreased levels, and consequently suppressed migration, invasion, and metastasis of HCC cells.[126] Furthermore, a recent study reported another example of chemerin acting on the tumor cell-intrinsic phenotype.[127] Indeed, exogenous chemerin treatment of human prostate and sarcoma tumor cell lines significantly upregulated PTEN expression/activity and suppressed programmed death ligand 1 (PD-L1) expression, leading to impaired tumor migration and increased T-cell mediated cytotoxicity.[127]

Finally, epithelial chemerin/CMKLR1 signaling was shown to be necessary for restricting microbiota-driven neutrophilic colon inflammation and tumorigenesis in a model of colitis-associated

cancer.[128] The epithelial peroxidase lactoperoxidase was identified as the downstream effector of the chemerin/CMKLR1 axis able to inhibit bacteria proliferation and invasion and prevent dysregulated CXCL1/2 production and pathological mucosal neutrophilia.[128]

7.3 Role of chemerin in the regulation of angiogenesis

Chemerin can play protumor effects by activating angiogenesis, which represents a key factor in favoring tumor growth.[129] In 2010, Kaur et al.[56] reported for the first time that CMKLR1 was expressed by human endothelial cells (ECs) and was significantly upregulated by proinflammatory cytokines. The authors also demonstrated that chemerin induced functional angiogenesis in ECs by promoting cell migration, capillary tube formation via MAPK and Akt pathways, and activation of endothelial gelatinases MMP-2 and MMP-9.[56] Additional evidence reported that chemerin could promote in vivo angiogenesis, stimulating the differentiation of human umbilical vein endothelial cells (HUVECs) into capillary-like structures via Akt phosphorylation and p42/44 ERK activation. The ablation of CMKLR1, but not of CCLR2, completely inhibited the chemerin-induced migration and angiogenesis of HUVECs, suggesting that chemerin promotes the migration and angiogenic activities of HUVECs mainly through the functional CMKLR1 receptor.[130] However, contrasting results were also described, showing that chemerin can promote the regression of neovessels during the development of the vascular retinal network, reduce the efficiency of reperfusion in the hindlimb ischemia model,[131] and inhibit the angiogenesis process of HUVECs in the bead sprouting assay.[132] However, this phenotype reverted to normal in CMKLR1-deficient mice, demonstrating the role of this receptor in the process.[131] In tumor graft models, a reduction of neoangiogenesis was observed in tumor-expressing CCRL2, mimicking the phenotype of chemerin-expressing tumors. Bioactive chemerin was shown to be retained locally by CCRL2 and to exert its antitumor effect by inducing impairment of the tumor vascularization, leading to an increase of necrotic and hypoxic areas and inhibiting tumor growth.[133]

These overall results suggest a very complex scenario in the regulation of tumor development and progression mediated by chemerin. This is due to the nature of chemerin as a multifunctional protein, playing a role in different immune and tumor responses. Based on the specific context and the signaling pathways, chemerin may engender pro- and antitumor effects, and its role in each specific tumor type needs to be carefully clarified before any potential clinical development.

8. Chemerin as a versatile adipokine

Chemerin was recently recognized as a multifunctional adipokine, with autocrine, paracrine, and endocrine roles in vivo linked to metabolic disorders, including obesity, diabetes, and cardiovascular diseases.[134] Moreover, serum chemerin levels were strongly correlated with body mass index, triglyceride levels, and blood pressure.[11,22] Both chemerin and its receptor CMKLR1 are highly expressed in white adipose tissue.[22] This axis is important for the correct establishment of the adipose tissue because in cultured 3T3-L1 cells, the silencing of either chemerin or CMKLR1 impaired the differentiation of 3T3-L1 cells into mature adipocytes.[22] The authors further demonstrated that chemerin silencing was linked to a downregulation of genes involved in both glucose and lipid homeostasis.[22] In addition, in the same cellular model, chemerin was shown to raise the insulin-dependent uptake of glucose and lipolysis via the ERK1/2 pathway upon CMKLR1 triggering.[135,136]

Abnormal or excessive fat accumulation can influence not only the expression of the chemerin gene but also the circulating levels of different chemerin proteoforms. For instance, in obese patients, the serum concentration of active chemerin forms was significantly increased compared to lean donors.[19] In the same obese cohort, a positive correlation was observed between C-terminal cleaved chemerin and C-reactive protein blood levels, leading to the assumption that chemerin activation is strongly dependent on the inflammatory status of the host.[19,137]

The strong association between chemerin and metabolic syndrome suggests the possible involvement of genetic factors in chemerin expression and regulation in adipose tissue.[138] In humans, it is predicted that about 25% of the variation in serum chemerin levels is attributed to genetic factors like EDIL3 (epithelial growth factor-like repeats and discoidin I-like domains 3), known to be involved in angiogenesis.[11] The RARRES2 polymorphism rs7806429 is an eQTL (expression quantitative trait locus) that is mapped within the RARRES2/LRRC61 genomic locus, and it is associated with a differential expression of RARRES2 in the adipose tissue.[138] In addition, environmental stimuli can modulate chemerin circulating levels. Indeed, several studies showed that chemerin circulating levels were inversely correlated with the level of physical exercise in obese women, as well as with a low-caloric diet.[38,139]

Both obesity and atherosclerosis are known risk factors for cardiovascular diseases. Plasma chemerin levels are considered an independent risk factor for atherosclerosis in hypertensive patients.[140]

Recent data obtained in a mouse model of atherosclerosis showed that chemerin treatment can increase lipid accumulation in atherosclerotic plaques and exacerbate their instability through the p38 MAPK pathway.[141] In line with a proatherogenic role of chemerin, *Cmklr1*-deficient *Apoe*$^{-/-}$ mice showed an increased proportion of M2 macrophages and a reduction in pDC frequencies in atherosclerotic lesions, which synergistically reduced the atherosclerotic plaque progression.[95]

Accumulating evidence links metabolism and cancer, showing that obesity is associated with a higher risk of developing cancer.[142] For instance, obesity is a known risk factor for clear cell renal carcinoma (ccRCC), which accounts for more than 70% of renal tumors.[143] Tan et al.[144] found that chemerin was overexpressed in ccRCC by an autocrine tumor–dependent pathway and a paracrine obesity-dependent mechanism. Chemerin was shown to promote tumor growth by regulating lipid metabolism and ferroptosis in ccRCC cells.[144] Very recently, by genetic and pharmacological ablation approaches, the protumorigenic role of the adipokine chemerin in ccRCC lipid metabolism was shown to be mediated by GPR1 and CMKLR1 chemerin receptors with different pathogenic roles.[145] Indeed, both GPR1 and CMKLR1 were able to reduce the adipogenic triglyceride lipase and elevate lipid oxidation and ferroptotic death, CMKLR1 uniquely regulated SREBP1c- and CD36-mediated de novo lipogenesis, and GPR1 uniquely suppressed autophagy,[145] shedding light on the mechanism of regulating lipid metabolism by chemerin in kidney cancer.

In conclusion, as a versatile adipokine, chemerin has been implicated in the pathogenesis of different metabolic disorders. Although further investigations are needed to better clarify the mechanisms by which chemerin contributes to obesity and associated pathological conditions, it might be considered a promising

candidate to be targeted in translational research aimed at the development of pharmacological strategies for metabolic disorders.

9. Conclusions and perspectives

Chemerin is a multifaceted protein, playing multiple roles in different pathophysiological conditions, including inflammation, tumor biology, and metabolic homeostasis. The pleiotropic activity of chemerin is related to distinct levels of regulation of its expression, proteolytic maturation, and receptor binding. The first level of complexity is related to the cell context where it is expressed. Although adipose tissue and liver have been confirmed as key sites of chemerin production and are responsible for the high nanomolar chemerin levels found circulating in plasma, chemerin is also expressed at epithelial barriers, including skin epidermis and endothelial cells. In addition, a regional variation in the distribution of chemerin in healthy vs diseased tissue has been described. Moreover, C-terminal–truncated chemerin variants display either more chemotactic or anti-inflammatory effects, determined by the cleavage at distinct sites by different classes of proteases. Moreover, different concentrations of chemerin can activate an opposite functional phenotype (e.g. anti- vs pro-inflammatory immune responses).

Three chemerin receptors, showing different expression patterns, signaling properties, distinct binding sites, and functional behaviors, are responsible for multiple biological activities. CMKLR1 is the functional chemotactic receptor, which triggers the recruitment of immune cells to inflammatory sites and the tumor microenvironment. On the contrary, GPR1, able to bind chemerin with high affinity, does not activate any intracellular signaling and behaves as a decoy receptor. Finally, CCRL2, an atypical receptor binding chemerin to the N-terminus, when expressed on barrier cells, including epithelial and endothelial cells, can regulate a gradient of local concentration of bioactive chemerin and act as a presenting molecule to the neighboring CMKLR1$^+$ cells.

Considering the different functional roles played by chemerin in various pathophysiological conditions, the perspective to modulate its activity represents an attractive target for the development of new pharmacological approaches. However, the chemerin pleiotropy can also be a limitation since its targeting can induce opposite effects in different biological properties and tissue contexts. Further research studies are needed to evaluate the efficacy and the safety of drugs affecting the chemerin/CMKLR1/CCRL2 axis in different pathological models in order to assess their potential clinical applications in inflammatory diseases, metabolic disorders, and cancer.

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Author contributions

M.L., T.S., and A.P. proposed and wrote the original draft. F.S., V.S., and L.T. helped to collect and analyze the literature. D.B. and T.M. supervised the revision work. A.D.P. and S.S. supervised the conception and writing of the manuscript. All authors have read and approved the final form of the manuscript.

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