NEW TRENDS IN HUMAN REPRODUCTION

Introduction to Guest Editor - Hong-Yuan Huang, MD

I would like to express my thanks to Dr. Hong-Yuan Huang for serving as the guest editor. The authors who have contributed articles to this special section “NEW TRENDS IN HUMAN REPRODUCTION” are all outstanding experts in their fields.


Dr. Hong-Yuan Huang

Dr. Hong-Yuan Huang graduated from Chung Shan Medical College in 1987 and completed his residency at the department of obstetrics and gynecology, Chang Gung Memorial Hospital in 1991. His further study included a postdoctoral research fellowship at Reproductive Immunology Laboratory of Stanford University Medical Center from March 1996 to August 1997.

Currently, Dr. Huang is the associate professor and chief of the division of Gynecology and Reproductive Endocrinology in the department of obstetrics and gynecology in Linkou Medical Center of Chang Gung Memorial Hospital. He is academically active with main research interests on reproductive immunology, extracellular matrix biology, mechanism of embryo implantation and ectopic pregnancy. He has published 41 articles in peer reviewed journals and won best paper prizes at various national and international conferences.

Fu-Chan Wei, MD
Editor-in-Chief

Genomic Analyses of the Evolution of LGR Genes

Ching-Wei Luo, PhD; Aaron J. W. Hsueh, PhD

Recent completion of the sequencing of genomes from several mammals, teleosts and invertebrates has shown that G protein-coupled receptors (GPCRs) are one of the conserved groups of cell surface receptors with an ancient origin. GPCRs play important roles in diverse physiological functions and are the most important targets for pharmaceutical discoveries. Recent work based on the search for gene with structural similarity to LH, FSH and thyroid-stimulating hormone (TSH) receptors in diverse genomes has led to the identification of a group of GPCRs called Leucine-rich repeat-containing, G protein-coupled Receptor (LGR). We present the genomic analyses of the evolution of LGR genes in the literature. *(Chang Gung Med J 2006;29:2-8)*

Key words: leucine-rich repeat-containing, G protein-coupled receptors (LGRs).

Introduction

Recent completion of the sequencing of genomes from several mammals, teleosts and invertebrates has shown that G protein-coupled receptors (GPCRs) are one of the conserved groups of cell surface receptors with an ancient origin.[1-3] GPCRs play important roles in diverse physiological functions and are the most important targets for pharmaceutical discoveries.

In the reproduction system, the interactions between GPCRs and ligands also play important roles in the regulation of gonadal development and fertility. Extensive studies have been performed on the interactions between luteinizing hormone (LH), follicle-stimulating hormone (FSH) and their receptors. It has been demonstrated that these receptors are important in regulating follicular development, ovulation, and steroidogenesis in females as well as testicular development, spermatogenesis, and steroidogenesis in males.[4,5]

Recent work based on the search for gene with structural similarity to LH, FSH and thyroid-stimulating hormone (TSH) receptors in diverse genomes has led to the identification of a group of GPCRs called Leucine-rich repeat-containing, G protein-coupled Receptor (LGR).[6-8] All receptors in the LGR sub-family contain a large ectodomain with multiple leucine-rich repeats (LRRs) likely involved in ligand binding, a seven-transmembrane domain responsible for G protein activation, and a unique hinge region between the LRRs and the transmembrane region (Fig. 1). Studies of LGRs from diverse species suggest that LGRs can be subdivided into three subgroups (group A, B and C) (Fig. 2). The group A LGRs includes FSH receptor, LH receptor and TSH receptor, important for signaling of the heterodimeric glycoprotein hormones FSH, LH, and TSH, respectively. The group B LGRs comprises mammalian LGR4-6, the functions and cognate ligands of which remain unclear. The group C LGRs consists of relaxin and INSL3 receptors, LGR7 and 8. All three groups of LGRs could be found in insects, suggesting that the common ancestor of these genes evolved early during metazoan emergence.[8] The current review briefly summarizes our recent studies on the characterization of LGRs and the identification of their cognate ligands. These findings allow further understanding of the physio-

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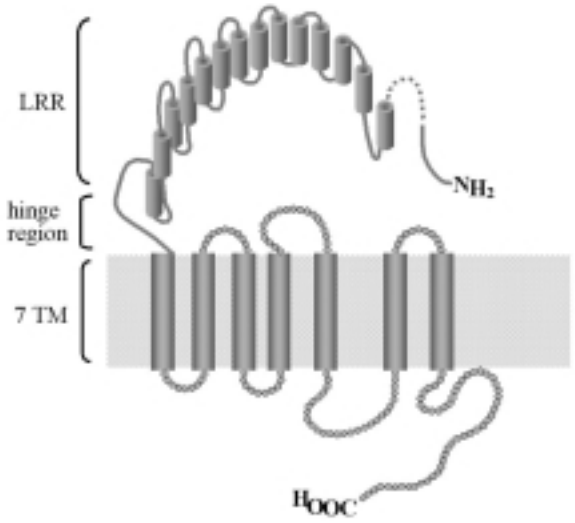

Fig. 1 Structural conservation of LGR family. All members in LGR family share a common structure with a large amino-terminal ectodomain containing leucine-rich (LRR) repeats for ligand interaction, a hinge region, and the seven transmembrane (TM) domains for downstream signal transduction.

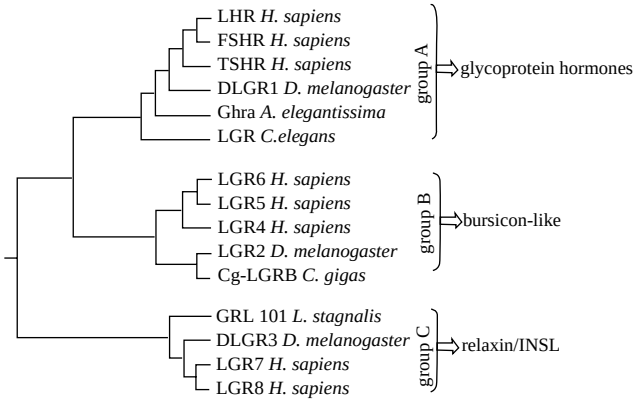

Fig. 2 The phylogenetic relationship between LGR members. Based on their respective phylogenetic placement and on the nature of their cognate ligand, LGRs could be subdivided into three groups (Group A, B and C). FSHR Homo sapiens (P23945), LGR4 H. sapiens (AF061443), LGR5 H. sapiens (AF061444), LGR6 H. sapiens (AF190501), LGR7 H. sapiens (AF190500), LGR8 H. sapiens (AF403384), Cg-LGRB C. gigas (AJ549813), Ghra Anthopleura elegantissima (Z28332), LGR Caenorhabditis elegans (NP_505548), DLGR1 Drosophila melanogaster (U47005), DLGR2 D. melanogaster (AF274591), DLGR3 D. melanogaster (AAO39507), LHCGR H. sapiens (M73746), TSHR H. sapiens (AAR07906), GRL 101 Lymnaea stagnalis (P46023). The tree was generated using the alignment in CLUSTAL X and manual inspection. Reproduced with permission from Luo et al. (unpublished).

logical roles of the ligand-receptor pairs and reveal the co-evolution of these receptors and ligands.

Characterization of the activation mechanisms of group A LGRs

Earlier studies using mutated LH and TSH receptors found in patients with male-limited precocious puberty and nonimmune hyperthyroidism, respectively, indicated that these diseases are associated with constitutive receptor activation as a result of point mutations of key residues in the transmembrane VI region of these receptors.[9-11] Based on these studies, we have performed detailed experiments on constitutive activation using point mutations of LH receptors and FSH receptors, and demonstrated that the region important for group A LGRs activation are mainly clustered in the hinge region, intracellular loop 3 and transmembrane V/VI/VII.[12,13] These findings allow a better understanding of the specific domains of glycoprotein hormone receptors in ligand interaction and signaling. Of interest, further experiments revealed that these gain-of-function strategies could apply to the related LGRs, including the fly DLGR2 in group B and the human LGR7 and LGR8 of group C LGRs.[6,14] The understanding of the downstream signaling mechanisms of these receptors facilitates the identification of their cognate ligands.

Identification of relaxin and INSL3 as ligands for LGR7 and LGR8 of group C LGRs, respectively

Most of functional characteristics of the relaxin signaling system has been obtained with a variety of biochemical and molecular techniques before the identification of the relaxin receptors. These studies have suggested that relaxin signaling is important in many reproductive events including the growth and softening of the cervix, mammary gland and nipple development, inhibition of uterine contractile activity, collagen remodeling, and dilation of blood vessels.[15,17] Based on the search of human genome for relaxin homologs, six additional relaxin family genes including RLN2, INSL3, INSL4, INSL5, INSL6 and INSL7/RLN3 have been identified.[18-22] Subsequently, our studies have shown that the type C LGRs are cognate receptors for relaxin and two related peptides, relaxin and INSL3.[23-25] LGR7 is the receptor for relaxin whereas LGR8 is the ligand for INSL3.

Disruption of the orphan group B LGR genes in transgenic mice

Unlike the group A and group C LGRs, the ligands and the physiological functions for the group B orphan LGR4-6 subfamily in mammals are unclear. In an attempt to elucidate the physiological roles of this subgroup of orphan LGRs, we analyzed the phenotypes of mutant mice with a deletion of LGR4 or LGR5 gene.

We generated transgenic mice using the secretory-trap approach with the trap vector containing the N terminus of LGR4 fused with the β-galactosidase protein driven by its endogenous promoter.[26] Taking advantage of the expression of the fusion reporter gene, we performed detailed analysis of the tissue expression pattern of LGR4. The LGR4 gene showed a wide tissue distribution including kidney, adrenal gland, stomach, intestine, bladder, heart, brain, bone and liver. Of interest, disruption of LGR4 gene led to perinatal lethality and intrauterine growth retardation associated with pronounced suppression of kidney and liver growths. Most of the LGR4 null newborn mice and some heterozygotes (~15%) died on the first day after birth.[26] The observed perinatal lethality of both homo- and heterozygous LGR4 pups suggests the importance of the LGR4 gene in embryonic development and newborn survival.

Furthermore, LGR5 null mice were also generated by targeted deletion of this seven-transmembrane protein.[27] LGR5 null mice exhibited 100% neonatal lethality characterized by gastrointestinal tract dilation with air and an absence of milk in the stomach. Gross and histological examination revealed the fusion of the tongue to the floor of the oral cavity in the mutant newborns (Fig. 3). The observed ankyloglossia phenotype provides a model for understanding the genetic basis of this craniofacial defect in humans and a model to elucidate the physiological role of the LGR5 signaling system during embryonic development.

In addition to its role in craniofacial formation during embryonic development, LGR5 may also play important roles in adult life. A recent study demonstrated the overexpression of LGR5 in human hepatocellular carcinomas with β-catenin mutations, suggesting that LGR5 may be involved in tumorgenesis.[28]

In flies, the DLGR2 gene has the same evolutionary origin as the mammalian group B LGRs. Interestingly, mutation of this gene in flies led to major changes in development including the wing expansion and tanning defects.[29] Therefore, group B

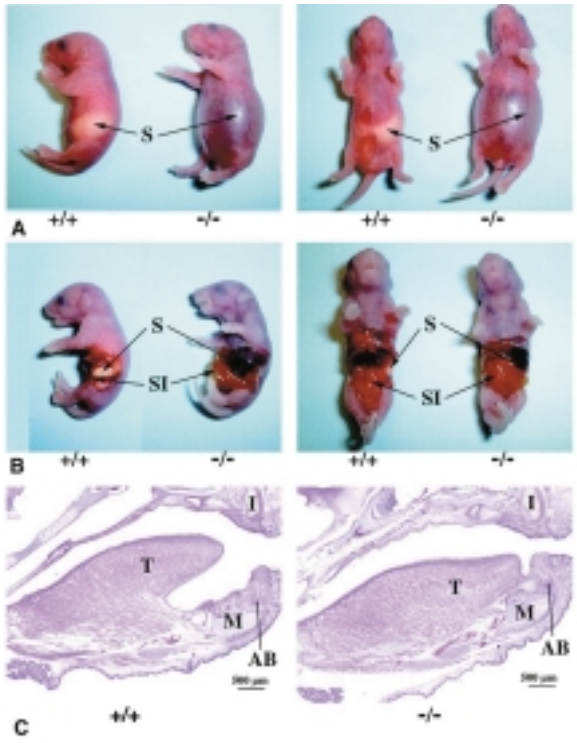

Fig. 3 Dilated gastrointestinal tract and abnormal craniofacial development in LGR5 null mice (27). (A) The wild-type LGR5 (+/+) neonates had milk in their stomachs (S), whereas the LGR5 null (-/-) neonates had dilated stomachs without milk. (B) The entire gastrointestinal tract of LGR5 null mice was dilated without milk, whereas the wild-type mice had a normal appearance. SI, small intestine. (C) In sagittal sections of the craniofacial region, the LGR5 null mice showed fusion of the tongue (T) to the mandible (M), whereas these two regions are separated in the wild-type mice. Identification of similar structures in the upper and lower jaws indicates the sections were taken at the same level. I, developing upper incisor; AB, developing alveolar bone of lower incisor. (D) In transverse serial sections of the mandible region, the tongue of LGR5 null mice was attached to the mandible, whereas the tongue of the wild-type animals in the same region was connected only in a posterior section. Similar sections are reflected by the morphology of the molar teeth (mt), and more anterior sections are shown on the right. (E) Immunostaining of LGR5 antigen in the epithelium of the tongue and the epithelium and mesenchyme of the mandible at E14.5. Ab, antibody. The boxed area in the upper panel is enlarged in the lower panels. Reproduced with permission from Mazerbourg et al.[26]

LGRs in both vertebrates and invertebrates are involved in early development in contrast to mammalian group A and C LGRs found to be important in different reproduction processes. This important role of group B LGRs in early development is unique and has not been described previously for the other known glycoprotein hormone receptors. Thus, identification of the cognate ligands for group B LGRs and the elucidation of the signaling pathway for these G protein-coupled receptors become crucial for the understanding of the molecular mechanisms and the physiological roles of this LGR subgroup conserved in vertebrates and invertebrates.

Evolutionary tracing of potential ligands for the remaining orphan LGRs based on genomic searches

Recently, we discovered bursicon as the cognate ligand for DLGR2, the group B LGR in *Drosophila melanogaster*.[30] We identified the chemical nature of bursicon, the first heterodimeric cystine knot hormone found in insects, and showed that this ligand consists of two proteins encoded by the genes burs and pburs (partner of burs). The pburs/burs heterodimeric binds with high affinity and specificity to activate the G protein-coupled receptor DLGR2, leading to the stimulation of cAMP signaling in vitro and tanning in neck-ligated blowflies *in vivo* (Fig. 4).

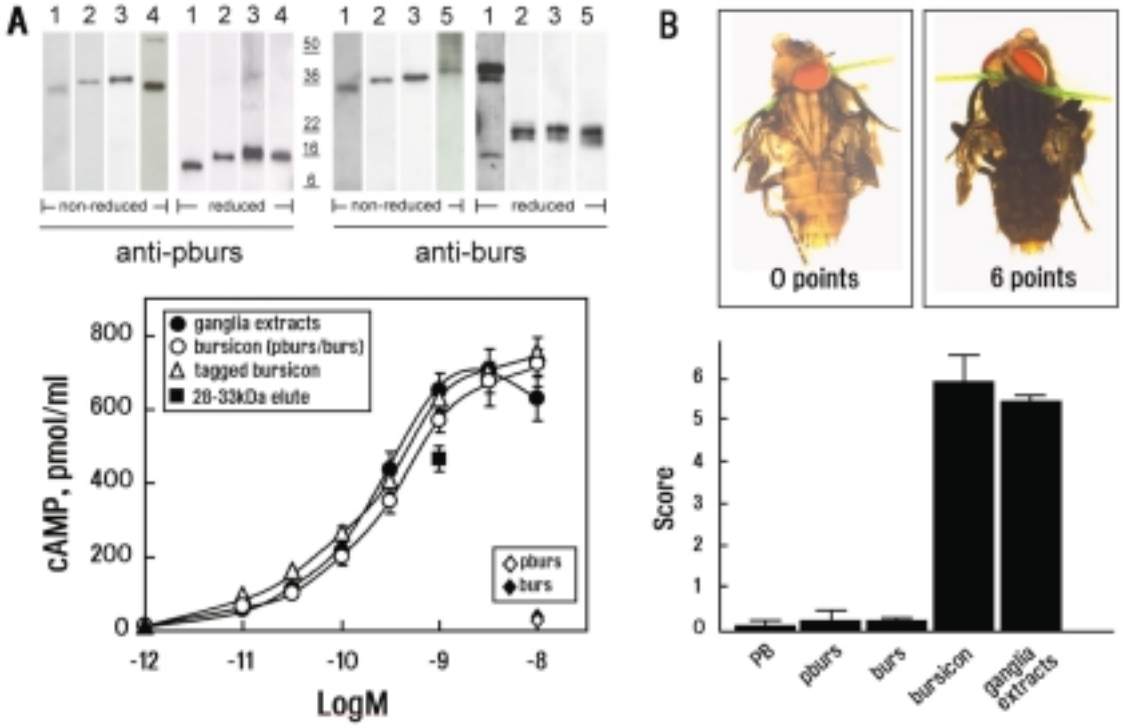

Fig. 4 Bursicon, a heterodimer of two cystine-knot-containing polypeptides, is the cognate ligand for DLGR2 (30). (A)(Upper) Immunoblot analyses of bursicon from P. americana ganglia extracts and conditioned media from 293T cells transfected with pburs and/or burs. Samples were run under nonreducing and reducing conditions. Lane 1, ganglia extracts from P. americana; lane 2, recombinant pburs/burs without epitope tags; lane 3, recombinant epitope-tagged pburs/burs; lane 4, recombinant pburs without a tag; and lane 5, recombinant burs without a tag. (Lower) Stimulation of DLGR2 by P. americana ganglia extracts or conditioned media from cells cotransfected with pburs/burs expression constructs (bursicon heterodimer), but not by the individual plasmid (pburs or burs). Both wild-type and epitope-tagged bursicon heterodimers were tested. In addition, proteins eluted from the 28- to 33-kDa region of a SDS gel loaded with P. americana ganglia extracts also were tested. Ligand levels were determined from immunoblots by using purified tagged bursicon heterodimers as a standard. (B) Neck-ligated fly bioassay. Recombinant bursicon or P. americana ganglia extracts stimulated complete tanning of flies with a maximum score (5-6 points), whereas flies injected with phosphate buffer (PB), pburs, and burs alone did not tan and received an average score of 0-0.3 points. In three separate experiments, 6-10 flies were injected, and their tanning score was averaged. Reproduced with permission from Luo et al.[30]

Our identification of two cystine knot-containing polypeptides as subunits for the heterodimeric bursicon in insects, together with the demonstration of specific binding and activation of a G protein-coupled receptor with leucine-rich repeats, allow us to trace the potential ligands for vertebrate LGR4-6, the ortholog for the fly DLGR2. Comparison of vertebrate genomic sequences with the insect pburs and burs genes indicated that the insect genes are homologous to the vertebrate bone morphogenetic protein (BMP) antagonist family of genes. Because BMP antagonists are important during embryonic development and organogenesis,[31,32] future studies may reveal if they are cognate ligands for the orphan LGR4 or LGR5 genes, which are also found to be important during embryonic development.[26,27] Up to the present, only some members of the BMP antagonist family have been found to be competitive antagonists capable of direct binding to BMPs,[31,33] and the exact mechanisms of actions of most proteins in this family are still unknown. More studies are needed to confirm whether these cystine knot proteins are ligands for vertebrate orphans LGR4/5/6. The eventual identification of the cognate ligands for these orphan receptors will advance our understanding of the physiological roles of mammalian group B LGRs.

Conclusions

Genomic analyses of genes with similar structures to mammalian LH and FSH receptors allow the identification of new LGR genes. Based on common mutant phenotypes of receptors and ligands, the ligand-receptor relationships between INSL3 and LGR8 as well as fly bursicon and DLGR2 have been elucidated. These findings allow further analyses of the co-evolution of the subgroup of LGRs and their ligands. The present paradigm of studying the co-evolution of polypeptide ligands and their receptors are useful for understanding hormone signaling for diverse receptors.

REFERENCES

1. Dehal P, Satou Y, Campbell RK, Chapman J, Degnan B, De Tomaso A, Davidson B, Di Gregorio A, Gelpke M, Goodstein DM, Harafuji N, Hastings KE, Ho I, Hotta K, Huang W, Kawashima T, Lemaire P, Martinez D, Meinertzhagen IA, Necula S, Nonaka M, Putnam N, Rash S, Saiga H, Satake M, Terry A, Yamada L, Wang HG, Awazu S, Azumi K, Boore J, Branno M, Chin-Bow S, DeSantis R, Doyle S, Francino P, Keys DN, Haga S, Hayashi H, Hino K, Imai KS, Inaba K, Kano S, Kobayashi K, Kobayashi M, Lee BI, Makabe KW, Manohar C, Matassi G, Medina M, Mochizuki Y, Mount S, Morishita T, Miura S, Nakayama A, Nishizaka S, Nomoto H, Ohta F, Oishi K, Rigoutsos I, Sano M, Sasaki A, Sasakura Y, Shoguchi E, Shin-i T, Spagnuolo A, Stainier D, Suzuki MM, Tassy O, Takatori N, Tokuoka M, Yagi K, Yoshizaki F, Wada S, Zhang C, Hyatt PD, Larimer F, Detter C, Doggett N, Glavina T, Hawkins T, Richardson P, Lucas S, Kohara Y, Levine M, Satoh N, Rokhsar DS. The draft genome of Ciona intestinalis: insights into chordate and vertebrate origins. Science 2002;298:2157-67.
2. Hill CA, Fox AN, Pitts RJ, Kent LB, Tan PL, Chrystal MA, Cravchik A, Collins FH, Robertson HM, Zwiebel LJ. G protein-coupled receptors in Anopheles gambiae. Science 2002;298:176-8.
3. Aparicio S, Chapman J, Stupka E, Putnam N, Chia JM, Dehal P, Christoffels A, Rash S, Hoon S, Smit A, Gelpke MD, Roach J, Oh T, Ho IY, Wong M, Detter C, Verhoef F, Predki P, Tay A, Lucas S, Richardson P, Smith SF, Clark MS, Edwards YJ, Doggett N, Zharkikh A, Tavtigian SV, Pruss D, Barnstead M, Evans C, Baden H, Powell J, Glusman G, Rowen L, Hood L, Tan YH, Elgar G, Hawkins T, Venkatesh B, Rokhsar D, Brenner S. Whole-genome shotgun assembly and analysis of the genome of Fugu rubripes. Science 2002;297:1301-10.
4. Hillier SG. Gonadotropic control of ovarian follicular growth and development. Mol Cell Endocrinol 2001;179:39-46.
5. Zhang FP, Poutanen M, Wilbertz J, Huhtaniemi I. Normal prenatal but arrested postnatal sexual development of luteinizing hormone receptor knockout (LuRKO) mice. Mol Endocrinol 2001;15:172-83.
6. Hsu SY, Kudo M, Chen T, Nakabayashi K, Bhalla A, van der Spek PJ, van Duin M, Hsueh AJ. The three subfamilies of leucine-rich repeat-containing G protein-coupled receptors (LGR): identification of LGR6 and LGR7 and the signaling mechanism for LGR7. Mol Endocrinol 2000;14:1257-71.
7. Hsu SY, Liang SG, Hsueh AJ. Characterization of two LGR genes homologous to gonadotropin and thyrotropin receptors with extracellular leucine-rich repeats and a G protein-coupled, seven-transmembrane region. Mol Endocrinol 1998;12:1830-45.
8. Hsu SY. New insights into the evolution of the relaxin-LGR signaling system. Trends Endocrinol Metab 2003;14:303-9.
9. Jasmine Parma, Laurence Duprez, Jacqueline Van Sande, Jacques Hermans, Pierre Rocmans, Guy Van Vliet, Sabine Costagliola, Patrice Rodien, Jacques E. Dumont, Gilbert Vassart. Diversity and prevalence of somatic mutations in the thyrotropin receptor and Gs alpha genes as a cause of toxic thyroid adenomas. J Clin Endocrinol Metab 1997;82:2695-701.

10. Shenker A, Laue L, Kosugi S, Merendino JJ, Jr., Minegishi T, Cutler GB, Jr. A constitutively activating mutation of the luteinizing hormone receptor in familial male precocious puberty. Nature 1993;365:652-4.
11. Laue L, Chan WY, Hsueh AJ, Kudo M, Hsu SY, Wu SM, Blomberg L, Cutler GB Jr. Genetic heterogeneity of constitutively activating mutations of the human luteinizing hormone receptor in familial male-limited precocious puberty. Proc Natl Acad Sci USA 1995;92:1906-10.
12. Nakabayashi K, Kudo M, Kobilka B, Hsueh AJ. Activation of the luteinizing hormone receptor following substitution of Ser-277 with selective hydrophobic residues in the ectodomain hinge region. J Biol Chem 2000;275:30264-71.
13. Kudo M, Osuga Y, Kobilka BK, Hsueh AJ. Transmembrane regions V and VI of the human luteinizing hormone receptor are required for constitutive activation by a mutation in the third intracellular loop. J Biol Chem 1996;271:22470-8.
14. Nishi S, Nakabayashi K, Kobilka B, Hsueh AJ. The ectodomain of the luteinizing hormone receptor interacts with exoloop 2 to constrain the transmembrane region: studies using chimeric human and fly receptors. J Biol Chem 2002;277:3958-64.
15. Weiss G, Goldsmith LT. Relaxin and the cervix. Front Horm Res 2001;27:105-12.
16. Zhao L, Samuel CS, Tregear GW, Beck F, Wintour EM. Collagen studies in late pregnant relaxin null mice. Biol Reprod 2000;63:697-703.
17. Sherwood OD, Downing SJ, Guico-Lamm ML, Hwang JJ, O'Day-Bowman MB, Fields PA.The physiological effects of relaxin during pregnancy: studies in rats and pigs. Oxf Rev Reprod Biol 1993;15:143-89.
18. Hsu SY. Cloning of two novel mammalian paralogs of relaxin/insulin family proteins and their expression in testis and kidney. Mol Endocrinol 1999;13:2163-74.
19. Bathgate RA, Samuel CS, Burazin TC, Layfield S, Claasz AA, Reytomas IG, Dawson NF, Zhao C, Bond C, Summers RJ, Parry LJ, Wade JD, Tregear GW. Human relaxin gene 3 (H3) and the equivalent mouse relaxin (M3) gene. Novel members of the relaxin peptide family. J Biol Chem 2002;277:1148-57.
20. Lok S, Johnston DS, Conklin D, Lofton-Day CE, Adams RL, Jelmberg AC, Whitmore TE, Schrader S, Griswold MD, Jaspers SR. Identification of INSL6, a new member of the insulin family that is expressed in the testis of the human and rat. Biol Reprod 2000;62:1593-9.
21. Conklin D, Lofton-Day CE, Haldeman BA, Ching A, Whitmore TE, Lok S, Jaspers S. Identification of INSL5, a new member of the insulin superfamily. Genomics 1999;60:50-6.
22. Chassin D, Laurent A, Janneau JL, Berger R, Bellet D. Cloning of a new member of the insulin gene superfamily (INSL4) expressed in human placenta. Genomics 1995;29:465-70.
23. Hsu SY, Nakabayashi K, Nishi S, Kumagai J, Kudo M, Sherwood OD, Hsueh AJ. Activation of orphan receptors by the hormone relaxin. Science 2002;295:671-4.
24. Sudo S, Kumagai J, Nishi S, Layfield S, Ferraro T, Bathgate RA, Hsueh AJ. H3 relaxin is a specific ligand for LGR7 and activates the receptor by interacting with both the ectodomain and the exoloop 2. J Biol Chem 2003;278:7855-62.
25. Kumagai J, Hsu SY, Matsumi H, Roh JS, Fu P, Wade JD, Bathgate RA, Hsueh AJ. INSL3/Leydig insulin-like peptide activates the LGR8 receptor important in testis descent. J Biol Chem 2002;277:31283-6.
26. Mazerbourg S, Bouley DM, Sudo S, Klein CA, Zhang JV, Kawamura K, Goodrich LV, Rayburn H, Tessier-Lavigne M, Hsueh AJ. Leucine-rich repeat-containing, G protein-coupled receptor 4 null mice exhibit intrauterine growth retardation associated with embryonic and perinatal lethality. Mol Endocrinol 2004;18:2241-54.
27. Morita H, Mazerbourg S, Bouley DM, Luo CW, Kawamura K, Kuwabara Y, Baribault H, Tian H, Hsueh AJ. Neonatal lethality of LGR5 null mice is associated with ankyloglossia and gastrointestinal distension. Mol Cell Biol 2004;24:9736-43.
28. Yamamoto Y, Sakamoto M, Fujii G, Tsuiji H, Kenetaka K, Asaka M, Hirohashi S. Overexpression of orphan G-protein-coupled receptor, Gpr 49, in human hepatocellular carcinomas with beta-catenin mutations. Hepatology 2003;37:528-33.
29. Baker JD, Truman JW. Mutations in the Drosophila glycoprotein hormone receptor, rickets, eliminate neuropeptide-induced tanning and selectively block a stereotyped behavioral program. J Exp Biol 2002;205:2555-65.
30. Luo CW, Dewey EM, Sudo S, Ewer J, Hsu SY, Honegger HW, Hsueh AJ. Bursicon, the insect cuticle-hardening hormone, is a heterodimeric cystine knot protein that activates G protein-coupled receptor LGR2. Proc Natl Acad Sci USA 2005;102:2820-5.
31. Sudo S, Avsian-Kretchmer O, Wang LS, Hsueh AJ. Protein related to DAN and cerberus is a bone morphogenetic protein antagonist that participates in ovarian paracrine regulation. J Biol Chem 2004;279:23134-41.
32. Canalis E, Economides AN, Gazzerro E. Bone morphogenetic proteins, their antagonists, and the skeleton. Endocr Rev 2003;24:218-35.
33. Avsian-Kretchmer O, Hsueh AJ. Comparative genomic analysis of the eight-membered ring cystine knot-containing bone morphogenetic protein antagonists. Mol Endocrinol 2004;18:1-12.

LGR 基因發展的基因分析

Ching-Wei Luo, PhD; Aaron J. W. Hsueh, PhD

在生殖系統中，G 蛋白質的感受體扮演著生殖腺及生育的重要角色，LGR 可以活化 G 蛋白質，我們將介紹 LGR 基因發展的基因分析。(長庚醫誌2006;29:2-8)

關鍵字：性腺激素，基因，G 蛋白配對受體。

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