A novel chemerin receptor 1 (Chemerin$_1$) takes part in the immune response of cobia (Rachycentron canadum)

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**ABSTRACT**

Chemerin receptor 1 (Chemerin$_1$) plays a critical role in innate and adaptive immune systems. In this study, a cobia (Rachycentron canadum) Chemerin$_1$ was identified, and its molecular characterization and expression patterns were analyzed. Multiple sequence alignment revealed that the RcChemerin$_1$ possessed a typical dynein regulatory complex (DRC) motif. There was also a potential N-glycosylation site in the extracellular regions of the N-terminus and intracellular loops (ICL) 1 region. Phylogenetic analysis demonstrated that the RcChemerin$_1$ was clustered together with homologous proteins from other fish species. RcChemerin$_1$ was constitutively expressed in a wide range of tissues (especially in immune-related tissues) with different expression levels, which suggests that the RcChemerin$_1$ plays different roles in un-stimulated tissues. RcChemerin$_1$ expression showed up-regulation in the head kidney after Vibrio harveyi challenge. Up-regulation in the head kidney and spleen was also observed after polyinosinic-polyribidylic acid (poly I: C) challenge, which suggests that RcChemerin$_1$ may play vital roles during bacterial and viral infection. The differential responses of immune organs to bacteria and poly I: C imply the differences in defense mechanisms against viruses and bacteria.

1. Introduction

Chemerin is a kind of protein generally secreted from white adipose tissues, mainly as a chemoattractant protein directing immune cells toward sites of inflammation, involving in both adaptive and innate immunity [1–2]. The functions have been attributed to the activation of the G protein-coupled receptor. To date, three G-protein-coupled receptors ([chemokine-like receptor 1 (CMKLR1), general receptor for phosphoinositides-1 (GRP1), and chemokine receptor like 2 (CCRL2)] have been identified that bind to chemerin [3]. Most known chemerin functions have been attributed to activation of the CMKLR1 (also known as ChemR23). In 2018, CMKLR1 was officially renamed to chemerin receptor 1 (abbreviated as Chemerin$_1$) by the International Union of Basic and Clinical Pharmacology CII [4]. Chemerin$_1$ expression has been found in various leukocyte populations and several other cell types, such as adipocytes, chondrocytes, skeletal muscle cells, and endothelial cells [5–6]. Chemerin$_1$ has two ligands: the eicosapentaenoic acid-derived lipid mediator resolvins E1 (RvE1) and the peptide chemerin. RvE1 is an oxygenated product of the essential fatty acid eicosapentaenoic acid, and can promote the resolution of inflammation-inducing macrophage phagocytosis of apoptotic neutrophils [7]. Chemerin is a 14-kDa protein secreted as prochemerin, an inactive form of chemerin, and is activated when cleaved at its C-terminus by serine proteases of the coagulation, fibrinolytic or inflammatory cascades [8].

Chemerin$_1$ is expressed on several leukocytes, such as immature DCs, macrophages, monocytes, and CD4$^+$ T lymphocytes [9]. Its activation can lead to up-regulation of the phosphatidylinositol 3-kinase/protein kinase B (Akt) signalling pathway and down-regulation of nuclear factor-kappa B (NF-kB) [9–10]. Chemerin$_1$ can induce cell migration toward the site of inflammation when it binds to the active chemerin [3, 11]. In-vivo study in the Chemerin$_1$-deficient mice showed that the expression level of some cytokines were reduced even under the lipo-polyaccharide (LPS) induction, including interleukin (IL)-6, interleukin-1 beta (IL-1β), chemokine ligand 1 (CXCL1) and tumor necrosis factor (TNF) [12]. Chemerin$_1$ was reported as an adipokine regulating adipogenesis and adipocyte metabolism, and showed marked effects on the development of several disease states, including chronic

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hepatitis C, cardiovascular disease, cancer, and obesity [13-15], which indicates that Chemerin is a multi-functional receptor.

In contrast to many Chemerin-related studies in mammals, little work has been done on this receptor in fish. Current studies mainly focus on the classic chemokine receptors of fish, but a few have looked at the atypical chemokine receptors. Cobia (Rachycentron canadum) is an important economic fish species cultivated in China. However, there are no effective means for the controlling infections in cobia the immune systems in this fish species remain unknown. In this study, a full-length complementary DNA (cDNA) of Chemerin (designated RcChemerin) was cloned from cobia. The messenger RNA (mRNA) expression profiles of this gene were examined in the healthy and challenged specimens, and its role in immune response was then analyzed. This study was done intended to broaden our knowledge of Chemerin in fish.

2. Materials and methods

2.1. Fish collection and RNA extraction

Healthy cobia with an average body weight of 100 g were purchased from a fish farm in Xincun, Hainan Province, China, and kept in 1000-L tanks of aerated sand filtered seawater (salinity 32 ± 1‰, pH 7.4 ± 0.4) at 30 ± 1 °C. All fish were acclimatized for 2 weeks prior to experiments. Blood was collected from anesthetized (tricaine methanesulfonate, MS-222, Sigma, St. Louis, MO, USA) fish by cutting the tail. The blood cells were separated in two times the volume of anticoagulant solution (0.48% citric acid, 1.32% sodium citrate, and 1.47% glucose) by centrifugation at 800 g for 5 min at 4 °C and were stored in RNAlater (Ambion, Austin, TX, USA) immediately. Heart, brain, mid-gut, stomach, gill, blood, spleen, liver, skin, head kidney, trunk kidney, and muscle were dissected out and stored in RNAlater at -20 °C for RNA extraction. Each tissue was obtained from three randomly selected cobia.

Total RNA was isolated using Trizol reagent (Invitrogen, Waltham, MA, USA) following the manufacturer’s protocol. Total RNA was incubated with RNase-free DNase I (Promega, Madison, Wisconsin, USA) to remove any contaminating genomic DNA (gDNA). First-strand cDNA was synthesized from total RNA by M-MLV reverse transcriptase (Promega, Madison, Wisconsin, USA), following the manufacturer’s protocol with oligo (dT) primer-adaptor primer (Table 1).

2.2. Selection of a novel partial Chemerin1 sequence

The cDNA library was constructed earlier with the mixed head kidney and spleen tissues of cobia following vaccination against Vibrio harveyi, Proteus vulgaris and Streptococcus sp. [16], Basic Local Alignment Search Tool (BLAST) analysis revealed that an EST was similar to the fish CMKL1 gene. The EST was selected for further cloning of the novel chemerin receptor 1 gene of cobia.

2.3. Cloning full-length cDNAs for RcChemerin1

Based on the identified EST sequence, specific primers (Table 1) were designed to clone the full-length cDNA sequences by the rapid amplification of cDNA ends (RACE) approach with spleen cDNA as a template. For 3' RACE, the polymerase chain reaction (PCR) was done by semi-nested PCR with forward primers (Ch1-F1 and Ch1-F2), and reverse primer adaptor (Table 1). For 5' RACE, the first-strand cDNA was tagged with poly(C) at the 5’ end using terminal deoxynucleotidyl transferase (Takara, Shiga, Japan). PCR was done by semi-nested PCR with forward primer oligo-dG and reverse primers (Ch1-R1 and Ch1-R2 for RcChemerin1; Table 1). Cycling parameters for RACE consisted of an initial denaturation period of 3 min at 94 °C, followed by 35 cycles of 45 s at 94 °C, 45 s at 60 °C, 1 min at 72 °C and 72 °C for 10 min. The PCR products were purified with a Qiagen Gel Extraction Kit (Qiagen, Hilden, Germany), ligated with PMD18-T vector (Takara, Shiga, Japan), transformed into Escherichia coli TOP10 (Invitrogen, Waltham, MA, USA) and sequenced (BGI, Shenzhen, China).

2.4. Sequence analysis

Based on the full-length cDNA sequence of RcChemerin1, the nucleotide and deduced amino acid sequences were analyzed using BLAST at the National Center for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov/blast/) and edited with DNASTAR 5.0 software. Protein analysis was performed using ExPaSy online tools (http://us.expasy.org/tools). The transmembrane helices were predicted according to TMHMM (http://www.cbs.dtu.dk/services/TMHMM-2.0/). Multiple sequence alignment was done with the ClustalW2 program (http://www.ebi.ac.uk/Tools/msa/clustalw2/). Prediction of N-linked glycosylation sites was performed using NetNGlyc 1.0 [17], while tyrosine sulfation sites were predicted using Sulfinator [18]. The multiple alignment was produced using ClustalW, and conserved amino acids were shaded using BOXSHADE (version 3.21). An unrooted phylogenetic tree was constructed by the neighbor-joining method with MEGA 5 software. Confidence calculation was done by bootstrapping 1000 replications.

2.5. Immune challenge

To determine the effects of immune response on RcChemerin1 expression, a total of 90 acclimatized fish were randomly divided into three groups: an intraperitoneal (IP) injection of 0.2 mL of sterile phosphate-buffered saline (PBS) alone (control group), IP injection of 0.2 mL of 10 mg/mL polyinosinic polycytidylic acid (poly I: C) Sigma, St. Louis, MO, USA) dissoluted in PBS (poly I : C group), and IP injection of 0.2 mL of formalin-inactivated V. harveyi [1.0 × 10^8 colony forming unit (cfu)/mL, bacterial vaccine group]. Bacterial antigen preparation, fish rearing, IP injection, and tissue sampling were done as described previously [19]. The head kidney and spleen tissues from three individuals in all groups were collected at 0, 3, 6, 12, 24, 48, and 72 h post-injection. All samples were placed in 1.5 mL tubes containing RNAlater at -20 °C for RNA extraction.

2.6. Reverse transcription-quantitative polymerase chain reaction (RT-qPCR) analysis of RcChemerin1 expression

Expression levels of RcChemerin1 in different tissues of non-stimulated cobia and the head kidney and spleen tissues after immune challenge were identified by RT-qPCR in a Mastercycler ep realplex Real-time PCR system (Eppendorf, Hamburg, Germany) with a Platinum SYBR Green qPCR SuperMix-UDG Kit (Invitrogen, Waltham, MA, USA). The housekeeping gene, β-actin, was used as an internal control for cDNA normalization. Gene-specific primers (Table 1), β-actin F/R for β-actin and Ch1-qF/qR for RcChemerin1 were used to amplify specific fragments. The RT-qPCR amplifications were done in a total volume of

| Primer name | Nucleotide sequence (5'–3') | Purpose | Gene |
|-------------|-----------------------------|---------|------|
| Oligo-dG    | GGGGGSGGGGGGAAGGGG        | 5'      | RACE  |
| Oligo-dT/adaptor | GGGCGGGCGACTGACCT        | 3'      | RACE  |
| adaptor     | GGGCGGGCGACTGACCT        |         |      |
| Ch1-F1      | AGGAGCTTGGCAGGATGTG        | 3'      | RACE  |
| Ch1-F2      | CCTCAACCACCTGCTAGT        | 3'      | nested |
| Ch1-R1      | CAGGCGGATAGAATGTTG        | 5'      | RACE  |
| Ch1-R2      | TGGACCACTATATAGGTTG        | 5'      | nested |
| Ch1-qF      | GCACAGAAGCAGCGAAGG        | RT-qPCR | Chemerin1 |
| Ch1-qR      | AGGAGCTTGGCAGGATGTG        | RT-qPCR | Chemerin1 |
| β-actin F   | AGGGAATTTGTCGGTGGG        | RT-qPCR | β-actin |
| β-actin R   | AGGGGTGGTTGCGGTCCT        | RT-qPCR | β-actin |
20 μL containing 10 μL of 2× Supermix, 1 μL of cDNA, 1 μL of forward or reverse primer, and 7 μL of PCR-grade water. PCR conditions were as follows: 50 °C for 2 min, 95 °C for 2 min, 40 cycles of 95 °C for 15 s, and 60 °C for 30 s. After the PCR program, the data were analyzed with Mastercycler ep realplex software. Melting curve analysis of amplification products was done at the end of each PCR reaction to confirm that only one PCR product was amplified and detected. Samples were run in triplicate, and the comparative Ct method was used to analyze the expression level of RcChemerin1. The expression levels were calculated by the $2^{-\Delta\Delta Ct}$ method [20]. Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) software (version 19.0). Data were expressed as the mean ± standard error (SE). Statistical significance was determined by one-way analysis of variance (ANOVA). In all cases, significance was set at $P < 0.05$. 

Fig. 1. Nucleotides and the deduced amino acids sequences of RcChemerin1. The start codon (ATG) and the stop codon (TAG) are marked in boxes. The polyadenylation signal (AATAAA) and two ATTTA motifs are indicated in red and green, respectively. The translation transmembrane domains are indicated in blue, and the conserved DRC motif is underlined with a red dotted line.
3. Results and Discussion

3.1. Characteristics of RcChemerin1

Based on the EST in the cDNA library of cobia, the full-length cDNA sequence of RcChemerin1 was obtained. The full-length cDNA of RcChemerin1 (GenBank accession number: KT748875) contained an ORF of 1038 bp encoding 345 amino acids flanked by 87 bp of 5′ UTR and 1096 bp of 3′ UTR with a single polyadenylation site (2167AATTTA2172) and two ATTTA motifs (Fig. 1). The RNA instability motifs (ATTTA) play a role in post-transcriptional regulation [21]. The putative Mw of RcChemerin1 was 39.57 kDa, and pi was 9.10. Seven transmembrane (TM) regions, including an extracellular amino-terminal domain (N-terminal), three extracellular loops (ECL), three intracellular loops (ICL), and a cytoplasmic carboxyl-terminal (C-terminal) were predicted in RcChemerin1 (Fig. 2). Potential N-glycosylation sites were found in RcChemerin1 at Asn12 and Asn73. Five conserved cysteine residues were identified in RcChemerin1, including ECL-1, ECL-2, TM-5, TM-6, and ICL-2. A characteristically conserved dynein regulatory complex (DRC) motif (134DRC136) was present in ICL-2. Fish CMKLR1 amino acid sequences were aligned (Fig. 3). Vertebrate CMKLR1 molecules were well conserved in the seven TM domains, with sequences possessing two cysteine residues forming two disulphide bonds from ECL1 to ECL2 region, which is fully conserved for this receptor family. RcChemerin1 shared a highly conserved DRC motif at the beginning of the ICL2 region as other CMKLR1s instead of the Asp-Arg-Tyr (DRY) motif in the classical chemokine receptors, which is involved in coupling to G-proteins [8,13]. The DRY motif, which is important for interacting with the G-protein for signal transduction, is located right after the third transmembrane domain in most fish chemokine receptors [22–23]. The RcChemerin1 is a DRC motif with its human orthologues suggesting unique intracellular signaling and is a known modification of the G-protein–binding motif that does not affect signaling [24]. There are conserved N-glycosylation and tyrosine O-sulfation sites at the N-termini of the mammalian sequences. These are not conserved in the fish sequences, although fish CMKLR1 sequences have several putative residues that do not align with the mammalian ones or each other (Fig. 3). N-glycosylation sites and tyrosine O-sulfation sites at the N-terminal of chemokine receptors are important for activation or their functions [25]. These sites are also important for RcChemerin1 ligand binding, internalization, and scavenging.

3.2. Sequence identity and phylogenetic analysis

Fish CMKLR1 shared high deduced amino acid (aa) sequence identities with each other (59.59–74.13%) and showed low aa identities than other vertebrate CMKLR1 molecules (39.16–44.24%) (Table 2). In accordance with the standard International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification rules of nomenclature, the CMKLR1 receptor was renamed the chemerin receptor in 2013 [26]. As the GPR1 is a second signaling chemerin receptor at the protein level, CMKLR1 is referred to as chemerin receptor 1, and GPR1 is referred to as chemerin receptor 2 [4]. A phylogenetic tree (Fig. 4) constructed based on the aa sequences of the CMKLR1 sequences with the other known GPR1s, human chemoattractant receptor, and chemokine receptor sequences showed that all the CMKLR1 molecules formed a chemerin receptor 1 clade, which was different from chemerin receptor 2 clade containing all the vertebrate GPR1s, human chemoattractant receptors, and chemokine receptors clades. In the chemerin receptor 1, lineage-specific groups with over 99% bootstrap supports (i.e., mammals, birds, reptiles, amphibians, and fish) were observed. Therefore, the fish CMKLR1 molecules formed the corresponding subclade. RcChemerin1 was genetically closest to the common ancestor large yellow croaker (Larimichthys crocea), tongue sole (Cynoglossus semilaevis), and Nile tilapia (Oreochromis niloticus) CMKLR1, which was similar to that of the amino acid identity analysis. These results demonstrated that the same ancestral gene gradually evolved into the chemerin receptor genes in fish and other vertebrates.

3.3. Tissue distribution of expression of the RcChemerin1

In the present study, the relative expression levels of the RcChemerin1 were examined in twelve tissues from healthy cobia by RT-qPCR. The expression of the receptor was detected in all tissues. However, these transcripts ranged across different types of tissues, suggesting that the RcChemerin1 might play an important role in maintaining the homeostasis of cobia. The results showed that the RcChemerin1 mRNA expression was relatively higher in blood, gill, liver, spleen, trunk kidney, and

Fig. 2. Diagrammatic representation of the domain structure and the topology of transmembrane regions in RcChemerin1. The N-terminal, seven-transmembrane domains (TM1–7), three extracellular loops (ECL1–3), three intracellular loops (ICL1–3) and C-terminal are shown. The DRC motif in the ICL2 region is also indicated. Putative cysteine residues (C) involved in disulfide bonding are shown with a black dotted line. Potential N-glycosylation sites are marked in red shaded boxes.
muscle, while low mRNA expression was detected in skin, heart, stomach, brain, head kidney, and mid-gut (Fig. 5). The high expression levels of RecChemerin in the blood, gill, liver, and spleen are the major sites the recognition and elimination of bacterial pathogens occurs, which suggests its functional roles in regulating leukocytes.

However, the CMKLR expression levels of Atlantic salmon (Salmo salar) [27] and rainbow trout (Oncorhynchus mykiss) [28] were detected at a relatively higher level in the head kidney and were observed at a lower level in gill, muscle, and liver, which is inconsistent with the results in cobia. The CMKLR1 is highly expressed in mammalian adipose tissues and has been proved to mediate chemerin’s actions in insulin signaling and adipocyte metabolism [29-30]. In this study, the high expression of RecChemerin was also observed in the liver and muscle associated with adipose tissue, reflecting the roles of the protein in adipogenesis and energy metabolism. Tissue-specific expression patterns of Chemerin were studied in many mammals, which revealed the different expression patterns. For example, the CMKLR1 is highly expressed in the spleen, lymph nodes, and skin in humans, while low
expression was observed in those tissues in mice [31–33]. The varying tissue expression patterns of the Chemerin gene might be due to differences in the fish species or physiological status.

3.4. Expression analysis of RcChemerin1 after challenge with V. harveyi and poly I: C

Chemerin is regulated by several cytokines and pathogen-associated molecular patterns (PAMPs), and its activation leads to up-regulation of the phosphatidylinositol 3-kinase/Akt signaling pathway and down-regulation of NF-κB [9–10]. Previous studies demonstrated that expression levels of some pro-inflammatory cytokines, e.g., IL-1β, IL-8, TNF-α, and chemokine CC (CCR3) [36–37], and chemokine receptor, CCR9 [38–39], were up-regulated in immune organs of cobia following bacterial or poly I: C challenge. V. harveyi is a gram-negative, rod-shaped, facultatively anaerobic, and non-spore forming bacterial species, which can infect cobia and other fish species [34], and poly I: C is a synthetic double-stranded RNA (dsRNA), which can mimic the viral infection [35]. Hence, we examined the mRNA levels of RcChemerin in vivo using head kidney and spleen tissue to analyze their expression patterns in response to Aeromonas veronii and poly I: C challenge.

After V. harveyi challenge, the RcChemerin expression level was significantly increased at 3 h and reached its peak level at 6 h in the head kidney. Subsequently, the expression decreased gradually to the hardpan at 48 h and then sharply increased at 72 h (Fig. 6A). However, in the spleen (Fig. 6B), down-regulated RcChemerin expression was observed at 24 h but had no impact at other time points. The findings observed in this study are consistent with the previous studies that examined the RcCCR3 and RcCCR9 of cobia post V. harveyi infection, which were the key chemokine receptors mediating the local inflammatory responses. The up-regulation of RcChemerin, RcCCR3, and RcCCR9 in head kidney post V. harveyi infection, implies that more leukocytes migrate to these tissues against the bacteria.

Following poly I: C stimulation, the RcChemerin transcripts in the Table 2

| Different lineages | Species                  | Identities (%) | Accession numbers |
|-------------------|--------------------------|----------------|-------------------|
| Teleosts          | Cynoglossus semilaevis   | 74.13          | XP_008335490      |
|                   | Larimichthys crocea      | 71.81          | KKF32274          |
|                   | Oreochromis niloticus    | 69.41          | XP_005473396      |
|                   | Oncorhynchus mykiss      | 67.54          | CQ62781           |
| Amphibian         | Xenopus tropicalis       | 39.16          | NP_00135487       |
| Reptile           | Alligator mississippiensis | 41.96      | KQ010112          |
| Bird              | Gallus gallus           | 40.24          | NP_001269336      |
| Pan troglodytes   | 44.24                    | JAA05460       |
| Mammalian         | Homo sapiens             | 43.94          | Q99788            |
|                   | Sus scrofa               | 43.87          | NP_001116572      |
|                   | Bos taurus               | 43.21          | NP_001138707      |
|                   | Mus musculus             | 41.82          | EDL19943          |

Fig. 4. Phylogenetic analysis of partial vertebrate chemerin receptor 1 and other chemokine receptors. A neighbor-joining tree was constructed using Mega 5.1 software. Numbers on the lines indicate the percentages of bootstrap values after 1000 replicates. The GenBank accession numbers are listed in Table S1.
head kidney were elevated from 3 to 12 h, then decreased gradually to the hardpan in 48 h, and recovered to their normal levels (Fig. 6C). No significant difference was observed in the expression of \( \text{RcChemerin}_1 \) in the spleen from 0 to 6 h, but the expression significantly increased and reached its peak level at 12 h. Subsequently, the expression level fluctuated from 24 to 72 h (Fig. 6D). The up-regulation of \( \text{RcChemerin}_1 \)
expression implied that this receptor could be involved in the viral-induced mobilization of head kidney and spleen cells to primary sites of viral encounter. In addition, ReChemerin1 had a faster antivirus response in the head kidney than the spleen. The ReChemerin1 expression was up-regulated in immune organs, suggesting its role in regulating the inflammatory response during bacterial and viral infection.

4. Conclusions

In conclusion, a Chemerin gene was identified from cobia. The putative amino acid sequence contains the conserved structural characteristic of the Chemerin receptor. According to phylogenetic analysis and sequence alignment, ReChemerin1 is more closely related and has a higher sequence identity to homologs from other fish. ReChemerin1 expression was detected in all tested tissues, and its expression could be regulated by V. harveyi and poly I:C.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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