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Human Olfactory Receptors Expression and Their Role in Non-Olfactory Tissues – A Mini-Review

Tatjana Abaffy*

Department of Molecular and Cellular Pharmacology, University of Miami, Miami, USA

***Corresponding author:** Tatjana Abaffy, Department of Molecular and Cellular Pharmacology, University of Miami, Miami, USA, Tel: 305 243 1508; E-mail: tabaffy@med.miami.edu

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Abstract

The expression of human olfactory receptors in non-olfactory tissues has been documented since the early nineties, however, until recently their functional roles were largely unknown. Many studies have demonstrated that these G-protein coupled receptors (GPCRs) are actively involved in various cellular processes. Here, we summarized current evidence describing the most prominent expression and functional data for these ectopic olfactory receptors. Further studies focused on discovering their ligands, both agonists and antagonists, will be necessary to fully characterize molecular mechanisms underlying their functional roles in human physiology and pathophysiology.

Keywords: Olfactory receptors; GPCRs; Ectopic expression

Introduction

Olfactory receptor (OR) genes discovered by Buck and Axel in 199, constitute the largest gene family in the human genome with 418 intact and potentially functional genes [**1**,**2**]. These genes are classified into 18 families, each family having >40% sequence identity (Figure 1). Based on the evolutionary data OR sequences are separated into two classes, class I and class II. Class I receptors resemble the family initially found in aquatic animals, thus it was suggested that these receptors may be specialized in detecting the water-soluble odorants [**2-4**]. Class II receptors are found only in terrestrial animals. Sequence differences between these two receptor classes are mainly in the extracellular loop 3 [**4**]. In humans all class I genes are clustered on chromosome 1, while class II genes are expressed on all chromosomes except chromosomes 20 and Y [**2**]. Within class I ORs 52% are pseudogenes, while pseudogene fraction in class II ORs is much higher, about 77% [**2**].

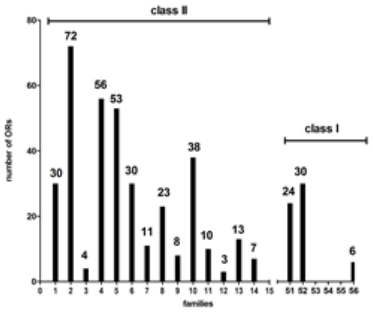

Figure 1: The number and distribution of human ORs within different classes and families [**5**,**6**]. Class I consists of family 5, 52 and 56 with about 60 functional genes. Families 53, 54 and 55 do not have any functional genes. Class II ORs group has 14 families and 358 functional genes.

The existence of olfactory receptors outside the olfactory sensory system was first documented in mammalian germ cells, and it was suggested that these "ectopic" ORs could have a role in chemotaxis during fertilization [**7-9**]. After this initial discovery, mammalian ORs genes were found in various additional non-olfactory tissues [**10**], like: prostate [**11**,**12**], tongue [**13-15**], erythroid cells [**16**], heart [**10**,**17**,**18**], skeletal muscle [**19**], skin [**20**], lung [**18**], testis [**18**], placenta [**21**], embryo [**22**], kidney [**23-26**], liver [**18**,**27**], brain [28] and gut [**29**].

In the olfactory sensory system only one allele of OR gene is expressed in each olfactory neuron [**30**], while in the non-olfactory tissues several ORs were found to be co-expressed in the same cell type, as demonstrated for the B- and T- lymphocytes and polymorphonuclear leukocytes [**31**], human sperm cell [**32**] and BON cells, a metastatic cell line derived from the human carcinoid tumor of the pancreas [**33**]. In leukocytes, several ORs are co-expressed with the taste, TAS2R and TAS1R, and trace amine associated receptors, TAAR1 [**31**]. Thus, various ORs can be co-expressed within the same cell type, and also various ORs can be co-expressed with other GPCRs in the non-olfactory tissues; however, more research is necessary to prove that this is indeed a general rule.

What is the functional role of these ectopically expressed olfactory receptors?

Conserved orthologous ectopically expressed olfactory receptor genes are evolutionary constrained, implying that these genes may have additional functions [**18**]. The first evidence demonstrating evolutionary conservation of ectopic OR between mouse, rat and humans, was provided for the OR51E2 receptor [**34**]. Niimura et al. identified two additional receptors OR51E1 and OR6B13, which together with OR51E, are the most evolutionary conserved olfactory receptors in placental mammals [**35**]. OR51E, OR51E, OR2A1 and OR2W3 are the most broadly expressed genes among various tissues examined [**36**]. The highest ORs transcript levels were found in the prostate (OR51E2), thyroid (OR2W3) and testis tissue (OR4N4) [**36**]. The evidence is accumulating that, apart from their well-established role in the odorant detection, these GPCRs have additional functions and are actively involved in various fundamental cellular processes.

Here, we presented a summary of ectopic ORs expression data, and when available this information is supported by functional data. It is important to mention, that additional functional data are necessary to support predicted cellular functions of ectopic ORs. Some of their most prominent functions are presented in Figure 2. In some cases, there is a lack of correlation in the expression profiles between human and mouse OR orthologous pairs [**10**]; thus, a simple assumption of their function in particular tissue based on correlation with mouse data is not always possible nor accurate, and further studies are necessary to investigate the role of these ectopic ORs.

Cell-Cell Communication and Recognition

Cutaneous chemo-sensation (Figure 2: A-1)

Recently, it was demonstrated that the activation of some ORs mediates cell-cell communication in the skin. The following ORs, belonging to class II, have been identified in the skin: OR6V, OR5V, OR2AT4, OR11A, OR6M1. Odorant sandalwood was able to activate OR2AT4 receptor present in the skin keratinocytes [**20**]. This activation led to the release of ATP from the keratinocytes and subsequent activation of P2X purinergic receptors on the neighboring trigeminal neurons [**37**], thus establishing a communication between keratinocytes and trigeminal neurons.

Embryogenesis (Figure 2: A-2)

ORs have also been detected in various "*extrasensory tissues*" during embryonic development. The OL1 receptor was found to be expressed in the developing rat heart [**38**]. Few ORs were also detected in the fetal tongue, however, no clear involvement in the perception of taste could be demonstrated [**15**]. Several ORs were detected in the pyramidal neurons of developing mouse cortex [**39**]. Furthermore, few ORs have been detected in mouse placenta (MOR125-, 126-, 140-, 145-5 and 216-1) [**21**], and in order to explain their presence, "*an area code hypothesis*" was proposed [**22**]. This hypothesis states that cell-cell recognition, migration and tissue assembly during embryogenesis requires a complex addressing system and that ORs may be the recognition molecules encoding cell identity and allowing appropriate positioning during embryogenesis. The involvement of ORs in the cell-cell cooperation during mouse embryogenesis was indeed recently demonstrated using a genome-wide cheater screen analysis [**40**]. It is tempting to believe that some ORs may have a similar role in the human embryogenesis.

Tissue Injury, Repair and Regeneration

Skeletal muscle/ cardiomyocytes (Figure 2: B-1)

Griffin et al. detected 13 mouse ORs in the highly proliferative myoblasts and demonstrated that some of these receptors show increased expression in *in vivo* muscle regeneration experiments [**19**]. One of these, MOR23 receptor, previously detected in the olfactory sensory neurons and testis [**7**,**41**,**42**], was able to influence myofiber branching and fusion of myoblasts into myofibers [**19**,**43**,**44**]. Activation of this receptor promoted cell adhesion and muscle regeneration [**43**]. Several ORs transcripts were detected in the human skeletal muscle (OR51E, OR51E, OR2A, OR7C, OR1E1 and OR2B6) [**36**], however, their function has yet to be investigated.

Skin (Figure 2: B-2)

Human OR2AT4 receptor (also known as the OR11-265) is expressed in keratinocytes and when activated by its odorant-ligand sandalwood, it can induce cell migration, proliferation and regeneration of skin tissue, as demonstrated by *in vitro* wound scratch assay [**20**]. No endogenous ligand for this receptor has been identified.

Nerve injury and regeneration

A significant number of rat ORs were found to be up-regulated in a sciatic nerve and in a dorsal root ganglia (DRG) following nerve injury [**45**]. Hydrogen peroxide stimulation of Schwann cells in culture mimics oxidative stress and increases expression of 14 ORs, indicating that these receptors may be directly or indirectly involved in neuronal injury and peripheral nerve regeneration. In humans, several neurodegenerative diseases, like Alzheimer disease, Progressive Supranuclear Palsy, and Creutzfeldt-Jakob disease, have been associated with dysregulated ORs expression levels [**46**], however, at present, it is not clear if these changes are implicated in a disease progression or are just secondary consequences of diseases. Down-regulated ORs were documented in the mesencephalic dopaminergic neurons [**47**] and in the frontal cortex in the brains of Parkinson disease (PD) patients [**28**]. It seems that this down-regulation is not merely a result of neuronal loss, and it is unrelated to drug therapy. It is unknown if this down-regulation has a role in the olfactory dysfunction observed in PD patients. Several olfactory and taste receptors were found to be down-regulated in the prefrontal cortex of schizophrenia patients, and it was suggested that they may be either directly involved in the disease progression or are dysregulated as a consequence of antipsychotic treatment [**48**], however, at the moment, there is no conclusive proof for either statement.

Chemotaxis

Sperm (Figure 2: C)

The microarray analysis indicates that over 80 different ORs were found in testis [**18**,**49**], and some of these receptors are exclusively expressed in testis and were not found in the olfactory epithelium. Increased cell motility towards the odorant-ligand-attractant has been demonstrated for the OR1D, also known as the OR17-4 receptor [**50**] and also for OR4D1 and OR7A5 [**32**]. When activated by specific agonists, the latter two receptors can increase flagellar beating frequency and sperm velocity [**32**]. In addition to these ORs, a CatSper, a cationic channel that controls intracellular Ca+2 concentration and swimming behavior of sperm, is also activated by various odorants [**51**], adding an additional layer of complexity when studying sperm motility. It has been demonstrated that the activation of OR1D2 receptor in the mature spermatozoa induces a PKA-dependent translocation of β-arrestin2 to the nucleus, indirectly mediating gene expression [52]. These results indicate that some ORs expressed in the sperm, may be involved in the early gene transcription events following fertilization.

Cancer growth, progression and metastasis (Figure 2: D)

Many studies demonstrated expression of ORs in the cancer tissue. Here, the most prominent receptors are discussed. The OR51E1 is a class I OR (Synonyms: GPR136, POGR; DGPCR; PSGR2; D-GPCR;

POGR; GPR164; OR51E1P; OR52A3P [**53-55**]. This gene is found to be over 100 fold increased in gastrointestinal neuroendocrine carcinomas [**55**,**56**]. Both, transcript and protein levels, are found to be increased in the prostate cancer [**57**,**58**], and in the somatostatin receptor SSTR-negative lung carcinoid tumors [**59**]. The OR51E1 protein is broadly expressed in healthy human tissues [**60**] and www.proteinatlas.org. Currently identified ligands for this receptor are nonanoic or pelargonic acid, butyl-butyryl lactate [**61**], and isovaleric acid [**62**]. Another member from the same class I and the same 51 olfactory family, OR51E2 (Synonyms: OR11-16, HsOR11.3.16, ORL3397, PSGR), was also found to be widely expressed in healthy tissues examined [**36**], with the highest expression in the prostate gland [**11**]. This gene is also highly up-regulated in the prostate cancer [**12**,**63**,**64**]. Although, Neuhaus et al. demonstrated that activation of the OR51E2 by β-ionone in prostate cancer cells inhibits cell proliferation [**65**], evidence is accumulating that the up-regulation of this receptor promotes tumor growth [**63**] and correlates with prostate cancer progression [**66**]. This receptor is also likely to be involved in the early stages of prostate carcinogenesis, since it has been demonstrated that its up-regulation induces chronic inflammatory response with a consequent development of premalignant prostate intraepithelial neoplasia, PIN [**11**,**12**,**63**]. Currently identified ligands for this receptor are short chain fatty acids, acetate and propionate [**61**], androstenone-derivatives [**65**] and plant isoprenoid β-ionone [**65**].

OR2W3 belonging to a class II genes, is another widely expressed olfactory receptor with the highest transcript expression detected in the thyroid gland [**36**]. A T240P mutation in this gene was found to be associated with pancreatic ductal adenocarcinoma [**67**]. Furthermore, R142W mutation in the OR2W3 was identified as a potentially causative mutation for autosomal dominant retinitis pigmentosa [**68**].

Nutrient Sensing and Regulation of Blood Pressure

Kidney

Olfr78, Olfr90, MOR31-6, Olfr1373, Olfr1392 and Olfr1393 and MOR42-1 were detected in the mouse kidney, where they were able to modulate renal secretion and glomerular filtration rate along with another GPCR, Gpr41 [**23-26**]. Short chain fatty acids, acetate and propionate were identified as ligands for one of these receptors, mouse Olfr78, and also for its human orthologue OR51E2 [**23**,**61**]. Both, acetate and propionate are produced by fermentation of carbohydrates by gut microbiota [**25**]. Thus, food-derived metabolites act as agonists for olfactory and other GPCRs localized in the kidney and are able to modulate renin secretion and blood pressure [**69**].

Gastrointestinal system

ORs presence has been detected in the enterochromaffin cells of the gut (OR73, hOR17-7/1, OR1G, hOR17-210) and also in neuroendocrine carcinomas of the gut [**29**,**56**]. It has been demonstrated that various ligands derived from food spices are able to activate these ORs and induce serotonin release, indicating their potential role in regulating motility of the gastrointestinal tract [**29**].

Cell Migration - Angiogenesis

Human Umbilical Vein Cells (HUVEC) is widely used as a model system to study endothelial cell physiology. Olfactory receptor OR10J5 was detected in the HUVEC cells, as well as in the aorta and in the coronary artery, and it was demonstrated that its activation by odorant-ligand lyral in *in vitro* assay, increases cell migration *via* AKT- and ERK- mediated pathways [**70**]. These results suggest that some ectopic ORs may be involved in the endothelial cell migration and proliferation during angiogenesis.

Energy Homeostasis and Cellular Metabolism

OR4N4 receptor is highly expressed in the thyroid and testis tissue [**36**]. However, currently, there is no evidence related to its function in these tissues. It is interesting to note, that type 2 taste receptors (TAS2Rs) are also expressed in human thyrocytes. It has been demonstrated that polymorphisms in the TAS2R genes are associated with differences in the circulating levels of thyroid hormones [**71**]. Whether the ORs expressed in the thyroid tissue are also able to modulate thyroid hormones, and thus affect thyroid function remains to be determined.

Cytokinesis

OR2A1 and OR2A4 receptors are involved in the cell division, mainly in its last and highly coordinated step – cytokinesis. OR2A4 knockdown caused cytokinesis failure in the HeLa, human cervical cancer cell line and in the HCT116, human colon cancer cell line. In addition to these olfactory receptors, TAS1R2 and TAS1R13 taste and OPN1SW opsin receptors were also found to play a role in cytokinesis [**72**].

ORs with Unknown Functional Roles Detected In Various Tissues

Atrioventricular node

High expression of human ORs was detected in the atrioventricular node of the heart [**10**].

Thrombocytes (platelets)

Few ORs were detected in activated platelets, as part of the non-secreted fraction (OR51E, OR2T11 and OR4L, Data Supplement 3) [**73**]. Platelets have an important role in hemostasis, and are also recruited to the sites of injury or infection where they modulate inflammatory processes by secreting cytokines, chemokines and interacting with leukocytes. Elevated platelet counts are present in many cancer patients and it has been shown that they are able to promote cancer cell proliferation [**74**,**75**]. The exact function of these ORs in the platelets is currently unknown.

Leucocytes

53 class I ORs were detected in monocytes, NK cells, B-cells and PMN cells, with the highest expression of OR51B6, OR52A4 and OR56B4 [**31**], suggesting that some ORs may be involved in various immune reactions.

Tongue

Several OR were also detected in the lingual cDNA libraries (OR10A4, OR7A5, OR6Q1 and OR6C1) [**14**], however, their function is currently unknown.

Genetic Deletion of ORs

Class I ORs genes are localized on chromosome 11 and surround the complex of β-globin genes [**76**]. It has been reported that patients with β-thalassemia (reduced or absent synthesis of hemoglobin β chain), have a homozygous deletion of the 118 kb region which encompasses not only the entire β-globin gene, but also extends to a deletion of 6 ORs genes, four of which have been predicted to be functional (OR51A4, OR51Z, OR52A1 and OR52A5) [**77**]. The effects of this deletion on olfaction or other physiological functions are currently unknown.

OR genes are highly polymorphic and this polymorphism results in functional variability in the olfactory perception [**78-84**]. Future studies will show whether the polymorphism within the ectopic ORs has significant consequences for various pathophysiological processes, some of which have been outlined here. Many studies demonstrated highly up-regulated expression of ectopic ORs in various tumors and more research is necessary to identify their ligands and to fully characterize their role in cancer pathology. Evidence exists that some GPCRs, when persistently activated, can turn into oncogenes, and it has been demonstrated for several GPCRs like: 5HT1c receptor [**85**], m, m3 and m5 muscarinic receptors [86] and α1B-ADR [**87**]. Thus, agonist-induced cellular proliferation, as a phenomenon is not a unique feature of ORs. Recently it was demonstrated that chronic exposure to the agonist - lyral in early postnatal stage, increases sensitivity of the mouse MOR23 receptor within the olfactory sensory system [**88**], however, it remains to be seen whether the similar process occurs in human ORs expressed in non-olfactory tissues.

Data presented here indicate that olfactory receptors can have different functions in the human tissues. This functional versatility is related to a great structural plasticity of these GPCRs. ORs can have various conformations, and depending on the physicochemical nature of their ligands these GPCRs can adopt a new conformation, an "induced-fit", with which this receptor-ligand complex can activate various signaling pathways. The activation of particular signaling pathway will depend on the available ligand and on the specific cellular/tissue phenotype, and will ultimately result in a specific cellular process. Identifying ligands for these ectopic ORs using both computational, *in silico* and *in vitro* approaches will enable future progress in unraveling additional functions of these receptors in non-olfactory tissues [**61**,**89-97**]. Furthermore, a chemical protein interactome approach (CPI) may be used to discover additional potential interacting partners of the newly identified ligands [**98-100**].

GPCRs can also form dimers [**101**], and in case of heterodimerization, a novel signaling pathway may be activated and result in a different cellular process and function, as recently demonstrated for angiotensin II AT1 receptor and alpha2C adrenergic receptor [**102**,**103**].

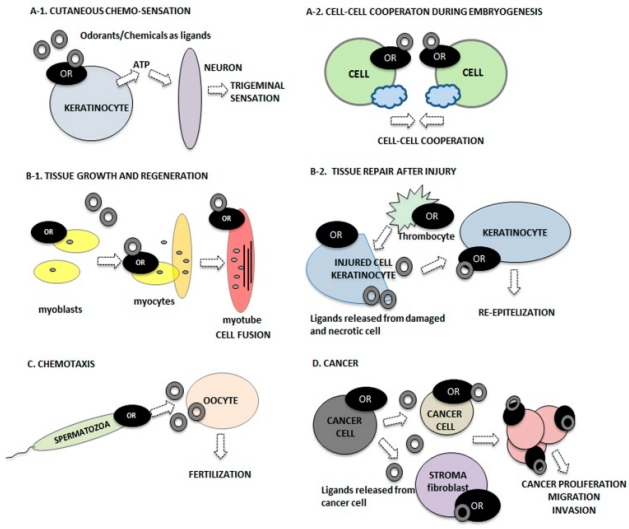

Figure 2: The most prominent functional roles of ORs expressed in non-olfactory tissues.

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