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Invited Review

Chemerin: A comprehensive review elucidating the need for cardiovascular research

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ABSTRACT

When chemerin was discovered in 1997, it was relegated to being a protein associated with the normal skin function contrasting the setting of psoriasis. However, with the discovery of multiple receptors for the chemerin protein and a vast collection of associations with various pathologies, chemerin has global influence capable of regulating chemotactic, adipokine, autocrine/paracrine, adipogenic, angiogenic, and reproductive functions. These individual abilities of chemerin are important for understanding its basic pharmacology and physiology, but application of these principles to human pathology relies on the ability of scientists and physicians to view this protein from a much wider, all-encompassing angle. A global participant in the action of chemerin is the cardiovascular system (CVS). Although the CVS may not have as many direct interactions (*e.g.* smooth muscle in endothelium) with chemerin as it does indirect (*e.g.* chemerin activation in the lumen by proteases), our basic understanding of the CVS and its relation to chemerin is necessary to form a proper grasp of its individual actions and make the applications to pathology. This review provides a fundamental, yet comprehensive review of chemerin that inherently identifies the CVS as a necessary link between chemerin and its associated pathologies, but also calls for basic cardiovascular research as the solution to this chasm between knowledge and application.

Contents

Abbreviations: AP-4, adaptor protein-4 complex; BMI, body mass index; CRP, C-reactive protein; CPB, carboxypeptidase B; CPN, carboxypeptidase N; CVS, cardiovascular system; C/EBP, CCAAT/enhancer binding protein; CCL, CC chemokine ligands; CSF, cerebrospinal fluid; ChemR23, chemerin receptor 23; CMKRL3, chemoattractant receptor-like 3; CCRL2, chemokine (CC motif) receptor-like 2; CMKLR1, chemokine-like receptor 1; DC, dendritic cell; DEZ, actual name; EDIL3, discoidin I-like domains 3; ERK1/2, extracellular signal-regulated kinase 1 and 2; GPR1, G protein-coupled receptor 1; GATA, nucleotide sequence; GLUT4, glucose transporter type 4; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment for insulin resistance; HCR, human chemokine receptor; HIV, human immunodeficiency virus; IGF1, Insulin-like Growth Factor 1; ICAM-1, intercellular adhesion molecule 1; IL-1β, Interleukin 1β; IL-6, Interleukin 6; IL-12, Interleukin 12; KLK7, Kallikrein 7; LPS, lipopolysaccharide; LDL, low-density lipoprotein; MMP, Matrix Metalloproteinase; MAPK, mitogen-activated protein kinase; MCP, monocyte chemotactic protein; MafA, musculoaponeurotic fibrosarcoma oncogene homolog A; mDC, myeloid dendritic cell; NK, natural killer cell; NAFLD, non-alcoholic fatty liver disease; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; OM, omental fat; pDC, plasmacytoid dendritic cell; Akt, protein kinase B; PKC, protein kinase C; RvE1, resolvin E1; RARRES2, retinoic acid receptor responder gene 2; RA, rheumatoid arthritis; SIV, simian immunodeficiency virus; SP-1, specificity protein-1; SCCOT, squamous cell carcinoma of the tongue; SspB, staphopain B; SC, subcutaneous fat (subscapular fat is also referenced in the text but is not referred to by "SC"); TIG2, tazarotene-induced gene 2; TNFα, tumor necrosis factor α; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; WAT, white adipose tissue.

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1. Introduction

Although the fields of medical research tend to be divided into basic, translational, and epidemiology, the communication and interplay between these three fields is of greatest importance in the unearthing and analysis of new drugs and their functions. Chemerin is a protein that emerged in 1997 [1] but due to a lack of these essential exchanges, has largely failed to produce useful medical applications. The epidemiology and associations between the protein and certain disorders is being investigated in great depth, but without knowledge of its mechanisms the epidemiology argues correlative conclusions without finding causative ones.

The discovery of chemerin (as tazarotene-induced gene 2, TIG2; also known as retinoic acid receptor responder gene 2, RARRES2) was in the context of psoriasis and hypothesized to be involved in cell–cell or cell–extracellular matrix interactions [1]. However, our knowledge of its receptors is just as important as the investigation of chemerin itself. G protein-coupled receptor 1 (GPR1) was first described in 1994 in the human hippocampus [2] but was not linked to chemerin until 2007 [3].

As mentioned above, CMKLR1 is also a receptor associated with chemerin and was next to be discovered in 1996 [4] followed by the chemerin receptor 23 (ChemR23) in 1998 [5]. Coincidentally, these separately described receptors are one in the same. Although it is unclear when the scientific community came to this realization, Zabelet al. [6] seemed to be acutely aware of this situation when they pointed this out in 2004. ChemR23 was linked to chemerin in 2003 [7,8]. The mouse ortholog of ChemR23 is also known as DEZ (named in 1997) [9] and a rat ortholog was once named CMKRL3 [10].

The last receptor to be associated with chemerin is chemokine (CC motif) receptor-like 2 (CCRL2) which was first discovered in the human in 1998 (then named human chemokine receptor, HCR) [11]. The link to chemerin was not made until 2008 when Zabel et al. [12] investigated the mechanisms of the receptor.

Chemerin and these receptors can be found throughout the human body and the evidence seems to point toward it playing a multifunctional role as a chemokine, adipokine, and possibly a growth factor. When thinking about inflammation, it seems to have connections to all three of these areas but centers both passively (using the system for transport) and actively (having an effect on the endothelium or smooth muscle) around the cardiovascular system. The field of basic research currently has strong support for the connections between chemerin and its respective specific functions (relating chemerin as a chemokine to immune cells or as an adipokine to adipose cells), but lacks the next step in its connection to the cardiovascular system.

2. Biochemistry

2.1. Sequencing: chemerin protein and receptors

When chemerin and many of its receptors were discovered, amino acid sequencing was quickly performed on chemerin because the biochemistry of the protein offered an identification of the new receptor or ligand as well as insights to its possible actions. Upon the cloning of the cDNA analog of chemerin (TIG2), the 830 bp unit was found to code for a 164 amino acid sequence. At the N-terminus of the sequence was a hydrophobic residue that led researchers to believe chemerin was membrane-associated [1]. Wittamer revealed a 20 amino acid signal peptide and a resulting 143 amino acid sequence which is released from the cell. More importantly, she found that in active chemerin, the carboxyl-terminal end of the eighth peptide was missing six of its predicted amino acids. These missing amino acids led to the proposal that they were lost in proteolytic processing and created the active protein (about 137 amino acids) known as chemerin (see Fig. 1) [8].

Initial processing of the ChemR23 gene revealed it to be closer related to chemoattractant receptors (*e.g.* anaphylatoxin C3a and C5a receptors) rather than CC or CXC chemokine receptors. It was also discovered that the receptor did not contain the extra cysteine residues that normally link the N-terminus with the extracellular loop, a common characteristic of chemokine receptors, therefore setting it apart. The mouse receptor DEZ was also found to contain 80.3% homology and determined to be the mouse counterpart of human ChemR23 [5] with similar methods of regulation [13].

Discovery and sequencing of the GPR1 revealed a close relationship with the G protein-coupled receptor family. There was also a high level of homology between the rat and human analogs (80%) [2]. Thanks to the sequencing and publishing of these data, the GPR1 was shown to have significant homology with the ChemR23 receptor and was linked to chemerin [3].

CCRL2 contains a reading frame with a predicted 345 amino acids. Because of its similarity to other human chemokine receptors it was first named human chemokine receptor (HCR) [11]. Just before its association with chemerin, scientists discovered that CCRL2 had an unusual DRYLAIV motif and postulated it may cause CCRL2 to be a silent receptor capable of binding ligands but not transducing a signal. The function of this receptor is to present