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Authors: Kusakabe, Takehiro, and Suzuki, Norio

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[REVIEW]

The Guanylyl Cyclase Family in Medaka Fish *Oryzias latipes*

Takehiro Kusakabe and Norio Suzuki*

Division of Biological Sciences, Graduate School of Science, Hokkaido University, Sapporo 060-0810, Japan

ABSTRACT—Guanylyl cyclase (GC) converts GTP into cGMP, an intracellular second messenger involved in a wide variety of cellular, developmental, and neuronal processes. Medaka fish, a small teleost, *Oryzias latipes* has been used to study organization and transcriptional regulation of the guanylyl cyclase gene family. Medaka fish expresses virtually all types of GCs found in mammals. Eight membrane GCs (OlGC1-7 and OlGC-R2) have been identified in medaka fish. OlGC1, OlGC2, and OlGC7 belong to the natriuretic peptide receptor subfamily. OlGC6 is a homologue of the mammalian GC-C, an enterotoxin/guanylin receptor, expressed predominantly in the intestine. OlGC3, OlGC4, OlGC5, and OlGC-R2 are members of the sensory organ-specific GC subfamily where they are differentially expressed in rods and cones of the retina and in the pineal organ. Complete genomic DNA sequences have been determined for the *OlGC1* and *OlGC6* genes. Their exon-intron organization is highly conserved between fish and mammals. The medaka fish genome also contains genes encoding α and β subunits of the cytoplasmic form of GC (soluble GC), which is activated by nitric oxide. The two subunit genes are closely linked in tandem in the order of α and β. Function of *cis*-regulatory regions of medaka fish GC genes have been investigated in transgenic medaka fish embryos and in mammalian cell lines. The upstream region of the α subunit gene of soluble GC appears to regulate expression of both α and β subunit genes, suggesting a mechanism of coordinated transcription of the two subunit genes. The upstream regions sufficient for the tissue-specific expression of sensory organ GCs also have been determined by transgenic analysis. Readiness for genetics and genetic manipulations in medaka fish would make this small fish a useful experimental system for studying the regulation of gene expression and roles of the guanylyl cyclase family in vertebrates.

INTRODUCTION

Guanylyl cyclase (GC) converts GTP into cGMP, an intracellular second messenger involved in a wide variety of physiological and developmental processes, including fertilization, body fluid homeostasis, smooth muscle relaxation, phototransduction, synaptic plasticity, and neuronal development (Drewett and Garbers, 1994; Suzuki, 1995; Truman *et al*., 1996; Pugh *et al*., 1997; Gibbs and Truman, 1998). There are two forms of GCs, those found on the plasma membrane (membrane GC) and those found in the cytoplasm (soluble GC) (Fig. 1). Primary structure of the membrane GC was first determined for the egg peptide receptor in sea urchin spermatozoa (Singh *et al*., 1988). Since then, various membrane GC isoforms have been identified in vertebrates and invertebrates . Some of these membrane GCs are cell-surface receptors for peptides, such as natriuretic peptides and heat-stable enterotoxins, but others remain orphan receptors (Drewett and Garbers, 1994; Wedel and Garbers, 1997). The soluble GC is a heme-containing heterodimeric protein that is activated by binding of nitric oxide (NO) (Kamisaki *et al*., 1986; Gerzer *et al*., 1981; Drewett and Garbers, 1994).

Medaka fish *Oryzias latipes* is a small freshwater teleost with various advantages for developmental and molecular genetic studies (Ozato and Wakamatsu, 1994; Ishikawa *et al*., 1997). Their generation time is short, about 3 months, fertilization occurs externally, and the transparency of eggs facilitates observation and manipulation of embryos. Medaka fish daily produce many eggs and the spawning can be controlled by the use of an artificial light cycle. There are a number of spontaneous and artificially-induced mutants and several inbred strains of medaka fish (Hyodo-Taguchi and Egami, 1985; Ozato and Wakamatsu, 1994; Ishikawa, 1996). A detailed genetic map is also available (Wada *et al*., 1995). The size of the medaka fish genome is about 800 Mbp, half that of zebrafish and one forth of that of human and mouse (Tanaka, 1995). Methods for transgenesis, nuclear transplantation into eggs, and generation of germ-line chimeras have been developed in medaka fish (Wakamatsu *et al*., 1993; Ozato and Wakamatsu, 1994; Niwa *et al*., 1999), and embry-

* Corresponding author: Tel. +81-11-706-4908;
FAX. +81-11-706-4461.
E-mail: norio-s@sci.hokudai.ac.jp

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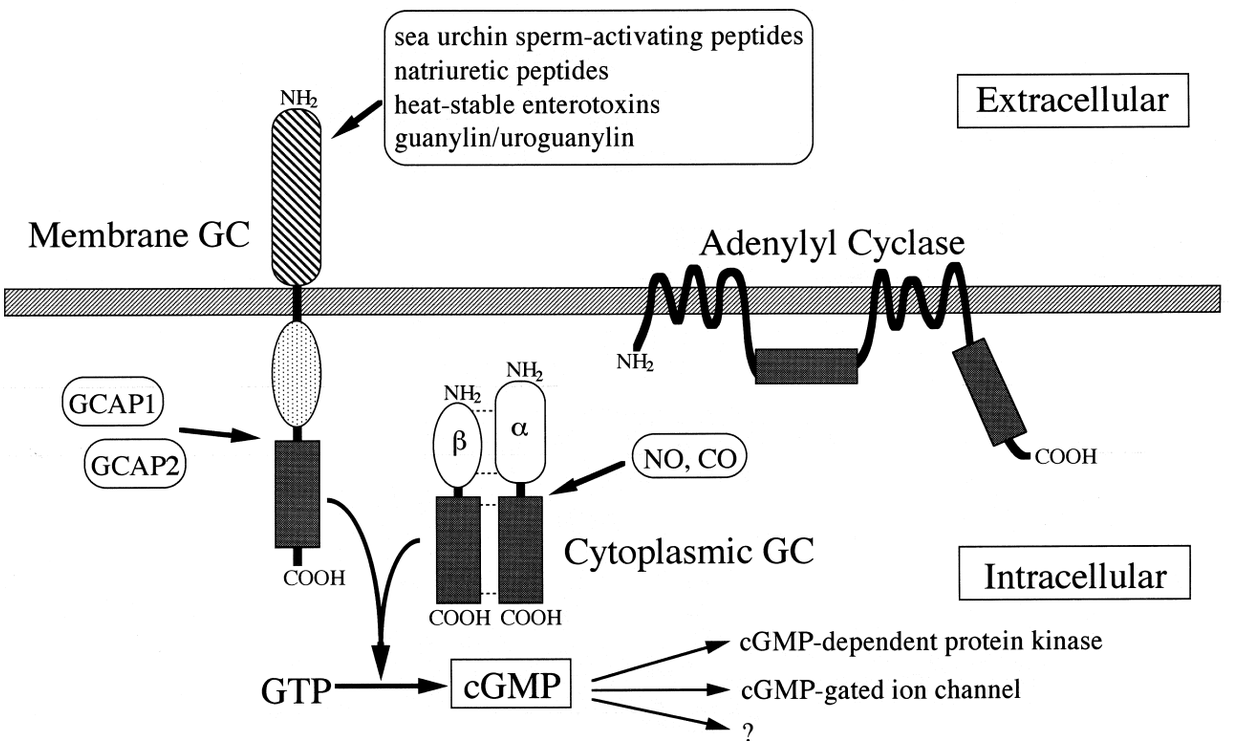

Fig. 1. A schematic diagram illustrating the general structure, activators, and downstream targets of the GCs. The horizontal bar represents the plasma membrane. Structure of the cyclase catalytic domains (shaded boxes) are conserved between GC and adenylyl cyclase. The membrane GC has an intracellular protein kinase homology domain that locates between the transmembrane region and the carboxyl terminal catalytic domain. Membrane GCs are activated by either extracellular ligands or intracellular activating proteins (GCAP1, GCAP2), while heterodimeric cytoplasmic GC (soluble GC) is stimulated by binding of nitric oxide (NO) or carbon monoxide (CO) to a prosthetic heme group. Cyclic GMP (cGMP) produced by GC regulates the activity of cGMP-dependent protein kinase and cyclic nucleotide gated channel.

Fig. 2. Expression of foreign protein or mRNA in medaka fish embryos after microinjection of DNA constructs or synthetic mRNA. (**A**) A 7-day old embryo developed from eggs injected with a promoter-*GFP* fusion construct of the soluble GC α subunit gene *OlGCS-α*$_1$. GFP fluorescence was observed in the brain. (**B**) Whole-mount *in situ* hybridization showing expression of green fluorescent protein (GFP) mRNA in a hatching stage embryo developed from eggs injected with a promoter-*GFP* fusion construct of the medaka fish retinal GC gene *OlGC3*. *GFP* mRNA is expressed in retinal photoreceptor cells. (**C**) A 1-day old embryo developed from eggs injected with synthetic β-galactosidase mRNA. β-Galactosidase activity was observed in cells throughout the embryo.

onic pluripotent cell lines have been established (Wakamatsu *et al.*, 1994; Hong *et al.*, 1996). Transposable elements have been identified in the medaka fish genome and they may be used as a tool for genetic manipulation (Koga *et al.*, 1996). Foreign DNA transfer and expression in medaka fish embryos have been used to investigate transcriptional regulation of tissue-specific genes (Fig. 2A, B) (Mikami *et al.*, 1999; Kusakabe *et al.*, 1999). Exogenous proteins can be expressed in medaka fish embryos by microinjection of synthetic mRNA into eggs (Fig. 2C). Thus medaka fish has been adopted as a model

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Table 1. Guanylyl cyclases identified in medaka fish

Type	Subfamily	Isoform	Mammalian homologues	Reference
Membrane form	Natriuretic peptide receptor	O1GC1	GC-B	Takeda and Suzuki (1999)
		O1GC2	GC-A	Mantoku *et al.* (1999) Yamagami *et al.*, unpublished
		O1GC7	GC-A	Yamagami *et al.*, unpublished
	Enterotoxin/guanylyn receptor	O1GC6	GC-C	Mantoku *et al.* (1999)
	Sensory Organ-specific GC	O1GC3	GC-D, GC-E, GC-F	Seimiya *et al.* (1997)
		O1GC4 (O1GC-R1)	GC-D, GC-E, GC-F	Seimiya *et al.* (1997) Hisatomi *et al.* (1999)
		O1GC5 (O1GC-C)	GC-D, GC-E, GC-F	Seimiya *et al.* (1997) Hisatomi *et al.* (1999)
		O1GC-R2	GC-D, GC-E, GC-F	Hisatomi *et al.* (1999)
Solube form	alpha subunit	O1GCS-α_1	α_1-subunit	Mikami et a. (1998) Mikami *et al.* (1999)
	beta subunit	O1GCS-β_1	β_1-subunit	Mikami *et al.* (1998) Mikami *et al.* (1999)

vertebrate to study organization and transcriptional regulation of the GC gene family. Here we describe recent progress in studies of medaka fish GCs and discuss their potential of future contribution to understanding roles and gene regulation of the GC family in vertebrates.

DIVERSITY OF VERTEBRATE GUANYLYL CYCLASES

Seven isoforms of membrane GC each encoded by a different gene have been identified in mammals (Chinkers *et al.*, 1989; Schulz *et al.*, 1989; Schulz *et al.*, 1990; Fülle *et al.*, 1995; Yang *et al.*, 1995; Schulz *et al.*, 1998). The mammalian genomes also contain multiple genes encoding α and β subunits of soluble GC (Wedel and Garbers, 1997). Analyses of cDNA and genomic DNA clones have shown that medaka fish has virtually all types of GCs found in mammals (Table 1, Fig. 3). Eight membrane GCs and two subunits of soluble GC have been identified in medaka fish (Seimiya *et al.*, 1997; Mikami *et al.*, 1998; Hisatomi *et al.*, 1999; Mantoku *et al.*, 1999; Takeda and Suzuki, 1999; S. Yamagami, K. Suzuki and N. Suzuki, unpublished data). Molecular phylogenetic analyses of various GCs from mammals and medaka fish have shown that vertebrates have three major subfamilies of membrane GCs: (i) natriuretic peptide receptor subfamily, (ii) enterotoxin/guanylin receptor subfamily, and (iii) sensory organ-specific GC subfamily (Fig. 3) (Seimiya *et al.*, 1997).

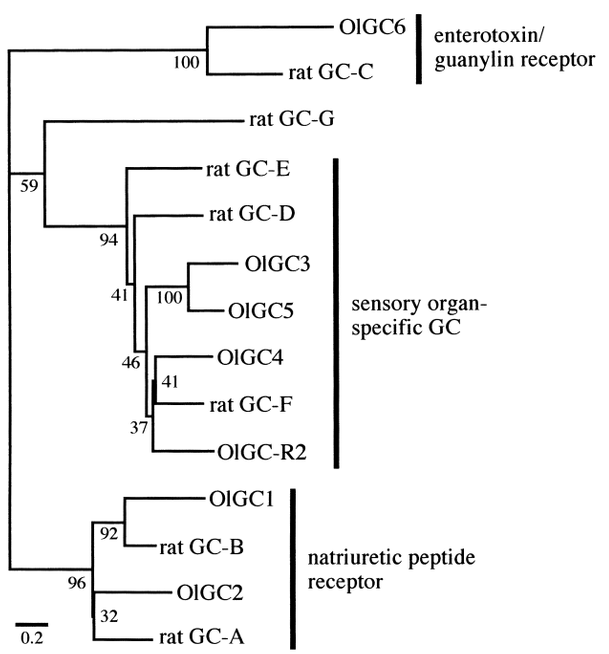

Fig. 3. Molecular phylogenetic analysis of vertebrate membrane GCs. A phylogenetic tree was inferred by the neighbor-joining method (Saitou and Nei, 1987). Branch length is proportional to evolutionary distances. Scale bar indicates an evolutionary distance of 0.2 amino acid substitution per position in the sequence. Numbers represent the percentages of bootstrap pseudoreplications supporting the corresponding node (Felsenstein, 1985). The three major subfamilies are supported by high bootstrap values (94% or more). Accession numbers for GC sequences are: X14773, rat GC-A; M26896, rat GC-B; M55636, rat GC-C; L37203, rat GC-D; L36029, rat GC-E; L36030, rat GC-F; AF024622; rat GC-G; AB004921, OlGC1; AB030274, OlGC2; AB000899, OlGC3; AB000900, OlGC4; AB000901, OlGC5; AB007192, OlGC6.

NATRIURETIC PEPTIDE RECEPTORS

In mammals, two membrane GCs, GC-A and GC-B, are known as receptors for natriuretic peptides (Drewett and Garbers, 1994). GC-A and GC-B homologues are also identified and characterized in the euryhaline eel *Anguilla japonica* (Katafuchi *et al.*, 1994; Kashiwagi *et al.*, 1999). Different types of natriuretic peptides differently activate GC-A and GC-B. Low concentrations of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) stimulate GC-A but not GC-B, while low concentrations of C-type natriuretic peptide (CNP) activate GC-B but not GC-A (Koller *et al.*, 1991). The natriuretic peptide/guanylyl cyclase signaling pathways are thought to be involved in regulation of blood pressure, kidney function, and bone formation (Kishimoto and Garbers, 1997; Yasoda

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et al., 1998). Because the natriuretic peptide receptor GCs are expressed in a wide variety of tissues (Chinkers and Garbers, 1991; Suga *et al*., 1992), they may have other physiological roles yet to be recognized.

OlGC1 is a medaka fish homologue of the mammalian GC-B (Takeda and Suzuki, 1999). Genomic DNA and cDNA clones encoding OlGC1 have been isolated. In Northern blot analysis, 3.9-kb transcripts of *OlGC1* were detected in the eye and brain, but not in the liver and intestine. However, RT-PCR analysis demonstrated the presence of the *OlGC1* transcripts in the brain, liver, kidney, gill, intestine, heart, spleen, testis, and ovary. The *OlGC1* expression was also examined during embryogenesis by RT-PCR. The transcript was first detected at 1 day after fertilization, with the signal becoming more intense as development proceeds.

A complete genomic DNA sequence of 93 kbp for the *OlGC1* gene was determined (Takeda and Suzuki, 1999) (Fig. 4). The *OlGC1* gene comprises 22 exons. The intron positions are highly conserved between *OlGC1* and mammalian *GC-A* and *GC-B* genes (Takeda and Suzuki, 1999; Yamaguchi *et al*., 1990; Takahashi *et al*., 1998; Rehemudula *et al*., 1999). However, the *OlGC1* gene is conspicuous for its huge size, compared with mammalian membrane GC genes. This is mostly due to the large size of introns in the *OlGC1* gene (Fig. 4; Takeda and Suzuki, 1999). *OlGC1* spans approximately 93 kbp, while the sizes of the mammalian *GC-A* and *GC-B* genes are 16–20 kbp. The large size of *OlGC1* is rather paradoxical, because the medaka fish genome (ca. 800 Mbp) is much smaller than that of mammals (Tanaka, 1995). Introns of *OlGC1* contain some sequences found in other regions of the medaka fish genome or in other species (Takeda and Suzuki, 1999): the intron 15 contains *OLR1*, a highly repetitive interspersed sequence found in the medaka fish genome (Naruse *et al*., 1992); the intron 6 contains a truncated version of the retrotransposon *Rex3*, which has been found in the melanoma fish *Xiphophorus* (Volff *et al*., 1999), and a novel repetitive sequence of 564 bp, which shares 96.5% identity with the nucleotide sequence found in the 5' flanking region of the *OlGC6* gene, a medaka fish homologue of the mammalian *GC-C* gene (Mantoku *et al*., 1999).

Two other members of the natriuretic peptide receptor GC subfamily have been identified in medaka fish and designated as OlGC2 and OlGC7 (Mantoku *et al*., 1999; S. Yamagami, K. Suzuki, R. Muramatsu and N. Suzuki, unpublished data). Molecular phylogenetic analyses with the full-length cDNA sequences of *OlGC2* and *OlGC7* have suggested that both are medaka fish homologues of GC-A (S. Yamagami, K. Suzuki and N. Suzuki, unpublished data). Tissue distribution and developmental expression of *OlGC2* and *OlGC7* mRNAs have been examined by RNase protection assay (S. Yamagami and N. Suzuki, unpublished data). The expression patterns of *OlGC2* and *OlGC7* are similar but not identical. The transcripts of both genes are present in various tissues, but they are expressed at higher levels in a different set of tissues. *OlGC2* mRNA is abundant in the gill, kidney and testis, while higher amounts of *OlGC7* transcripts are present in the kidney, brain, ovary, gill than in other tissues. A genomic DNA sequence of the 3' part of the *OlGC2* gene encoding the catalytic domain has been determined (Mantoku *et al*., 1999). The intron positions are highly conserved in the catalytic domain-coding region between *OlGC2* and other membrane GC genes in mammals and medaka fish.

Although ligands for OlGC1, OlGC2, and OlGC7 have not been yet identified, the presence of three natriuretic peptide receptor GCs in medaka fish, while only two appear to exist in mammals, suggests an additional member of the natriuretic peptide family in medaka fish. In this regard, it may be noteworthy to mention that ventricular natriuretic peptide

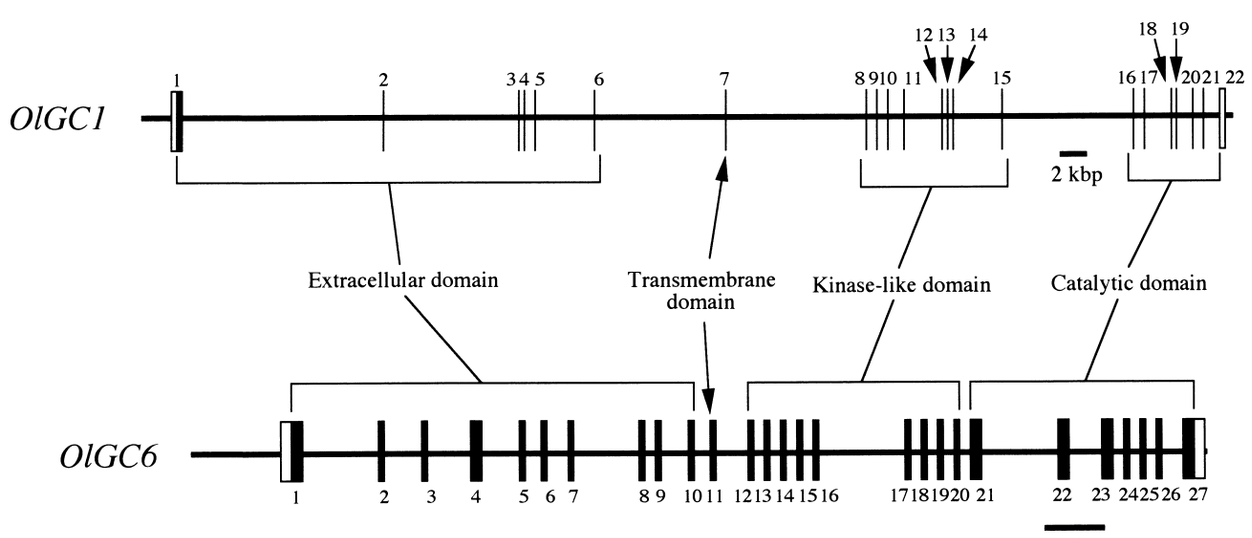

Fig. 4. Structural organization of two medaka fish membrane GC genes, *OlGC1* and *OlGC6* . Open boxes indicate 5' and 3' untranslated regions, while solid boxes represent protein-coding regions. Introns and untranscribed regions are indicated by lines. The scale is different for the two genes as shown by each scale bar.

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(VNP), of which mammalian counterpart is unknown, have been identified in the euryhaline eel (Takei *et al*., 1991). It is also possible that unidentified members of the natriuretic peptide receptor GC subfamily are present in mammals. Future studies on natriuretic peptide receptor GCs in medaka fish would provide important information about roles and diversity of the natriuretic peptide/cGMP signaling pathway in vertebrates.

ENTEROTOXYN/GUANYLYN RECEPTORS

Mammalian GC-C is a receptor for *Escherichia coli* heat-stable enterotoxins (STa) and endogenous peptides, guanylin and uroguanylin (Schulz *et al*., 1990; de Sauvage *et al*., 1991; Singh *et al*., 1991; Currie *et al*., 1992; Hamra *et al*., 1993). GC-C is abundant in mammalian intestine and, depending upon species, in other tissues as well (Schulz *et al*., 1990; Laney *et al*., 1992, 1994; London *et al*., 1997). STa cause an acute secretory diarrhea and their actions are mediated through the activation of GC-C (Schulz *et al*., 1997). Although the guanylin and uroguanylin are thought to regulate the chloride/bicarbonate secretion via GC-C in the intestinal epithelial cells, physiological roles of GC-C still remain unclear, especially in extraintestinal tissues (Schulz *et al*., 1997).

A cDNA clone encoding a GC-C homologue, *OlGC6*, was isolated from a medaka fish intestine cDNA library and the full-length cDNA sequence was obtained by subsequent cloning of 5' RACE products (Mantoku *et al*., 1999). The complete nucleotide sequence of the entire *OlGC6* gene was also determined (Mantoku *et al*., 1999). The *OlGC6* gene is about 16 kbp in length and contains 27 exons (Fig. 4). Northern blot analysis demonstrated that *OlGC6* mRNA is expressed predominantly in the adult intestine (Mantoku *et al*., 1999). The *OlGC6* transcripts were not detected in the eye, brain, and liver on Northern blots, whereas RT-PCR analysis demonstrated the presence of the *OlGC6* transcripts in the kidney, spleen, liver, pancreas, gallbladder, ovary, testis, brain, and eye of adult medaka fish (Mantoku *et al*., 1999). In the RT-PCR, signals in the intestine, pancreas, and gallbladder were stronger than those in the other tissues. These results suggest that a member of the STa/guanylin receptor GC-C subfamily plays previously unrecognized roles in these organs.

The RT-PCR analysis during medaka fish embryogenesis demonstrated that the OlGC*6* transcript is expressed only zygotically and that transcripts are present from 1 day after fertilization (Mantoku *et al*., 1999). The intestinal tissues develop at much later stages. Therefore, in early developmental stages of the embryos, OlGC6 may play a role different from that in the adult intestine. Future studies on OlGC6 would elucidate the role of STa/guanylin receptor GC-C subfamily during development and in extraintestinal tissues.

In order to examine the transcriptional regulation of the *OlGC6* gene, the 5' flanking region of *OlGC6* have been isolated and sequenced (Mantoku *et al*., 1999; M. Nakauchi and N. Suzuki, unpublished data). Transcriptional activity of the 5' flanking sequences has been analyzed in medaka fish embryos and mammalian cell lines using the luciferase gene as the reporter (M. Nakauchi and N. Suzuki, unpublished data). When the *OlGC6* promoter-luciferase fusion genes were transfected into the human intestinal Caco-2 cell line, which express GC-C (Mann *et al*., 1996; Swenson *et al*., 1999), the reporter gene was expressed at a high level (M. Nakauchi and N. Suzuki, unpublished data). Thus, a part of regulatory machinery for the intestinal expression of *GC-C* may be conserved between fish and mammals.

SENSORY ORGAN-SPECIFIC GUANYLYL CYCLASES

Retinal photoreceptors, pineal cells, and olfactory cells of vertebrates express specific isoforms of membrane GC, of which amino acid sequences are closely related to each other in both extracellular and intracellular domains (Shyjan *et al*., 1992; Lowe *et al*., 1995; Yang *et al*., 1995; Fülle *et al*., 1995; Seimiya *et al*., 1997). Rat GC-D is specifically expressed in a subpopulation of olfactory sensory neurons (Fülle *et al*., 1995). Two retina-specific GC cDNAs (*RetGC-1* and *RetGC-2*) have been isolated and characterized from a human retina cDNA library (Shyjan *et al*., 1992; Lowe *et al*., 1995). *RetGC-1* and *RetGC-2* are expressed mostly in the photoreceptor cells and their expression patterns are indistinguishable. Rat *GC-E* and *GC-F* are thought to be orthologues of human *RetGC-1* and *RetGC-2*, respectively (Yang *et al*., 1995). *GC-E* is expressed in the eye and pineal organ, whereas the expression of *GC-F* is confined to the eye. No extracellular ligand has been reported for the sensory organ-specific GCs. Instead, two Ca^{2+} binding proteins GCAP-1 and GCAP-2 were shown to be cytoplasmic activators for the retinal membrane GCs (Lowe *et al*., 1995; Dizhoor *et al*., 1995; Gorczyca *et al*., 1995).

Seimiya *et al.* (1997) isolated cDNA clones for three membrane GCs (OlGC3, OlGC4, OlGC5) from a medaka fish eye cDNA library. Amino acid sequences of OlGC3, OlGC4, and OlGC5 are closely related to mammalian GCs expressed in sensory organs (Seimiya *et al*., 1997). Hisatomi *et al.* (1999) independently isolated cDNA clones for three sensory organ-specific GCs designated as OlGC-R1, OlGC-R2, and OlGC-C from a medaka fish retinal cDNA library. Comparison of nucleotide and deduced amino acid sequences of these cDNAs suggested that OlGC-R1 and OlGC-C correspond to OlGC4 and OlGC5, respectively. OlGC-R2 is distinct from OlGC3, OlGC4, and OlGC5, suggesting that OlGC-R2 is the forth member of the sensory organ GC subfamily in medaka fish. The relative positions of some amino acids, including six cysteine residues, are highly conserved within the extracellular domains among the medaka fish and mammalian sensory organ-specific GCs (Seimiya *et al*., 1997). The conservation of amino acid residues suggests a functional importance of the extracellular domains of the sensory organ-specific GCs, which might interact with unidentified extracellular ligands.

The primary structure of the medaka fish retinal GCs is similar, but each domain of the protein exhibits a different degree of similarity between different GCs (Seimiya *et al*., 1997; Hisatomi *et al*., 1999). The intracellular cyclase catalytic domain is highly conserved, whereas the intracellular protein-kinase and extracellular domains, both of which are

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thought to be important for the regulation of the enzymatic activity, are less conserved, suggesting that activity of these GCs is regulated differently.

In situ hybridization and RT-PCR analyses revealed that the expression patterns are different among *OlGC3*, *OlGC4*, *OlGC5*, and *OlGC-R2* genes. In the embryos, the expression of *OlGC3* and *OlGC5* is restricted to retinal photoreceptor cells, whereas *OlGC4* is expressed in the retinal photoreceptors, pineal organ, and olfactory pits (T. Kusakabe and N. Suzuki, unpublished data). In the adult retina, *OlGC4* and *OlGC-R2* are expressed in rods, while the *OlGC5* transcripts are found in all four types of cone cells (Hisatomi *et al*., 1999). As is in the embryos, *OlGC4* is expressed in the pineal organ of adult medaka fish (Hisatomi *et al*., 1999). Weaker hybridization signal for *OlGC5* was also detected in the adult pineal organ (Hisatomi *et al*., 1999) although the *OlGC5* expression was not detected in the pineal organ of embryos (T. Kusakabe and N. Suzuki, unpublished data). The *OlGC4* expression in the pineal organ begins as early as 4 days after fertilization, and about 2 days before the onset of the retinal expression of *OlGC4* and about 5 days before hatching (T. Kusakabe and N. Suzuki, unpublished data). Thus, the pineal organ may be a major photosensory organ in the embryo, and OlGC4 is probably required for its function. Because the hatching of medaka fish embryos is regulated by light conditions (Schoots *et al*., 1983), the cGMP signaling pathway mediated by OlGC4 might be involved in timing control of hatching. RT-PCR analyses demonstrated that *OlGC3*, *OlGC4*, and *OlGC5* are expressed in some tissues other than the sensory organs (Seimiya *et al*., 1997). The *OlGC3* transcripts were shown to be present in the brain, heart, liver, pancreas, and ovary, while the *OlGC4* mRNA was detected in the liver and *OlGC5* in the heart. RT-PCR also showed that the *OlGC3* and *OlGC4* transcripts are present in unfertilized eggs (Seimiya *et al*., 1997). The expression patterns imply the possible involvement of these GCs in oogenesis, development, and olfaction as well as in phototransduction. Considering the structure of membrane GCs as a cell surface receptor, it is possible that these GCs play a role in cell-cell interactions during development.

The 5' flanking regions of *OlGC3* and *OlGC4* were isolated and sequenced (T. Kusakabe and N. Suzuki, unpublished data). Both genes have an intron in the 5' untranslated region. The transcriptional regulation of *OlGC3* and *OlGC4* has been studied by microinjection of the promoter-GFP fusion constructs into medaka fish embryos (Fig. 2B) (T. Kusakabe and N. Suzuki, unpublished data). The first introns of *OlGC3* and *OlGC4* genes present in the 5' untranslated regions were not essential for gene expression in retinal photoreceptor cells. The upstream regions of 0.4 kbp for *OlGC3* and 1.2 kbp for *OlGC4* were sufficient to drive gene expression in the retinal photoreceptors, although longer upstream regions gave more efficient gene expression. The retinal and olfactory expression of *OlGC4* was reproduced by the reporter gene expression in embryos injected with a *GFP* fusion gene containing a 2.4-kbp upstream region of *OlGC4* (T. Kusakabe and N. Suzuki, unpublished data). Studies on transcriptional regulation of the sensory organ GC genes using transgenic medaka fish embryos will provide important information to understand molecular basis of differentiation and function of photoreceptor cells and olfactory sensory cells.

OTHER MEMBRANE GUANYLYL CYCLASES

Recently, a novel membrane GC, GC-G, has been identified in mammals (Schulz *et al*., 1998). Although the extracellular domain of GC-G shows structural similarity, to some extent, with that of the natriuretic peptide receptor, GC-G is not activated by any known ligands for membrane GCs, including natriuretic peptides and heat-stable enterotoxins (Schulz *et al*., 1998). GC-G is predominantly expressed in the lung, intestine, and skeletal muscle (Schulz *et al*., 1998). The nematode *Caenorhabditis elegans* genome contains at least 29 genes encoding GC (Yu *et al*., 1997). Many of the genes encode orphan receptor membrane GCs and they are expressed in specific sensory neurons (Yu *et al*., 1997). Recently, cDNA fragments encoding membrane GCs that are distinct from any known GC subfamilies have been isolated by PCR from the medaka fish testis (K. Suzuki and N. Suzuki, unpublished data) and the lamprey *Lampetra japonica* (K. Morita, T. Kusakabe, T. Harumi, and N. Suzuki, unpublished data). Together these findings raise the possibility that a large number of membrane GCs, which belong to either known or unrecognized subfamilies, are yet to be discovered in vertebrates. The existence of many orphan receptor GCs in vertebrates also suggests the existence of unidentified extracellular ligands that activate the cellular cGMP signaling pathway.

GENOMIC ORGANIZATION AND EVOLUTION OF MEMBRANE GC GENES

The complete nucleotide sequences of *OlGC1* and *OlGC6* were determined (Takeda and Suzuki, 1999; Mantoku *et al*., 1999). Each of the four functional and structural domains is encoded by a group of exons in these genes (Fig. 4). That is, introns are located at the boundaries between different domains, as reported for mammalian GC genes (Yamaguchi *et al*., 1990; Yang *et al*., 1996; Perrault *et al*., 1996). This conserved feature suggests that "exon-shuffling" events played an important role in the establishment of the basic structure of the ancestral membrane GC genes (Mantoku *et al*., 1999).

The exon-intron organizations of *OlGC1* and *OlGC6* were compared with those of the mammalian membrane GC genes, *GC-A* and *GC-E* (Yamaguchi *et al*., 1990; Yang *et al*., 1996; Mantoku *et al*., 1999; Takeda and Suzuki, 1999). The intron positions are highly conserved in the genomic region encoding the intracellular domain. In the catalytic domain-coding region, the intron positions are identical in the *OlGC6* and *GC-E* genes, and also highly conserved between *OlGC6* and *GC-A*. This conservation of the exon-intron organization in the intracellular-coding regions suggests a common origin of these domains (Mantoku *et al*., 1999). In spite of the divergent primary structure of the extracellular domains, the relative positions of some introns seem to be conserved in the

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extracellular domain-coding regions among the three major subfamilies of membrane GCs. This imply that the extracellular domains of the three different groups of membrane GCs evolved from common ancestor. Cysteine residues are conserved in the extracellular domains of nematode and vertebrate GCs (Yu *et al*., 1997). The conserved intron positions and cysteine residues in the extracellular domain suggest that all membrane GCs originated from a common ancestral protein consisting of extracellular, transmembrane, protein kinase-like, and catalytic domains (Mantoku *et al*., 1999).

THE SOLUBLE GUANYLYL CYCLASE

The soluble GC is a heme-containing heterodimer composed of a and b subunits (Kamisaki *et al*., 1986) and is activated primarily by nitric oxide (NO) (Gerzer *et al*., 1981; Drewett and Garbers, 1994; Garbers *et al*., 1994) and also possibly by carbon monoxide (CO) (Snyder, 1992; Friebe *et al*., 1996) (Fig. 1). The NO/soluble GC signaling pathway is thought to play important roles in smooth muscle relaxation and in neuronal development and function. Soluble GC activated by NO derived from the endothelium induces relaxation of vascular smooth muscle through cGMP dependent protein kinase I (Pfeifer *et al*., 1998). NO affects synaptic plasticity via generation of cGMP in the hippocampus and olfactory bulb in mammals (Haley *et al*., 1992; Zhuo *et al*., 1994; Kendrick *et al*., 1997). Soluble GC localized in the inner segments of photoreceptor cells is activated by NO (Koch *et al*., 1994) and modulates synapses between cone and horizontal cells (Savchenko *et al*., 1997). The NO/cGMP signaling pathway is also expected to participate in synaptogenesis (Truman *et al*., 1996) and synaptic suppression in neuromuscular junctions (Wang *et al*., 1995).

There are at least two α (α_1, α_2) and two β (β_1, β_2) subunits of the soluble GC in mammals (Wedel and Garbers, 1997). Although both α and β subunits possess a catalytic domain homologous to the catalytic domain of membrane GC (Nakane *et al*., 1990), coexpression of both subunits appears to be necessary for the enzyme activity (Harteneck *et al*., 1990; Buechler *et al*., 1991). Therefore, transcriptional regulation of the two subunit genes can be an important mechanism for regulation of the soluble GC activity.

Isolation and characterization of cDNA clones demonstrated that medaka fish has at least one α subunit and one β subunit of soluble GC (Mikami *et al*., 1998). Amino acid sequences of the α and β subunits of medaka fish soluble GC are closely related to mammalian α_1 and β_1 subunits, respectively, and therefore they are designated as OlGCS-α_1 and OlGCS-β_1 (Mikami *et al*., 1998). RT-PCR analysis showed that *OlGCS-α_1* and *OlGCS-β_1* transcripts were abundant in the brain, eye, spleen, and testis. During development, RT-PCR analysis demonstrated that both transcripts are present in unfertilized eggs and reduced immediately after fertilization, and then increased again. Consistently, NO-sensitive GC activity at a significant level were detected in the adult brain and hatching stage embryos.

Genomic organization and transcriptional regulation of the *OlGCS-α_1* and *OlGCS-β_1* genes have been investigated (Mikami *et al*., 1999). In the genome, *OlGCS-α_1* and *OlGCS-β_1* are organized in tandem (Fig. 5). The two genes are only 986 bp apart and span approximately 34 kbp in the order of *OlGCS-α_1* and *OlGCS-β_1*. The nucleotide sequence of a large part of the 5' upstream region of *OlGCS-α_1* is complimentarily conserved in that of *OlGCS-β_1*. To analyze the promoter activity of each gene, a fusion gene construct in which the 5' upstream region was fused with the GFP gene was injected into medaka fish 2-cell stage embryos. When the fusion gene containing the *OlGCS-α_1* upstream region was injected, GFP fluorescence was detected in the embryonic brain (Fig. 2A). The 5' upstream region of *OlGCS-β_1* alone was insufficient for the reporter gene expression in the embryos. When the *OlGCS-α_1* upstream region was located upstream of the *OlGCS-β_1-GFP* fusion gene, the reporter gene was expressed in the brain and trunk region of the embryos. These results suggest that the 5' upstream region of *OlGCS-α_1* can affect the expression of *OlGCS-β_1*. Thus, the upstream region of the a subunit gene of medaka fish soluble GC seems to regulate expression of both α and β subunit genes, suggesting a mechanism of coordinated transcription of the two subunit genes (Mikami *et al*., 1999). Recent experiments have shown that the 5' upstream region of *OlGCS-α_1* connected to a luciferase reporter gene are expressed efficiently in a mammalian COS1 cell line (T. Yamamoto and N. Suzuki, unpublished data). Although genomic organization and transcriptional regulation

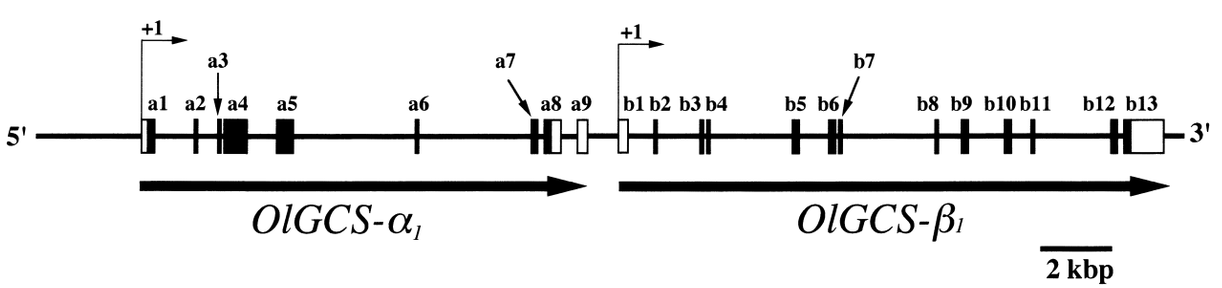

Fig. 5. Diagrammatic representation of structure of the medaka fish soluble GC gene complex. Noncoding exons are indicated by open boxes and protein-coding exons are by solid boxes. The exons of *OlGCS-α_1* and *OlGCS-β_1* are indicated as *a* and *b*, respectively, followed by a number. The two *OlGCS* subunit genes are transcribed from each transcription initiation site (+1), but the transcriptional regulation seems to be coordinated (see text for detail).

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of soluble GC in mammals have not been reported to date, it has been shown that the α_1 and β_1 subunit genes are colocalized in human and rat chromosomes (Giuili *et al.*, 1993; Azam *et al.*, 1998). Therefore, mechanisms of transcriptional regulation of soluble GC genes may be conserved between medaka fish and mammals.

PERSPECTIVES

Recent studies have shown that medaka fish has a set of GC isoforms similar to that in mammals. This fact further prompts us to use medaka fish as a model animal to study common features of the GC family in vertebrates. In particular, easiness of observation and manipulation of embryos together with recent progress in molecular genetic approaches in medaka fish will facilitate studies on gene regulation and roles of GCs during early development, which might be somewhat difficult in mammalian systems. Foreign DNA transfer into medaka fish embryos will be used to analyze function of *cis*-regulatory regions and transcription factors. Transgenesis and RNA microinjection techniques can also be used to investigate developmental and physiological roles of the GC family *in vivo* by introducing dominant-negative mutants (Thompson and Garbers, 1995; Gao *et al.*, 1997) and constitutively hyperactive mutants (Wedel *et al.*, 1997) of GCs.

Medaka fish may also utilize GCs for a system characteristic of fish, such as osmotic regulation. Comparative studies between fish and other vertebrates will contribute to understanding evolutionary aspects of the GC signaling pathway. Another intriguing feature of medaka fish is the existence of closely-related species whose habitat differ to various extent. Considering the importance of the GC signaling at the interface between organisms and the environment, medaka fish and its related species can also provide a unique opportunity to study evolutionary changes in roles and regulation of GCs during adaptation and speciation.

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