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Chemerin and its receptors in leukocyte trafficking, inflammation and metabolism

Benjamin Bondue, Valérie Wittamer, Marc Parmentier *

Institut de Recherche Interdisciplinaire en Biologie Humaine et Moléculaire (I.R.I.B.H.M.), Faculté de Médecine, Université Libre de Bruxelles, Brussels, Belgium

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ABSTRACT

Chemerin was isolated as the natural ligand of the G protein-coupled receptor ChemR23. Chemerin acts as a chemotactic factor for leukocyte populations expressing ChemR23, particularly immature plasmacytoid dendritic cells, but also immature myeloid DCs, macrophages and natural killer cells. Chemerin is expressed by epithelial and non-epithelial cells as an inactive precursor, present at nanomolar concentrations in plasma. Processing of the precursor C-terminus is required for generating bioactive forms of chemerin. Various proteases mediate this processing, including neutrophil serine proteases and proteases from coagulation and fibrinolytic cascades. ChemR23-expressing cells are recruited in human inflammatory diseases, such as psoriasis and lupus. In animal models, both pro-inflammatory and anti-inflammatory roles of chemerin have been reported. Recently, two other receptors for chemerin were described, GPR1 and CCRL2, but their functional relevance is largely unknown. Both chemerin and ChemR23 are also expressed by adipocytes, and the emerging role of chemerin as an adipokine regulating lipid and carbohydrate metabolism is an area of intense research.

ChemR23, also known as CMKLR1, was cloned as an orphan G protein-coupled receptor (GPCR) structurally related to receptors for chemoattractants, such as bacterial and mitochondrial formyl peptides (FPR1, FPR2 and FPR3), complement fragments (C5a and C3a) and prostaglandin D2 (DP_2, previously known as CRTH2 or GPR44) [1,2]. Chemerin was later identified as the natural ligand of ChemR23 [3]. A cell line expressing ChemR23 was used to search for bioactive molecules in fractions from human inflammatory fluids and tissue extracts, using a calcium-mobilization assay based on the luminescence of aequorin. Bioactivity was detected in an ascitic fluid secondary to an ovarian carcinoma, and following purification of this activity through HPLC steps, mass spectrometry analysis resulted in the identification of a protein derived from Tazarotene-induced gene 2 (Tig2). Tig2 was previously described, following a subtraction hybridization approach, as a gene up-regulated by retinoic acid and its synthetic analog tazarotene in skin raft cultures [4]. Provided its activity on the ChemR23 receptor, the active form of the Tig2 gene product was named chemerin.

1. Structure of chemerin

Chemerin structure is unrelated to that of chemokines or other chemoattractant factors for leukocytes. It is predicted to share a so-called cystatin fold with a set of extracellular proteins, which include cystatins type 2 (cysteine protease inhibitors), cathelicidins (precursors of bactericidal peptides) and kininogen (precursor of bradykinin). Extracellular proteins sharing the cystatin-like fold have in common 4 conserved cysteines, which were shown to stabilize the structure by forming two disulfide bonds (crystal structures available in PDB include chicken cystatin, 1CEW; human cystatin D, 1ROA; porcine protegrin 3, 1PFP). The chemerin primary structure is relatively divergent from other cystatin-like folds and contains six cysteines instead of four, suggesting the existence of an additional disulfide bond (Fig. 1). In addition to the cysteine pattern, the number and location of introns is highly conserved within the gene structure of chemerin, cathelicidins, cystatins and kininogen, further demonstrating their evolutionary relationship. Indeed, among the five introns of the chemerin gene, three split the coding sequence (each time between full codons), and the location of these introns relative to codons and cysteines is similar in the other genes encoding cystatin-like folds (Fig. 1). The classical cystatin fold includes an N-terminal α-helix followed by a 4-stranded antiparallel β sheet. An NMR assignment of ^{15}N and ^{13}C-labeled human chemerin expressed in *Escherichia coli* was reported [5]. The tri-dimensional structure of the protein was not described, but only two of the four β-strands of the cystatin fold,

* Corresponding author at: I.R.I.B.H.M., Université Libre de Bruxelles, Campus Erasme, Route de Lennik 808, B-1070 Brussels, Belgium. Tel.: +32 2 555 4171; fax: +32 2 555 4655.
E-mail address: mparment@ulb.ac.be (M. Parmentier).

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Fig. 1. Alignment of preprochemerin amino acid sequence with other proteins sharing the cystatin fold. Human preprochemerin sequence is aligned with human and mouse cathelicidin precursors (CAP-18 and CRAM respectively), the three cystatin-like domains of human high-molecular-weight kininogen, and human cystatin 3. The signal peptides are displayed as italic lowercase gray letters. The cysteines stabilizing the cystatin core structure are represented in red. Chemerin contains two additional cysteines that presumably form an additional disulphide bond. The location of the introns splitting the coding sequence in the corresponding genes are indicated by red triangles, and the amino acids in green correspond to the split codon, or to the two successive codons between which the intron is located. The sequences in blue correspond to the pro-sequence of chemerin, removed by proteolytic activation of the precursor, the bactericidal peptides released from cathelicidin precursors, and bradykinin, released by proteolysis from kininogen.

and a long additional C-terminal α-helix were proposed, suggesting divergence from the classical cystatin fold.

Noteworthy, cathelicidins and kininogens require proteolytic processing in order to generate the peptides displaying bioactivity. Cathelicidins are secreted as propeptides that generate by proteolytic cleavage a C-terminal peptide displaying bactericidal properties. High-molecular-weight kininogen is composed of three cystatin-like modules, and C-terminal proteolysis of this precursor generates bradykinin, which acts through members of the GPCR family (B_1 and B_2). Similarly, chemerin was shown to be secreted as an inactive precursor, prochemerin, which is 143 amino acid long in human, following removal of the 20 amino acid long signal peptide. Prochemerin has very low affinity for ChemR23, and activates very poorly the receptor. In order to acquire its bioactivity, prochemerin needs to be processed by proteolytic enzymes within its C-terminal domain, which lies outside the cystatin-like fold. The requirement for proteolytic processing was made clear from the purification of bioactive material from natural sources, and the expression of (pro)chemerin in recombinant systems. The main form purified from ascitic fluid lacked the last 6 amino acids from prochemerin and bioactive material purified following expression or prochemerin in CHO-K1 cells had the same structure [3]. In contrast, purification of the intact precursor by a monoclonal antibody recognizing specifically the prochemerin C-terminus led to very little activity on ChemR23 ($EC_{50} > 400$ nM).

2. Chemerin-derived peptides

The requirement for C-terminal processing of prochemerin pinpointed the role of this domain for the activation of ChemR23. By analogy, all chemokines share a structure, different from that of chemerin, composed of a disordered N-terminus essential for bioactivity, a three stranded β-sheet and a C-terminal α-helix. Chemokines are known to bind their respective receptors through interactions of their core structure with the extracellular N-terminal domain and loops of the receptor, while the unfolded N-terminus interacts with a second binding site located in the transmembrane helix bundle, triggering the conformational change and leading to G protein activation. The functional role of chemokine N-terminal peptides is illustrated by the important changes in bioactivity resulting from proteolytic trimming of this domain or other post-translational modifications such as citrullination [6]. In most cases however, peptides derived from chemokine N-terminus display very poor binding and functional properties. In contrast, short peptides derived from chemerin C-terminus were shown to display significant bioactivity [7]. Indeed, chemerin could be trimmed down to a C-terminal nonapeptide (Y^{149}FPGQFAFS^{157}, named chemerin-9), while keeping an EC_{50} of 5 nM for ChemR23 (compared to 0.1–0.2 nM for full size chemerin). In mouse, the corresponding nonapeptide L^{148}FPGQFAFS^{156} displays similar properties [8]. It appears therefore that chemerin interacts, similarly to chemokines, through two distinct domains with its receptor. The cystatin-like domain interacts presumably with the N-terminus and loops of ChemR23, although this has not been experimentally confirmed, while the C-terminus triggers activation, presumably through an interaction involving the helix bundle. Despite its cystatin-like structure, chemerin does not appear to inhibit cysteine proteases [9].

The use of C-terminal peptides also allowed to delineate how precise the C-terminal proteolytic processing needs to be, and what are structural determinants necessary for activation of ChemR23. It was shown that addition of a single amino acid or removal of two amino acids, relative to chemerin-9, modified the potency by four orders of magnitude [7]. Besides, Y^{149}, F^{150}, G^{152}, F^{154}, F^{156} and the terminal carboxyl group were shown as essential moieties for the bioactivity of the peptides. On this basis, binding tracers were developed, such as ^{125}I-YHSFFPGQFAFS, allowing the pharmacological characterization of ChemR23. Chemerin-derived peptides constitute interesting tools for studying the pharmacology of the receptor *in vitro*, but there is no evidence that such peptides are generated *in vivo*, and these peptides are short lived in plasma and other biological media, such as cell cultures, as a result of proteolytic degradation. The half-life of chemerin-9 in biological media was

estimated to less than 10 min [10], preventing its use for some bioassays on cells in culture (cAMP accumulation, chemotaxis), as well as *in vivo*. A peptide analog was therefore developed, D-Tyr^{147}-[D-Ser^{151}, D-Ala^{154}, Tic^{155}] mouse chemerin 148–156, which displays good potency (EC_{50}: 22 nM) and a considerable improvement of stability in biological media (half life > 240 min in plasma) [10]. Other peptides derived from mouse chemerin were described to display significant bioactivity *in vitro* and *in vivo*, despite the absence of key residues required for bioactivity. These include the C15 peptide, A^{140}GEDPHGYFLPGQFA^{154}, reported for its anti-inflammatory properties *in vitro* and in a model of peritonitis [11]. In line with the prediction based on its structure (lack of F^{155}), C15 was later shown to be devoid of any biological activity through ChemR23 [8,10]. Recently, the production of C-terminally truncated forms of chemerin in CHO cells allowed to confirm the previous data derived from C-terminal peptides [12]. Indeed, human chemerin ending by K^{158} had low potency (EC_{50}: 54 nM), and a shorter form ending with A^{155} was devoid of activity, as compared to the most active form ending by S^{157} (EC_{50}: 1.2 nM).

3. Processing of (pro)chemerin

Prochemerin leads to bioactive chemerin following the proteolytic removal of 6 or 7 amino-acids from its C-terminus. A number of proteases have been shown to activate chemerin, sometimes in a cooperative manner (Fig. 2). The first proteases shown to activate prochemerin are two neutrophil serine proteases, elastase and cathepsin G [13]. Elastase cleaves 6 amino acids and generates chemerin 21–157, which is the most active form. Cathepsin G removes 7 amino acids from the C-terminus, resulting in a slightly less active chemerin (21–156) form. As stated above, removal of one additional amino acid leads to a variant devoid of bioactivity [7,12]. Cathepsins L and K are also able to generate the 20–157 form directly from the prochemerin precursor [9]. Plasmin and tryptase, which cleave off 5 amino acids from the C-terminus, generate an inactive form of chemerin, but this activity can be complemented by that of carboxypeptidases N and B, which remove the resulting carboxy-terminal lysine, generating also the active chemerin 20–157 form [14,15]. Other proteases, including urokinase, tissue plasminogen activator (TPA) and factor XIIa were described as activators of prochemerin, but the precise cleavage

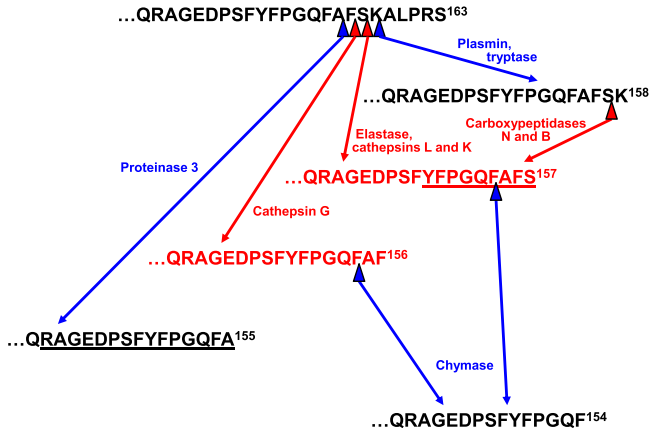

Fig. 2. Proteases regulating human (pro)chemerin bioactivity. The C-terminal sequence of various variants of human chemerin is displayed, with the position of the last amino acid relative to the full preprochemerin sequence. Variants represented in black are inactive, variants represented in red are active on ChemR23 and GPR1. Triangles represent cleavage sites by various proteases. Arrows and proteases represented in red correspond to pathways leading to active chemerin forms. Arrows and proteases represented in blue correspond to pathways leading to inactive chemerin forms.

sites were not determined [14]. It is likely that still other proteases can activate prochemerin. Indeed, expression of the precursor in a number of cell lines, including hamster CHO-K1, human HEK 293 or mouse Lewis lung carcinoma (LLC) results in the production of bioactive chemerin forms, but the enzymes responsible for the processing have not been identified. Proteases from human pathogens can also activate prochemerin. This was reported for staphopain B, a cysteine protease from *Staphylococcus aureus* [16]. This observation raises the question whether such processing may benefit to the bacteria, by influencing the profile of leukocyte populations recruited at the inflammatory site, or by other mechanisms, in the light of the anti-inflammatory actions of chemerin that are described below. Besides the proteases able to generate bioactive chemerin forms from prochemerin, a number of other proteases were shown to inactivate bioactive chemerin or process prochemerin into short inactive forms of chemerin, thereby competing for prochemerin with the activating proteases. Bioactive chemerin 21–157 and 21–156 (but not prochemerin) is cleaved by mast cell chymase into the inactive variant chemerin 21–154. Prochemerin (but not the bioactive chemerin forms) is processed by neutrophil proteinase 3, generating the inactive 21–155 form [17]. The information available presently suggests therefore a very complex regulation of chemerin bioactivity, in which various proteases from inflammatory, coagulation and fibrinolytic cascades modify the balance between active and inactive forms of chemerin. The many C-terminal variants of chemerin, with their important differences in relative activity, also make difficult the assessment of chemerin bioactivity by immunological means. Discriminating the two active forms (21–156 and 21–157 in human) from inactive forms, differing sometimes by one amino acid, is indeed an incompletely solved issue. ELISAs able to discriminate prochemerin (21–163), and chemerin 21–158 and 21–157, using antibodies raised against C-terminal peptides, were recently described [18], but they do not cover all active and inactive forms. Only bioassays, measuring the activity on ChemR23-expressing cells, are presently able to reliably estimate chemerin bioactive forms, but these assays require at least a partial purification of chemerin (from plasma or other sources), and are therefore not adequate for large scale studies.

4. Chemerin expression sites

Prochemerin expression is detected in most tissues by qRT-PCR or Northern blotting, with the notable exception of leukocyte populations. In contrast to inflammatory chemokines, recruited leukocytes are therefore not able to release chemerin and mark the path for further recruitment. Prochemerin is expressed at particularly high levels in liver, white adipose tissue and placenta, but is also present in skin, adrenal gland, all parts of the gut, pancreas, the airways, and the kidney. A number of cell populations were shown to contain prochemerin transcripts, display chemerin immunoreactivity and/or release chemerin bioactivity. These include various epithelial cells, endothelial cells, fibroblasts, chondrocytes and platelets [8,15,19,20]. Prochemerin is present at relatively high concentrations in plasma (6–12 nM, corresponding to 100–200 ng/ml, in control subjects), but the concentration of bioactive chemerin is apparently negligible in basal conditions. The source of plasma prochemerin is not known for sure, but liver and adipose tissue were reported as the main contributors [21,22]. Chemerin was also reported to be stored in platelet granules and released following activation by thrombin, collagen or ADP, in a partially activated form [15]. In the early study describing the Tig2 gene encoding prochemerin in skin, it was shown that prohemerin is not expressed in primary keratinocytes and fibroblasts in culture, nor induced by retinoids in such cultures. Prochemerin was expressed in keratinocytes and induced by tazarotene only when keratinocytes and fibroblasts were allowed

to form a tissue-like 3-dimensional structure [4]. These observations suggest a potential cross-talk between stromal and epithelial cells in the regulation of prochemerin expression.

5. ChemR23 as a high affinity functional receptor

ChemR23 (also known as CMKLR1) is presently the only receptor through which biological activities of chemerin have unambiguously been described, including *in vivo*. It is however possible that part of the properties of chemerin are mediated by other receptors, GPR1 and CCRL2, described below (Fig. 3).

ChemR23 is structurally related to a set of receptors for chemoattractant molecules (C5a, C3a, FPR1-3, DP2) that also include GPR1 and the orphan receptors GPR32 and GPR33. ChemR23 is expressed in various leukocyte populations, particularly the monocytic lineage, including monocytes and macrophages, myeloid (mDC) and plasmacytoid dendritic cells (pDC), microglial cells and NK cells [2,19,23,24]. B and T lymphocyte populations, granulocytes, Langerhans cells and platelets were reported not to express ChemR23. Both in mDCs and pDCs, expression of ChemR23 is downregulated during maturation [7,19]. ChemR23 expression is particularly high in immature pDCs, and ChemR23 is considered as one of the few functional receptors for chemoattractant molecules in these cells. It is therefore postulated that chemerin might play an important role in the trafficking of pDCs, which are professional type I interferon producers involved in anti-viral immune responses [19,25]. In macrophages, ChemR23 is downregulated by proinflammatory cytokines and TLR ligands, but upregulated by TGF-β, suggesting a potential involvement of chemerin in the recruitment of M2-polarized macrophages with an anti-inflammatory phenotype, during the resolution phase of inflammation and wound healing [26]. ChemR23 expression was also described in a growing number of non-leukocyte cell populations. These include preadipocytes and adipocytes, osteoclasts, chondrocytes, skeletal muscle cells and endothelial cells [20,21,27,28].

6. ChemR23 and resolvin E1

Besides chemerin, a second ligand, resolvin E1 (RvE1), was proposed for ChemR23 [29]. RvE1 is an oxygenated product of the essential fatty acid eicosapentanoic acid, and is believed to mediate the beneficial effects of this fatty acid in a number of inflammation-associated human disorders. RvE1 was shown to display anti-inflammatory properties in mice, inhibiting leukocyte recruitment in an air pouch model in response to TNF-α, and reducing the production of IL-12 by DCs and the trafficking of DCs to spleen following stimulation by a *Toxoplasma gondii* soluble tachyzoite antigen extract. Following a screen of receptors related to the lipoxin A_4 receptor (FPR2), the authors identified ChemR23 as activated by RvE1, inhibiting the TNF-α-stimulated NF-κB activation in HEK293 cells. RvE1 and chemerin-derived peptides were however shown to stimulate different pathways on the same cells expressing ChemR23 [29]. So far, no other group has confirmed the activity of RvE1 on ChemR23, and we have failed doing so, in binding and a range of functional assays. In addition, a main target cell population for RvE1 is neutrophils, and it is well established that ChemR23 is not expressed in these cells. Since then, the same group has reported another candidate receptor for RvE1 activities, namely the leukotriene B4 receptor BLT1 [30]. BLT1 is expressed at high levels in neutrophils, which is more compatible with the action of the lipid mediator. Besides, in BLT1 kockout mice, the blockade of neutrophil recruitment by RvE1 was sharply reduced in a model of zymosan-induced peritonitis, suggesting that ChemR23 is not a major site of action of RvE1. Although not formally disproved at this stage, the activity of RvE1 on ChemR23 is highly questionable.

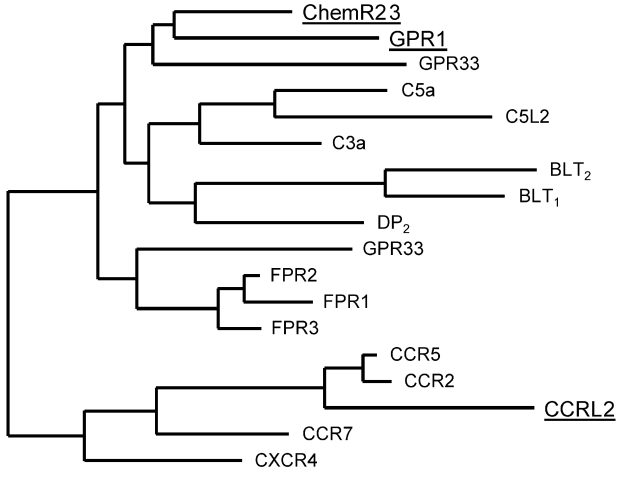

Fig. 3. Dendrogram representing structural similarities between chemerin receptors and other receptors for leukocyte chemoattractants. Sequences for the three known receptors of chemerin, ChemR23, GPR1 and CCRL2 (underlined) were aligned (not shown) with other chemoattractant receptors and related orphan receptors in order to generate a phylogenetic tree (http://www.phylogeny.fr/). The displayed receptors include the receptors for the complement fragments C3a and C5a, the leukotriene B receptors (BLT_1 and BLT_2), the prostaglandin D receptor DP_2, formyl peptide receptors (FPR1, FPR2 and FPR3) and a selection of chemokine receptors (CCR2, CCR5, CCR7 and CXCR4).

7. Other chemerin receptors

7.1. GPR1

Two other G protein-coupled receptors have been described so far to bind chemerin with high affinity. Activation of GPR1 by chemerin was reported in the frame of the development of a β-arrestin recruitment screening assay named Tango [31]. As GPR1 is the closest relative of ChemR23 from a structural point of view, it was an obvious candidate as a second chemerin receptor, and we had tested this receptor previously in a calcium mobilization assay with negative results. Indeed, GPR1 displays high affinity for chemerin, similar to that of ChemR23, but signals poorly in classical G protein-mediated pathways (Fig. 4). GPR1-expressing cell lines respond to chemerin by weak Ca^{2+} mobilization and ERK1/2 activation, but internalizes efficiently as a result of agonist binding. GPR1 might therefore behave as a decoy receptor for chemerin, and no GPR1-mediated activity has been described so far on primary cells or *in vivo*. GPR1 is not reported to be expressed by leukocyte populations, but is expressed in the central nervous system, skeletal muscle, skin and adipose tissue, where it might regulate the activity of chemerin.

7.2. CCRL2

Chemokine (C-C motif) receptor-like 2 (CCRL2, also called CKRX, HCR or CRAM in human, and L-CCR in mice), was recently described as a third receptor for chemerin [32]. CCRL2 belongs to the chemokine receptor family and is closely related to CCR1, CCR2, CCR3 and CCR5. Expression of the human receptor was reported in monocytes, macrophages, DCs, neutrophils, T cells, NK cells, mast cells and $CD34^+$ bone marrow precursors [33,34], while the mouse receptor is expressed by DCs and macrophages, but not by eosinophils and T cells [35]. The receptor is up-regulated upon activation of the cells by LPS or TNF-α. CCRL2 was previously reported to bind the chemokines CCL2, CCL5, CCL7 and CCL8 [36], but this was not confirmed afterwards. More recently, CCL19 was also reported as a ligand of CCRL2 [37]. Chemerin binds human and mouse CCRL2 with high affinity (K_D around 1 nM) similar to that of ChemR23 and GPR1. However, chemerin binding to the receptor does not seem to promote any signaling in the cells, and does not

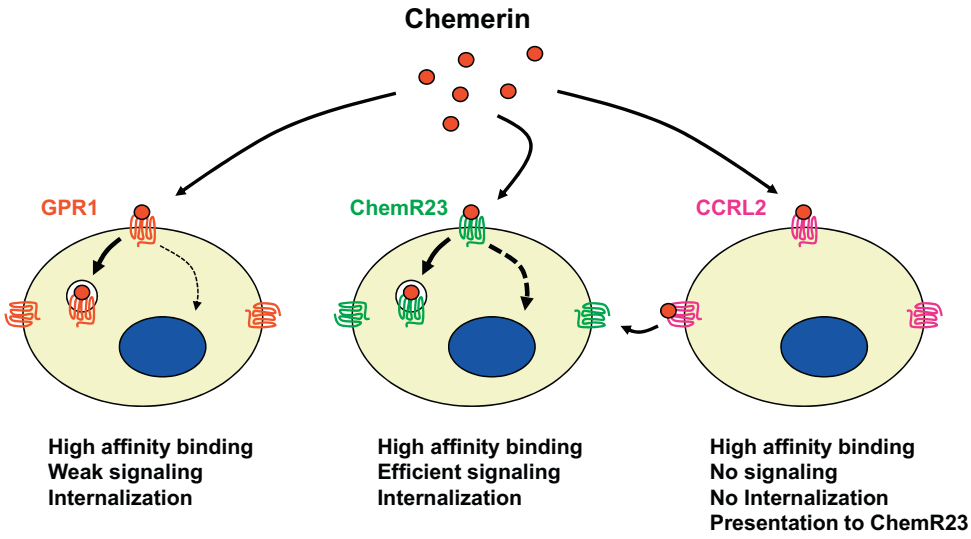

Fig. 4. Overview of the three receptors for chemerin. The three chemerin receptors, ChemR23, GPR1 and CCRL2 are represented at the surface of cells, together with the main events triggered by ligand binding. ChemR23 leads to strong signaling (promoting leukocyte chemotaxis) and internalization of the chemerin–receptor complex. GPR1 internalizes in response to chemerin, but signals inefficiently through classical cascades. CCRL2 does not signal nor internalizes, but might present chemerin to nearby cells displaying functional receptors.

induce CCRL2 internatization (Fig. 4). This absence of signaling is in line with the atypical structure of CCRL2, which does not display the canonical DRY motif at the cytosolic end of transmembrane segment 3, motif involved in GPCR activation and G protein coupling. CCRL2 was therefore suggested to increase the local concentration of chemerin and present the protein to other nearby cells displaying ChemR23 on their surface [32]. Recently, CCRL2 knockout mice were reported to display normal recruitment of circulating DCs to the lung, but defective trafficking of antigen-loaded lung DCs to mediastinal lymph nodes [35]. Consequently, these mice were partially protected in a model of ovalbumin-induced airway inflammation. Adoptive transfer experiments demonstrated that CCRL2 deficiency in DCs was specifically responsible for the phenotype. It is however unknown so far whether this defect in DC function is linked to the role of CCRL2 as a silent chemerin receptor.

8. The chemerin–ChemR23 system in leukocyte recruitment

As other receptors for chemokine and chemoattractant molecules, ChemR23 is coupled to the G_i family of G proteins. In recombinant cells expressing ChemR23, chemerin inhibits cAMP accumulation, activates phospholipase C, IP3 release and calcium mobilization, and triggers PI3K and ERK1/2 pathways, in a Pertussis toxin-sensitive manner. Efficient internalization of the receptor can also be monitored. Chemerin promotes chemotaxis of all leukocyte populations that express ChemR23. Macrophages, immature (but not mature) myeloid and plasmacytoid DCs and NK cells from human and mouse were shown to migrate toward chemerin in chemotaxis assays *ex vivo* [7,8,19,24]. Calcium mobilization, MAP kinase activation, and receptor internalization can also be recorded on primary cells. Invalidation of ChemR23 abrogated the chemotactic activity of chemerin on all tested leukocyte populations, demonstrating the lack of redundancy with other known or unknown receptors [8]. Chemotaxis involves the adhesion of cells to extracellular matrix components, and the pathway involved in the recruitment of human macrophages was investigated. It was found that chemerin promotes the clustering of the VLA-4 and VLA-5 integrins at the cell surface, leading to adhesion of macrophages to VCAM-1 and fibronectin [38]. The intracellular pathway was shown to involve G_i proteins, PI3K, Akt and p38.

9. Chemerin as a pro- or anti-inflammatory agent

As a chemotactic factor generated in inflammatory conditions and acting on cells involved in innate immune responses, chemerin was initially expected to behave as a pro-inflammatory agent. Recent data point however toward more complex activities that are either pro- or anti-inflammatory, according to the disease model investigated.

Bioactive chemerin is elevated in tissues and fluids in inflammatory conditions, and ChemR23-expressing cells were shown to be recruited in a number of chronic inflammatory diseases. Circulating levels of chemerin are increased in chronic inflammatory diseases such as ulcerative colitis and Crohn's disease [39]. In lupus erythematous skin lesions, chemerin was detected by immunohistochemistry in the endothelium of dermal blood vessels, and in high endothelial venules of secondary lymphoid organs [19]. ChemR23-expressing pDCs were also found in skin lupus lesions, suggesting that chemerin is involved in the recruitment of these cells and other leukocyte populations in this disease. More recently, it was also shown that chemerin is expressed in proximal tubular cells and lymphatic endothelial cells in the kidneys of patients with severe lupus nephritis, which is associated with the recruitment of ChemR23-expressing pDCs to the kidney parenchyma [40]. Similarly, expression of chemerin was reported in early psoriatic lesions and prepsoriatic skin adjacent to active lesions, in parallel to infiltration by pDCs and neutrophils [41]. In chronic plaques however, low chemerin levels and low pDC infiltration were found. Immunoreactive chemerin was found in fibroblasts, mast cells and endothelial cells in early lesions, and the release of bioactive chemerin from fibroblasts was confirmed *ex vivo*. Elevated chemerin levels were also described in the serum of psoriatic patients [42]. Chemerin was detected in cerebrovascular endothelial cells in lesions of multiple sclerosis and ChemR23 was expressed on infiltrating leukocytes, including pDCs [43]. These observations suggest a role of the chemerin/ChemR23 system in the recruitment of pDCs in lupus, the early phases of psoriasis development and multiple sclerosis. Chemerin expression was also reported in endothelial cells of dermal vessels in oral lichen planus, and it was suggested that such expression favors the co-recruitment of pDCs and NK cells and the important cross-talk between these two ChemR23-expressing cell populations [24].

The chemerin–ChemR23 system was also studied in mouse models of inflammatory diseases, using ChemR23 knockout mice. In a model of experimental autoimmune encephalomyelitis (EAE), mimicking some aspects of multiple sclerosis in humans, chemerin and ChemR23 were described to contribute to the pathogenesis [23]. This model involves immunization with the myelin oligodendrocyte glycoprotein (MOG). In mice with EAE, chemerin was found upregulated in lesions, together with myeloid DC infiltration. Partial protection was observed in ChemR23$^{-/-}$ mice, which displayed lower leukocytic infiltration in brain and less clinical signs. Adoptive transfer of MOG-reactive lymphocytes between ChemR23$^{+/+}$ and ChemR23$^{-/-}$ mice demonstrated that ChemR23 is involved both in the induction and effector phases of the disease.

ChemR23$^{-/-}$ mice were also tested in a model of chronic obstructive pulmonary disease (COPD) secondary to cigarette smoke exposure [44]. Chemerin levels were increased in the bronchoalveolar lavage (BAL) fluid of WT mice, following acute or chronic exposure of airways to cigarette smoke, while chemerin and ChemR23 transcripts were downregulated in the lung tissue. In ChemR23$^{-/-}$ mice, the inflammatory response to cigarette smoke was milder, with decreased levels of proinflammatory chemokines in BAL, and lower recruitment of neutrophils, DCs and CD4^{+} T cells in lung. These observations suggest that chemerin contributes significantly to the recruitment of innate and adaptive immune cells to cigarette smoke-exposed lungs and plays a pro-inflammatory role in this context.

In contrast, a number of studies have described anti-inflammatory properties of the chemerin–ChemR23 system. A first report described the effect of chemerin and chemerin-derived peptides on macrophages *ex vivo* and in a mouse model of zymosan-induced peritonitis [11]. Chemerin, and the chemerin-derived peptide C15, inhibited the production of inflammatory cytokines by mouse peritoneal macrophages following stimulation by LPS and IFN-γ. C15 was also shown to display anti-inflammatory activities at pM concentrations in the peritonitis model, preventing the recruitment of neutrophils and monocytes and the expression of proinflammatory cytokines. The same group reported later that C15, but not chemerin, enhanced phagocytosis of microbial particles and apoptotic cells by ChemR23$^{+/+}$ (but not ChemR23$^{-/-}$) macrophages [45]. As stated above, the C15 peptide (A^{140}–A^{154}) lacks key structural elements required for activation of ChemR23. We and others found C15 as totally inactive toward recombinant ChemR23-expressing cells (using functional and binding assays), and native leukocyte populations expressing the receptor, including mouse peritoneal macrophages, up to μM concentrations [8,10]. Observations made with the C15 peptide should therefore be interpreted with caution.

We have tested ChemR23 KO mice in models of lung inflammation and viral infection. Acute lung injury was promoted by direct lipopolysaccharide instillation into the airways. Co-administration of chemerin with LPS resulted in a much lower recruitment of neutrophils to the lung, and the production of chemokines (CXCL1) and cytokines (TNF, IL-1β, IL-6) was decreased as well [8]. In ChemR23$^{-/-}$ mice, the number of neutrophils recruited to the lung was higher than in wild-type mice, and the effect of chemerin was lost. In this model, both endogenous and exogenous chemerin were therefore shown to display anti-inflammatory properties in a ChemR23-dependent manner. More recently, we also tested ChemR23$^{-/-}$ mice in a model of viral pneumonia [46]. Pneumonia virus of mice (PVM) is considered as the mouse counterpart of the human respiratory syncytial virus (RSV), which is a major cause of acute bronchiolitis in infants and young children. As a result of PVM infection, the mortality rate was much higher and inflammatory parameters much more affected in the ChemR23$^{-/-}$ group. This included a severe impairment of lung function and marked neutrophilic infiltration in the lung. Recruitment of plasmacytoid dendritic cells and production of type I interferon production were also reduced in ChemR23$^{-/-}$ mice, resulting in delayed viral clearance. Adoptive transfer of ChemR23$^{+/+}$ pDCs (or bone marrow) to ChemR23$^{-/-}$ mice restored the type I interferon response, but increased further the morbidity and mortality. These observations demonstrated first that the chemerin/ChemR23 system is indeed involved in the recruitment of pDCs and in the anti-viral response *in vivo*, but suggest also an anti-inflammatory role of this system, independent from pDCs and other marrow-derived leukocyte populations. The precise mechanisms and cells involved in this process are however unknown at present.

10. Chemerin as an adipokine

Besides its role as a chemoattractant agent, chemerin was more recently reported as an adipokine regulating adipogenesis and adipocyte metabolism. This new function was first supported by the observation that both chemerin and ChemR23 were expressed by adipocytes [47–49]. Both genes were found to be upregulated during the differentiation process of mesenchymal stem cells or 3T3-L1 cells into adipocytes, and the autocrine/paracrine stimulatory loop was further shown to play an important role during the initial clonal expansion phase of the adipocyte differentiation process [47]. Interruption of the autocrine loop inhibited the differentiation of adipocytes in culture. During differentiation of bone marrow mesenchymal stem cells (BMSC) into adipocytes, chemerin upregulation was shown to correlate with that of PPARγ, the master regulator of adipogenesis [22]. Chemerin synthesis and secretion is increased by TNF-α and IL-1β in 3T3-L1 adipocytes, human primary adipocytes or mouse adipocytes *in vivo* [27,50], through a pathway involving NFκB and ERK1/2 [51]. Chemerin expression by adipocytes was also reported to be induced by free fatty acids, through the transcription factor SREBP2 [52].

Chemerin was reported to regulate mature adipocyte functions, by controlling the expression of key effectors of glucose and lipid metabolism, including the glucose transporter GLUT4, diacylglycerol acyltransferase (DGAT2), mediating the synthesis of triglycerides, and the adipokines leptin and adiponectin [21,47]. The global effect of chemerin on lipolysis is a matter of dabate. Some reports describe a reduction of basal or isoproterenol-evoked lipolysis in response to chemerin in 3T3-L1 or primary mouse white adipocytes [10,47]. Other reports suggest a stimulation of lipolysis by chemerin in 3T3-L1 adipocytes [49]. The effect of chemerin on glucose metabolism is also controvertial. In 3T3-L1 adipocytes, both an increase [53] and a decrease [51] of insulin-promoted glucose uptake and IRS-1 phosphorylation were reported following respectively a short stimulation by low concentrations (nM) and a longer stimulation by higher concentrations (μM) of chemerin. Inhibition of glucose uptake by chemerin was also reported in primary muscle cells [27,54]. Increased glucose intolerance was reported following chemerin treatment in ob/ob and db/db mice, as a result of decreased glucose uptake in adipose tissue, liver and skeletal muscle [55].

Obesity is frequently associated with a chronic systemic inflammatory state. Adipocyte enlargement is associated with the secretion of cytokines such as TNF-α and IL-6, which increase in the bloodstream, and adipose tissue becomes infiltrated by macrophages, T cells, NK cells and immature mDCs and pDCs. Proinflammatory cytokines secreted by adipocytes and macrophages interfere with insulin signaling and promote insulin resistance. Chemerin, as an adipokine able to promote chemotaxis of most leukocyte populations found in adipose tissue from obese individuals, was therefore considered as a potential link between obesity and inflammation. This role is however not established yet.

Serum chemerin levels are elevated in obese and type 2 diabetic patients, and were shown in a number of studies to correlate positively with body mass index (BMI), fasting glucose, fasting

insulin, triglycerides and total cholesterol, but negatively with HDL cholesterol [21,48]. Chemerin levels also correlate with serum concentrations of TNF-α, IL-6 and C reactive protein (CRP), and may reflect the inflammatory status associated with obesity rather than obesity itself [56]. In animal models as well, obesity and diabetes were associated with elevated circulating chemerin levels [55]. Chemerin is expressed at high levels in adipose tissue of obese Psammomys obesus [48] and serum chemerin was found elevated in genetically obese ob/ob and db/db mice in some studies [21,50]. Other studies reported low chemerin expression in adipose tissue of db/db mice [53], while increased chemerin expression was observed in brown but not white adipose tissue of ob/ob mice [47]. Chemerin is also increased in nonalcoholic fatty liver disease in human [57], and although serum chemerin cannot be considered as a marker of the extent of atherosclerosis lesions, local production of chemerin was suggested to contribute to the recruitment of macrophages to atherosclerotic plaques [58].

ChemR23, but not chemerin, was reported to be expressed by human skeletal muscle cells. ChemR23 expression was down-regulated during the differentiation of myoblasts into mature cells. Chemerin treatment of skeletal muscle cells impaired insulin signaling and glucose uptake, an effect involving the ERK1/2 MAP kinase cascade and an inhibitory phosphorylation on serine of IRS-1 [27].

11. Other effects of chemerin and chemerin receptors

ChemR23 expression was reported in endothelial cells. Upregulation of the receptor by inflammatory cytokines (TNF-α and IL-6) was reported in these cells, and chemerin was shown to induce proliferation of endothelial cells and the release of metalloproteases (MMP-2 and MMP-9), thereby promoting angiogenesis [28]. In fibroblast/endothelial cell cocultures, chemerin was reported to promote the formation of endothelial tubules in a MAPK-dependent manner [48].

Two of the chemerin receptors, ChemR23 and GPR1, were described as minor co-receptors for human and simian immunodeficiency virus (HIV and SIV) [2,59,60]. Many GPCRs, besides the main co-receptors CCR5 and CXCR4, have been described as HIV and SIV co-receptors in sensitive entry assays, and the functional relevance of this observation *in vivo* is questionable.

12. Perspectives

Chemerin plays a dual role as a chemoattractant factor for leukocyte populations and as an adipokine regulating lipid and carbohydrate metabolism. Whether these two roles are independent or interconnected is presently not known. Further studies will be required to clarify a number of open questions.

Three receptors have so far been described for chemerin. Most functional properties of chemerin can presently be attributed to ChemR23. It remains to be determined whether GPR1 and CCRL2 have their own signaling functions, independently of ChemR23, of it they only modulate the activity of the chemerin–ChemR23 axis. They might indeed act by scavenging chemerin, presenting chemerin to other receptors, or otherwise modulating the signaling properties of ChemR23 when coexpressed in the same cells. Delineating these potential functions will require *in vitro* as well as *in vivo* studies using knockout models for the various receptors.

In the frame of inflammation, pro-inflammatory and anti-inflammatory roles of chemerin have been proposed. How these apparently opposite activities are mediated, through which cell populations, leukocytes or other cell types, needs to be determined. Such studies will determine whether agonists of antagonists of ChemR23 or other receptors may be considered as therapeutic agents.

In the field of metabolism, numerous reports have described correlations of blood chemerin levels with body weight and parameters of the metabolic syndrome, and biological effects of chemerin on adipocytes *ex vivo*. The importance of this system *in vivo* is however still unclear, as ChemR23 knockout mice do not display obvious metabolic dysfunctions, and a number of discrepancies regarding the effects of chemerin on lipid and glucose metabolism need to be clarified.

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Benjamin Bondue obtained his MD degree in 2004 and defended his PhD thesis in 2010. He is studying the role of the chemerin/ChemR23 system in lung inflammatory diseases. He is presently working in the Pneumology Department of the Erasme Hospital in Brussels.

Valérie Wittamer obtained her Ph.D. from the Free University of Brussels in 2004. Her research was focused on the characterization of the orphan GPCR ChemR23. She was awarded the Belgium Galien Prize of Pharmacology in 2006 for this work. She is presently postdoctoral fellow at the University of California at San Diego, studying the ontogeny of the immune system.

Marc Parmentier is director of the Institute of Interdisciplinary Research of the Free University of Brussels (ULB) Medical School. He obtained his MD from ULB in 1981, and his PhD in 1990. His group is dedicated to the characterization of new G protein-coupled receptors, particularly in the frame of the control of immune responses.