G&I Genomics & Informatics

eISSN 2234-0742
Genomics Inform 2018;16(1):2-9
https://doi.org/10.5808/GI.2018.16.1.2

REVIEW ARTICLE

System-Wide Expression and Function of Olfactory Receptors in Mammals

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Olfactory receptors (ORs) in mammals are generally considered to function as chemosensors in the olfactory organs of animals. They are membrane proteins that traverse the cytoplasmic membrane seven times and work generally by coupling to heterotrimeric G protein. The OR is a G protein–coupled receptor that binds the guanine nucleotide-binding $G\alpha_{olf}$ subunit and the $G\beta\gamma$ dimer to recognize a wide spectrum of organic compounds in accordance with its cognate ligand. Mammalian ORs were originally identified from the olfactory epithelium of rat. However, it has been recently reported that the expression of ORs is not limited to the olfactory organ. In recent decades, they have been found to be expressed in diverse organs or tissues and even tumors in mammals. In this review, the expression and expected function of olfactory receptors that exist throughout an organism's system are discussed.

Keywords: chemosensory receptor, ectopic expression, G protein-coupled receptor, olfactory receptor, system-wide expression

Introduction

Animal olfactory receptors (ORs) make up a G protein-coupled chemosensory receptor (GPCR) family with 7 transmembrane alpha-helices located in the cytoplasmic membrane of cells. They are known to work by binding heterotrimeric guanine nucleotide-binding proteins (G proteins), composed of the olfactory $G\alpha$ ($G\alpha_{olf}$) subunit and the $G\beta\gamma$ dimer. GPCRs are classified by their sequence homology [1] or based on their phylogenetic origin [2], and there are more than 16 types of G protein α subunits [3, 4]. ORs are also known to recognize a wide spectrum of organic compounds in accordance with its cognate ligand. When it was originally identified from rat olfactory epithelium [5], the expression of the protein was thought to be confined to that tissue. After the discovery of $G\alpha_{olf}$ [6] and rat ORs [5], OR expression in mammalian germ cells [7, 8] and heart [9] was reported in the early 1990s. In the late 20th century, OR expression in an insulin-secreting cell line and the spleen of rats [10] and human erythroid cells [11] was reported. ORs are largely distributed in olfactory sensory neurons of the nasal epithelium but are also expressed in other non-olfactory tissues [12].

We discuss the physiological functions of ORs and suggest future perspectives for their research.

Olfactory Receptors in the Brain and Heart-Related Systems

Since the expression of ORs in mammalian germ cells was reported [7], OR expression in various organs and tissues in animals has been observed. The brain and the heart are the fundamental organs that form the basis of animal life. For example, controlling the fluctuation of blood pressure and pulse of an animal is accomplished by endocrine action through autonomic reflex and peptide hormone secretion. Brain and heart are closely connected to each other by various mechanisms, including the nervous system.

For the first time, prostate-specific G protein-coupled receptors (PSGRs), also known as RA1c, were reported to be expressed in the brain of rat [13] and mouse [14] and the heart of rat and mouse [15]. It was not expected to be expressed in human tissues other than prostate.

Brain

After it was demonstrated that RA1c homologs—Olr59 in rat [13] and Olfr78 in mouse [14]—were expressed in areas

Received March 6, 2018; Revised March 13, 2018; Accepted March 13, 2018

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of the brain and olfactory epithelium, much effort has been made to confirm the expression of ORs in the brain. MOL2.3, called Olfr78, was reported to be expressed in the ganglia of the autonomic nervous system [16]. Some mouse ORs—M71 (olfr151), C6 (Olfr49), and OR3—are detected in the cerebral cortex and might play a role in developmental processes, such as axon guidance and target recognition during the postnatal period [17]. OR expression (OR1E1, OR2J3, OR2L13, OR11H1, and OR52L1) in the frontal cortex is downregulated in Parkinson disease (PD) patients [18].

The expression of a mouse OR, Olfr110, was detected in the cerebral cortex of wild-type mice for 1 postnatal year, and its mRNA levels did not vary during that period [19]. It was observed that 8 ORs and 6 taste receptors (TASRs) are constitutively expressed in the frontal cortex, entorhinal cortex, and cerebellum in human control brains. These data imply that variable dysregulation of certain ORs and TASRs is common in several neurodegenerative diseases, including Alzheimer disease, Progressive Supranuclear Palsy, and Creutzfeldt–Jakob disease. The same research group also reported a decrease in olfactory and TASR expression in the dorsolateral prefrontal cortex in chronic schizophrenia [20]. There was a report that ORs are expressed in mouse mesencephalic dopaminergic (mDA) neurons. After screening ligands on Olfr287, carvone enantiomers were identified as agonists of Olfr287 and able to increase intracellular Ca^{2+} in solitary mDA neurons. The ORs were found to be expressed in human Substantia Nigra and downregulated in PD postmortem brains [21].

Gong *et al*. [22] found that some ORs are differentially expressed in the sciatic nerve and dorsal root ganglia after sciatic nerve injury in rats. The expression and expression profile of several ORs in the sciatic nerve were verified, and they also observed that the expression of some ORs in primary cultures of Schwann cells was upregulated under H_2O_2 stimulation [22]. Recently, there has been a report that Olfr544 is expressed in mouse brain and heart, as well as nose, adipose tissue, and spleen [23].

Heart-related system

In 1995, Drutel *et al*. [9] reported the expression of OL1 (Olr1654) in the developing rat heart and suggested its involvement in cardiac morphogenesis, where the OR was hardly detectable at the adult stages. As mentioned above, murine PSGRs (Olfr78 and Olr59) are expressed in the hearts of mouse [16] and rat [15], in addition to prostate. In 2007, Zhang *et al*. [24] reported that ORs (including OR10G4) are expressed in human heart and various organs using reverse transcription–polymerase chain reaction (RT-PCR) and microarray.

Recently, OR10J5 was found to be expressed in human aorta, coronary artery, and human umbilical vein endothelial cells [25]. In addition, Matrigel plug assay showed that lyral enhances angiogenesis *in vivo*. These results let us surmise the physiological role of OR10J5 in angiogenesis.

Chang *et al*. [26] showed that a short-chain fatty acid OR, Olfr78, is highly and selectively expressed in oxygen-sensitive glomus cells of the carotid body (CB). The CB is a chemosensory organ that monitors blood oxygen to control breath [27]. As lactate eventually activates Olfr78 in heterologous expression experiments, Chang *et al*. [26] proposed that Olfr78 may act as a hypoxia sensor in the breathing circuit, in addition to its role in olfaction. The next year, Zhou *et al*. [28] applied the single-cell RNA-Seq method to eliminate the contamination of genes derived from other cell types present in the CB to analyze the expression of ORs in CB glomus cells and identified Olfr78 as the most highly abundant OR in the CB in mice. More recently, Jovancevic *et al*. [29] reported that OR51E1 activation by the application of cognate agonists induces a negative chronotropic effect in human stem cell-derived cardiomyocytes and also provokes negative inotropic activity in cardiac trabeculae and slice preparations of human explated ventricles. These results imply that some ORs that are expressed in heart may be therapeutic targets for the metabolic regulation of cardiac function. A mouse OR—Olfr544, an ortholog of the OR52 family (OR52K1)—was reported to be expressed in the heart of mice [23]. The unexpected cardiac expression of ORs may regulate cell growth and morphogenesis.

General studies on OR expression show that ORs are expressed throughout systems and have diverse functions throughout the body of animals (Table 1) [7-11, 13-26, 28-73].

System-Wide Expression of Olfactory Receptors

Testis

In 1992, ectopic expression of OR-like proteins in dog testis was reported after the OR multigene family was originally isolated from rat olfactory epithelium [7]. Subsequently, many experiments were performed to trace the presence of ORs in animal testicular tissues for the investigation of OR function in sperm-oocyte chemotaxis, where it was thought that ORs should have chemotactic roles during fertilization. Moreover, ORs are also thought to be involved in chemotaxis [74] and cytokinesis [75], and dozens of ORs were found to be expressed in the testis of mammals using deep sequencing [32]. Several tens of ORs were expressed in testicular tissues of mammals, and their roles in sperm-oocyte chemotaxis were investigated. Very

recently, Milardi *et al*. [33] suggested that the presence of ORs, such as OR4S1, OR4C13, and OR1I1, on mature cells might be related to acrosome activity and sperm motility after a proteomic analysis. Itakura *et al*. [34] also identified $G\alpha_{olf}$ and several kinds of ORs from rat placenta using RT-PCR, western blotting, and immunochemical methods. They

Table 1. Selected list of olfactory receptors expressed in system-wide tissues

Tissue	Organism	Representative OR(s)	Remarks (methods, DB, ligand)	Reference
Brain	Rat	RA1c (Olr59)	PCR, NB, ISH	[13]
	Mouse	MOL2.3 (RA1c, Olfr78)	PCR, β-gal staining, ISH	[14]
	Mouse	MOL2.3 (Olfr78)	β-gal staining, ISH	[16]
	Mouse	M71 (Olfr151), C6 (Olfr49), (OR3)	Cerebral cortex	[17]
	Mouse	Olfr110	AD, PSP, CJD, RT-PCR, cerebral cortex	[19]
	Human	ORs (↓)	Frontal cortex, PD, microarray	[18]
	Mouse	Olfr287, etc.	mDA cell, RT-PCR, ISH, FANTOM5	[21]
	Human	OR51E1, OR52L1 (↓)	DPC, schizophrenia, PCR	[20]
	Mouse	Olfr544	RT-PCR, qPCR	[23]
Heart-related	Rat	OL1 (Olr1654)	PCR, ISH	[9]
	Mouse, rat	PSGR homolog: RA1c (Olfr78, Olr59)	NB	[15]
	Mouse	MOL2.3 (Olfr78)	β-gal staining, ISH	[16]
	Human	ORs	Microarray	[24]
	Mouse	Olfr78	RT-PCR, β-gal staining, luciferase assay	[30]
	Human	OR10J5	Human aorta, coronary artery, HUVEC	[25]
	Mouse	Olfr78	Carotid body, immunostaining	[26]
	Rat	ORs	Sciatic nerve, dorsal root ganglia	[22]
	Mouse	Olfr78	Carotid body, single-cell RNA-Seq	[28]
	Human	OR51E1, OR2W3, OR51E2, etc.	TRXM analysis, RT-PCR, WB	[29]
	Mouse	Olfr544	RT-PCR, qPCR	[23]
Testis	Dog	HGMP07J/I (OR10J1), DTMT	PCR, NB	[7]
	Dog	DTMT	Antibody	[8]
	Rat	OL1 (Olr1654)	PCR, ISH	[9]
	Rat	OR2	Antibody	[31]
	Human	OR4N4, OR2W3, OR3A2, OR10J1, etc.	RNA-Seq	[32]
	Human	OR4S1, OR1I1, OR4C13	Testicular tissues, MS, WB, CA	[33]
Placenta	Rat	ORs	RT-PCR, WB, IH	[34]
Development	Mouse	Olfr603	Embryonic tissue, IF	[35]
Erythroid	Human	HPFH1OR (OR52A1)	RT-PCR, erythroid (blood), all stages	[11]
Tongue	Rat	ORs	RT-PCR	[36]
	Human	ORs	RT-PCR	[37]
	Human	ORs	RT-PCR	[38]
	Human, mouse	ORs	RT-PCR, bioinformatics	[39]
GI tract	Mouse	PSGR (Olfr78)	NB	[15]
	Human	4 ORs	RT-PCR, IH, amperometry	[40]
	Human	OR51E1	Microarray, RT-PCR, IH	[41]
	Pig	OR51E1	RT-qPCR, IH	[42]
	Human, mouse	OR1A1, OR1G1, OR51E1, Olfr43	RT-qPCR, siRNA	[43]
Pancreas	Rat	OL2 (Olr857)	PCR	[10]
	Rat	Orl984 (↓)	RT-PCR	[44]
	Rat	Orls (↓)	Microarray, bioinformatics	[45]
	Mouse	Olfr544	IC, IF, RT-PCR, RNA-Seq, WB	[46]
Spleen	Rat	OL2 (Olr857)	MIN6 cell line	[10]
	Rat	OdRs	Degenerate primers	[47]
	Human, mouse, rat	OR51E2, Olfr78, Olr59	NB	[15]
Liver	Human, mouse, rat	OR51E2, Olfr78, Olr59	Hepatocyte	[15]
	Human	OR1A1	PCR, IB, IH	[48]
	Human, mouse	OR10J5, Olfr16	PCR, WB, siRNA	[49]
	Mouse	Olfr544	RT-PCR, qPCR	[23]

Table 1. Continued

Tissue	Organism	Representative OR(s)	Remarks (methods, DB, ligand)	Reference
Kidney	Human	ORs	Microarray	[24]
	Mouse	Olfr78, Olfr90, Olfr1373, Olfr1392, Olfr1393	RT-PCR, WB, IH	[50]
	Mouse	Olfr78	RT-PCR, β-gal staining, luciferase assay	[30]
	Human	OR51E1, OR11H7	RT-PCR, WB, IC, IH	[51]
	Mouse	Olfr1393	RT-PCR, IH, IB	[52]
Lung	Mouse	MOL2.3 (Olfr78)	β-gal staining, ISH	[16]
	Human	OR51E1	RT-PCR, IH	[53]
	Human	OR2J3	NSCLC	[54]
Skin	Human	OR2AT4	Calcium imaging, wound scratch assay	[55]
	Human	OR51E2	RT-PCR, WB, IC	[56]
Muscle	Mouse	Olfr16 (MOR23)	RT-PCR, IB	[57]
	Mouse	Olfr16 (MOR23)	RT-PCR, IB	[58]
	Human	OR51E2	RT-PCR, CRISPR-Cas9, WB	[59]
	Human	OR51E1, OR11H7	RT-PCR, WB, IC, IH	[51]
Prostate	Human, mouse, rat	OR51E2, Olfr78, Olr59	NB	[15]
	Human	OR51E2	RT-PCR, IH	[60]
Cancers	Human	PSGR (OR51E2)	CaP, RT-PCR	[61]
	Human	PSGR	CaP, RT-PCR	[62]
	Human	PSGR2 (OR51E1)	CaP, RT-PCR, NB	[63]
	Human	OR51E2	CaP, RT-PCR, IH	[60]
	Human	OR1D2 (OR17-4)	CaP, RT-PCR, CLSM, FACS	[64]
	Human	PSGR	LNCaP, RT-PCR, calcium imaging	[65]
	Human	PSGR	LNCaP, MS, IB, calcium imaging	[66]
	Human	OR51E1	SI-NEC	[67]
	Human	OR1A2	Hepatocarcinoma	[68]
	Human	OR51B5	Leukemia	[69]
	Human	OR7C1	CRC-CIC	[70]
	Human	OR3A4	Gastric cancer	[71]
	Human	OR2AT4	Myelogenous leukemia	[72]
	Human	ORs	Leukemia	[73]
	Human	OR2J3	NSCLC	[54]

OR, olfactory receptors; NB, northern blotting; ISH, *in situ* hybridization; β-gal staining, β-galactosidase staining; AD, Alzheimer disease; PSP, progressive supranuclear palsy; CJD, Creutzfeldt–Jakob disease; RT-PCR, reverse transcription polymerase chain reaction; PD, Parkinson disease; mDA, mesencephalic dopaminergic; DPC, dorsolateral prefrontal cortex; qPCR, quantitative polymerase chain reaction; PSGR, prostate-specific G protein-coupled receptor; HUVEC, human umbilical vein endothelial cells; RNA-Seq, RNA sequencing; WB, western blotting; MS, mass spectrometry; CA, confocal analysis; IH, immunohistochemistry; IF, immunofluorescence; GI, gastrointestine; RT-qPCR, reverse transcription quantitative polymerase chain reaction; IC, immunochemistry; IB, immunoblotting; NSCLC, non-small-cell lung cancer; CaP, carcinoma of prostate; CLSM, confocal laser scanning microscopy; FACS, fluorescence-activated cell sorting; LNCaP, lymph node carcinoma of the prostate; SI-NEC, small intestine neuroendocrine carcinoma; CRC-CIC, colorectal cancer cancer-initiating cell.

suggested that ORs may recognize some small molecules in the placenta as environmental signals and mediate the growth of the fetus.

Tongue and gastrointestinal tract

Since three transcripts of OR were identified in rat taste organs and reproductive tissues using an RT-PCR strategy [36], ORs, as well as TASRs, were isolated in the tongue of human [37, 38] and mouse [39]. In mouse, northern analysis revealed that the homolog of PSGR (Olfr78), an OR, was predominantly expressed in colon [15]. In the case of human, the expression of four ORs, including OR73 (OR5D18), hOR17-7/11 (OR1A1), OR1G1, and hOR17-210 (OR1E3), in the enterochromaffin cells of human gut was confirmed [40]. Amperometric detection using Ca^{2+} imaging and immunostaining studies revealed that the ligands of those ORs consequently caused serotonin release. Another human OR, OR51E1, was identified from enterochromaffin cells in the jejunum and ileum of neuroendocrine carcinomas [41]. In 2015, the porcine homolog of OR51E1 was also found to be expressed along the gastrointestinal (GI) tract of pigs and modulated by intestinal microbiota [42]. Recently, human ORs (OR1A1, OR1G1, and OR51E1) and the mouse homolog of OR1A1 (Olfr43) were found to

participate in glucose homeostasis during meal ingestion by inducing the secretion of gut peptides [43].

According to recent reports, ORs are expressed in non-olfactory tissues, including brain, heart, testis, tongue, GI tract, pancreas [46], spleen [15], liver [23], kidney [52], lung [53], skin [56], muscle [58], and diaphragm [30], and even cancerous tissues, such as prostate [64] and lung cancer cells [54] (Table 1).

In human primary keratinocytes, OR2AT4 is expressed and induces wound-healing processes by increasing cell proliferation and migration and regeneration of keratinocyte monolayers [55]. In this mechanism, the activation of OR2AT4 induces the phosphorylation of extracellular signal-regulated kinases (Erk1/2) and p38 mitogen-activated protein kinase (MAPK) by a cAMP-dependent pathway. This type of investigation should be applied in various fields of OR research. Another human OR, OR51E2, was detected in human epidermal melanocytes at the transcript and protein level, and its stimulation with its cognate ligand, β-ionone, significantly slows melanocyte proliferation [56]. Additional results also demonstrated that OR51E2 activation elevates cytosolic Ca^{2+} and cAMP using RNA silencing and receptor antagonists. These findings suggest that OR signaling can influence melanocyte homeostasis. We surmise that ORs play a pivotal role in maintaining organismal homeostasis according to the results above.

Olfactory Receptors in Cancer

After an OR was found to be overexpressed in human cancerous prostate and identified as a PSGR (OR51E2) [61], PSGR (OR51E2) [62], and PSGR2 (OR51E1) [63] were proven to be differentially expressed between prostate cells in malignant and benign tissues. In 2009, Neuhaus *et al*. [60] identified androstenone derivatives as ligands for recombinant OR51E2. Activation of endogenous OR51E2 by β-ionone resulted in the inhibition of prostate cancer cell proliferation. The mechanism of p38, including its trigger (Pky2) and a tumor suppressor protein (N-myc downstream regulated gene 1), was suggested later [65, 66]. Also, the expression of OR51E1 in microdissected small intestine neuroendocrine carcinoma cells was found to be higher than in adjacent microenvironment cells [67].

In the case of ORs other than PSGRs, mRNA overexpression of OR1D2 was confirmed in LNCap prostate carcinoma cells compared with non-prostate-derived cell lines using RT-PCR, confocal laser scanning microscopy, and fluorescence-activated cell sorting [64].

Recently, a kind of terpene, the major constituent of essential oils, was observed as an effector in cellular proliferation in hepatocarcinoma cells [68]. A human OR, OR1A2, was detected at the mRNA and protein levels and demonstrated its potential involvement in (–)-citronellal-induced calcium signaling in the Huh7 hepatocellular carcinoma cell line. Massberg *et al*. [68] reported that the activation of OR1A2 results in the phosphorylation of p38 MAPK and reduces cell proliferation. More recently, Kalbe *et al*. [54] reported that a human OR, OR2J3, in non-small-cell lung cancer (NSCLC) cells induces apoptosis and inhibits cell proliferation and migration with its cognate ligand, helional. NSCLC is known to be resistant to common chemotherapy, and approaches via OR pathways could be helpful for the treatment of NSCLC with the precedence of further in-depth studies. Along with the cases mentioned above, diverse types of cancer appear to have various ORs, according to their occurring tissues (Table 1).

Perspectives

Regardless of their discovery history, it would be better to have an extended view of ORs to get objective analysis results. Besides OR expression, its transportation to the cytoplasmic membrane of a cell is indispensable for correct function. Recently, Sharma *et al*. [76] reported a study on the relation between OR protein trafficking and OR transcriptional regulation using an *Rtp1* and *Rtp2* double-knockout mouse system; thus, a more sophisticated study of OR trafficking should be complemented.

In case of the cancer research, some identified ORs could serve as potential therapeutic targets for cancer diagnosis and its therapeutic applications. All biological phenomena, including cancers, are composite networks. Although much research has been done and is ongoing with regard to ORs, the relationship of the results is not clear. However, it has been proven that molecular functions and physiological changes in various parts could be caused by OR ligands in animal system. Therefore, the future task will be to identify at a holistic level the extent to which OR is involved in overall physiological phenomena *in vivo*. More in-depth and comprehensive studies on an OR production and delivery system from the viewpoint of chemosensory machinery are needed for the research of animal physiology and the application of OR-related mechanisms. Another additional point to consider is that the OR family is one of the most dynamic gene populations among individuals [77]. In order to discover new facts about the function of ORs, environmental issues, as well as internal factors, must be considered. The report that bats have a unique and diverse OR gene repertoire deserves consideration [78].

To advance the study of the various functions and roles of ORs, the modularity mechanism that acts between the receptor and its wide-ranged ligands should be addressed.

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