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HUMAN OLFACTORY RECEPTORS: NOVEL CELLULAR FUNCTIONS OUTSIDE OF THE NOSE

Désirée Maßberg and Hanns Hatt

Ruhr-University Bochum, Department of Cell Physiology, Bochum, Germany

Maßberg D, Hatt H. Human Olfactory Receptors: Novel Cellular Functions Outside of the Nose. *Physiol Rev* 98: 1739–1763, 2018. Published June 13, 2018; doi: 10.1152/physrev.00013.2017.—Olfactory receptors (ORs) are not exclusively expressed in the olfactory sensory neurons; they are also observed outside of the olfactory system in all other human tissues tested to date, including the testis, lung, intestine, skin, heart, and blood. Within these tissues, certain ORs have been determined to be exclusively expressed in only one tissue, whereas other ORs are more widely distributed in many different tissues throughout the human body. For most of the ectopically expressed ORs, limited data are available for their functional roles. They have been shown to be involved in the modulation of cell-cell recognition, migration, proliferation, the apoptotic cycle, exocytosis, and pathfinding processes. Additionally, there is a growing body of evidence that they have the potential to serve as diagnostic and therapeutic tools, as ORs are highly expressed in different cancer tissues. Interestingly, in addition to the canonical signaling pathways activated by ORs in olfactory sensory neurons, alternative pathways have been demonstrated in nonolfactory tissues. In this review, the existing data concerning the expression, as well as the physiological and pathophysiological functions, of ORs outside of the nose are highlighted to provide insights into future lines of research.

I. INTRODUCTION

Olfactory receptors (ORs) detect volatile chemicals that are common odorants in the environment. In 1991, Linda Buck and Richard Axel (21) discovered a very large multigene family (~1,400 members) that encodes G protein-coupled receptor proteins (GPCRs) in the genome of the rat and postulated that ORs are exclusively expressed in the olfactory epithelium. Starting with the first comprehensive study of ORs in the human genome (153), ~900 OR genes have been identified in humans, including ~400 OR genes that possess an intact open reading frame (207). Interestingly, nearly 7 years passed before the first deorphanization of an OR was successfully achieved via recombinant expression of ORs of zebrafish in human embryonic kidney HEK293 cells (193) and in vivo adenovirus-mediated gene transfer of the cloned rat OR I7. Electrophysiological recordings indicated that overexpression of this gene was sufficient to generate responses to C7–C10 aliphatic aldehydes (210). In parallel, the first demonstration of a human OR-odorant interaction was provided by expression of hOR17–40 (OR3A1) in HEK293 cells along with G proteins. Odorant screenings were performed, and specific odorants (helional and heliotropylacetone) were identified as ligands by measuring transient elevations in intracellular calcium levels using calcium imaging technology (198).

Despite the initial assumption that they were restricted to the olfactory epithelium (OE), 1 yr after the discovery of OR genes, Parmentier et al. (140) identified the first OR gene transcripts outside of the nose in mammalian germ cells. Over the following two decades, further descriptive studies demonstrated the ectopic expression of other OR genes in a multitude of human tissues throughout the human body (1, 35a, 44, 47, 50, 89). In general, the term *ectopic* is defined as a biological event or a process that occurs in an abnormal location or position within the body (44). However, the expression of ORs outside the OE occurs in a rather unexpected than in an abnormal place.

Although the sense of smell is not essential for human survival, its loss can indicate various neurodegenerative processes and significantly influence an affected person's quality of life. This may also serve as a starting point for future studies trying to understand the underlying pathologies. However, several ORs appear to be highly conserved among mammals and underlie stronger evolutionary constraints than OR genes expressed exclusively in the OE (35a).

In particular, some of the evolutionarily older fishlike ORs (OR51E1 and OR51E2) (51, 133) exhibit ~94% sequence similarity to their mammalian orthologs (136, 154, 208); however, they are expressed broadly and have pronounced transcript and protein levels in various human tissues (47, 118, 180). This phenomenon highlights the importance of conserved ORs outside the OE and their potential to function apart from the sense of smell. Initially, a minor or even artificial role of human ORs detected at the transcript level was predicted (44). However, to date, the protein abundance and cellular function of an increasing number of ORs have been elucidated. The first evidence for the function of an OR expressed outside the nose was shown for human hOR17–4 (OR1D2) (173) and mouse MOR267–13 (orthologous to human OR10J5) (54) in sperm chemotaxis and chemokinesis. Meanwhile, several essential physiological and pathophysiological processes have been described as targeted by human ORs, including path finding, cell growth, differentiation and apoptosis, migration, and secretion (4, 17, 24, 49, 60, 82, 88, 115, 116, 118, 119, 132, 150, 158, 164, 173, 179, 182, 191, 209). Ectopic ORs may play a role not restricted to humans as also in other mammals, mostly in mice, their involvement in similar physiological processes was discovered (36, 54, 67, 144, 145, 166).

However, the function of the majority of ORs in nonolfactory tissues remains uncertain because their activating odorants are currently unknown. This review summarizes the occurrence of human ORs outside of the nose with a focus on their effects on various human tissues. Understanding the molecular and cellular mechanisms of action provides the basis for the acceptance of the functional importance of extranasal ORs and suggests their clinical utility.

II. ECTOPICALLY EXPRESSED HUMAN OLFACTORY RECEPTORS

Since the first discovery of ectopically expressed ORs in mammalian testes (140), the number of studies that aimed to uncover OR expression in nonolfactory tissues is continuously increasing. By taking advantage of the rapid technical progress made over the previous two decades, comprehensive transcriptome analyses have further facilitated the systematic exploration of numerous OR genes transcribed throughout the entire human body (35a, 44, 47, 77). Currently, the detection of OR transcripts is largely based on (q)RT-PCR, microarray, or relatively new NGS (RNASeq) analyses. These methods have enabled a comparable and quantitative OR expression analysis at the mRNA level. Transcriptome data are available for more than 45 different human tissues, including the cardiovascular system, gastrointestinal system and accessory organs for digestion, the nervous system, the musculoskeletal system, the reproductive system, the respiratory system, and the urinary system, as well as the skin and blood. Within these tissues, each investigated tissue type has shown the expression of at least one OR (35a, 44, 47, 109, 180), as exemplarily shown for 16 tissues in the Bodymap project **(FIGURE 1)**. The expression pattern of ORs in a specific tissue is relatively stable; however, the number of ORs expressed in different human tissues varies substantially, ranging from only a few ORs in the liver or skeletal muscle to more than 60 ORs in the testis (47). Overall, OR genes generally have a lower average expression level in nonolfactory tissues compared with the human OE (135).

Several ORs exhibit a broad tissue distribution, whereas other ORs appear to be exclusively restricted to one specific tissue (44, 47). The most highly expressed OR, OR4N4 in

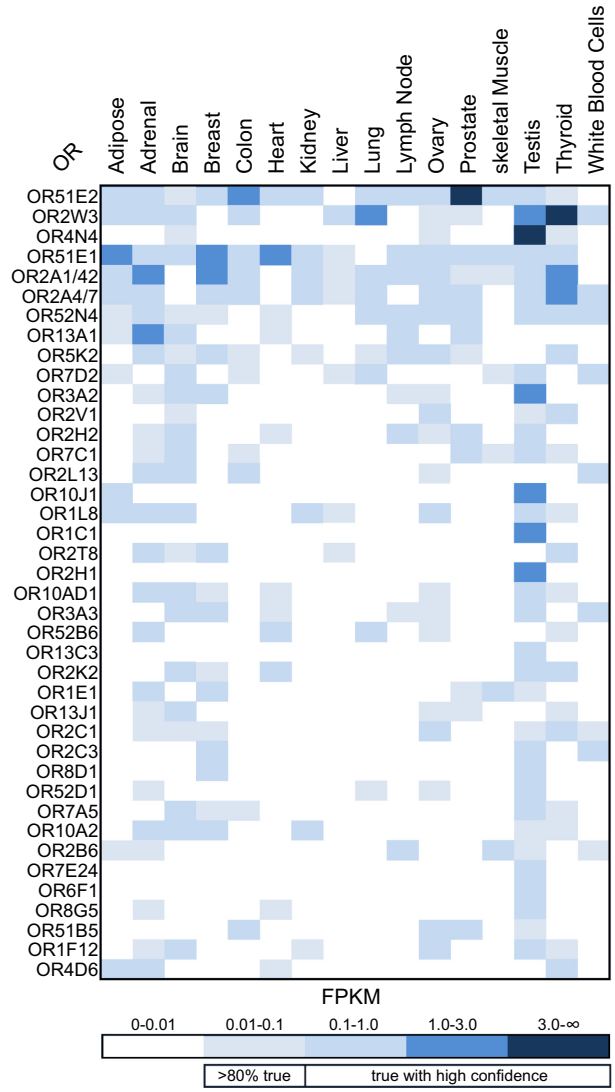

FIGURE 1. Olfactory receptor (OR) gene expression outside of the nose. This illustration indicates the 40 most highly expressed ORs detected in 16 human tissues from the Bodymap project. The results of this NGS-based transcriptome analysis are depicted as a heat map that shows the FPKM values (fragments per kilobase per million mapped fragments) (47). [From Flegel et al. (47), licensed under CC BY.]

human spermatozoa, is one example of a highly and selectively expressed OR. The expression of this OR is virtually nondetectable in other tissues, including the human OE (49, 135). However, despite the availability of a specific antibody, this receptor protein was not detected in different spermatozoal samples (49). Another specifically expressed receptor is OR6B3, which is highly expressed in the dorsal root ganglion (DRG), trigeminal ganglion (TG), and retina (48, 83).

In the case of another broadly expressed candidate, OR2A7 (OR2A4, 99% sequence homology), parts of its open reading frame (ORF) overlap with an exon of rho guanine nucleotide exchange factor 34 pseudogene (ARHGEF34P). However, OR2W3 and OR2A4/7 were detected via immunostaining in several cell lines and tissues (49, 56, 118, 179, 209), which indicates the ability of the transcript to produce OR proteins. These are convenient examples showing that ectopic OR expression underlies a highly variable and complex regulatory mechanism. It has been proposed that ectopic gene expression is a widespread phenomenon in multicellular organisms, which is linked to regulatory leaks in gene expression. This process may underlie a significant evolutionary importance, because gene expression is flexible for wide structural and functional diversity (151). This phenomenon is further strengthened by the multifunctional features of the same OR that is expressed in different human tissues (24, 115, 116, 179). Ectopic OR gene expression does not depend on the genomic locus; however, highly expressed non-OR gene clusters, which harbor the coding sequences for ORs, positively influence the OR transcript levels (44), with the exception of the highly expressed ORs OR51E1 and OR51E2, which do not possess highly expressed adjacent non-OR genes (47).

OR51E1 (PSGR2) and OR51E2 (PSGR) are examples of ORs that are ubiquitously expressed throughout the human body, although their abundance is substantially increased in prostate tissue, especially in prostate cancer (35, 192). Moreover, the expression of OR51E2 in prostate cancer tissue is even higher than in the human OE (135) and, in some individuals, comparable to highly expressed housekeeping genes (118). However, most ORs exhibit comparably low expression levels when considering the entire tissue transcriptome (47). In general, it appears plausible that the relatively low expression levels of ORs may be due to the low numbers of expressing cell types within the mostly complex and heterogeneously organized tissue structures.

OR2W3, which is one of the most broadly expressed candidates, is abundant in at least 20 different human tissues (47, 83, 111, 147). Detailed analyses, however, indicate divergent posttranscriptional splicing events of OR2W3 across human tissues. In the human brain, lung, thyroid, white blood cells, DRG, and presumably further tissues that have not yet been examined, the complete OR2W3 coding sequence is a part of chimeric transcripts with the upstream gene, E3 ubiquitin-protein ligase coding Trim 58 (47, 48). The oncogenesis of several common cancers has been attributed to recurrent gene fusion (124, 176); thus the functional relevance of OR2W3 remains an open but interesting question.

Previous reports of transcripts in the antisense orientation support the assumption that OR transcripts may perform functions in addition to coding for functional OR proteins (49). The functional role of OR antisense transcripts is currently unexplored; however, antisense transcription has been attributed to gene expression and chromatin modification regulation (125, 141).

In contrast to the OR repertoire of a single OSN (72), more than one ectopically expressed human OR has been identified in the same cell type (49, 60, 83, 85, 114, 115, 119, 158, 179, 182, 191). In the murine OE, OR expression is monoallelic, and each ORN expresses only one allele of an OR gene (29, 31, 72). In mice, this OR gene choice relies on several principles, including the effects of H elements (55, 108) or heterochromatic silencing by histone methyltransferases (110). In the case of ectopically expressed ORs outside of the OE, the mechanisms that regulate gene expression are markedly different. In many characterized cell types, more than one OR is coexpressed, and in the testis and spermatozoa, mRNAs for multiple receptors are potentially present in single cells (49). There are only limited reports of OR gene regulation outside of the OE. In the testes, a complex pattern of OR transcript variants has been observed (184). Here, for one OR gene (hs6M1–16, also known as OR2H1), six different transcriptional start points were found. For other ORs (hs6M1–18, −21, and −27, also known as OR11A1, OR5V1, and OR12D3), a common start site with potential bidirectional transcriptional activity was identified (184). Both a variety of alternative splicing events in the 5′ untranslated gene regions (5′UTRs) and the presence of different promoters have been identified for other ORs (47, 48, 135, 184). OR51E2 gene expression, for example, is controlled by different promoters in the OE and prostate (135).

Considering that ORs occur in nearly the entire human body, they appear to be substantially more functionally important than previously suggested. In the last decade, an increasing number of studies have shown their ability to operate in physiological and pathophysiological cell processes. This is primarily based on a growing number of deorphanized human ORs, although it must be noted that the identified ligands are often synthetic compounds, and their endogenous physiologically relevant activating substances are still unknown. Nevertheless, the cellular roles of ORs can be studied using synthetic substances. However, more effective natural ligands may exist that can activate

the receptor at much lower concentrations. In the following section, the most important findings are highlighted.

III. PHYSIOLOGICAL FUNCTIONS OF ECTOPICALLY EXPRESSED OLFACTORY RECEPTORS

A multitude of ORs have been discovered at the transcript level in different human tissues **(FIGURE 1)**; however, a substantially lower number of reports have been provided with respect to their protein incidences. Few studies have demonstrated the functional effects in cells or cell lines of the respective tissues **(FIGURE 2)**. Evidence has rapidly accumulated that ORs participate in important cellular processes outside of their primary sensorial organ, where they function in odor detection and discrimination **(TABLE 1)**.

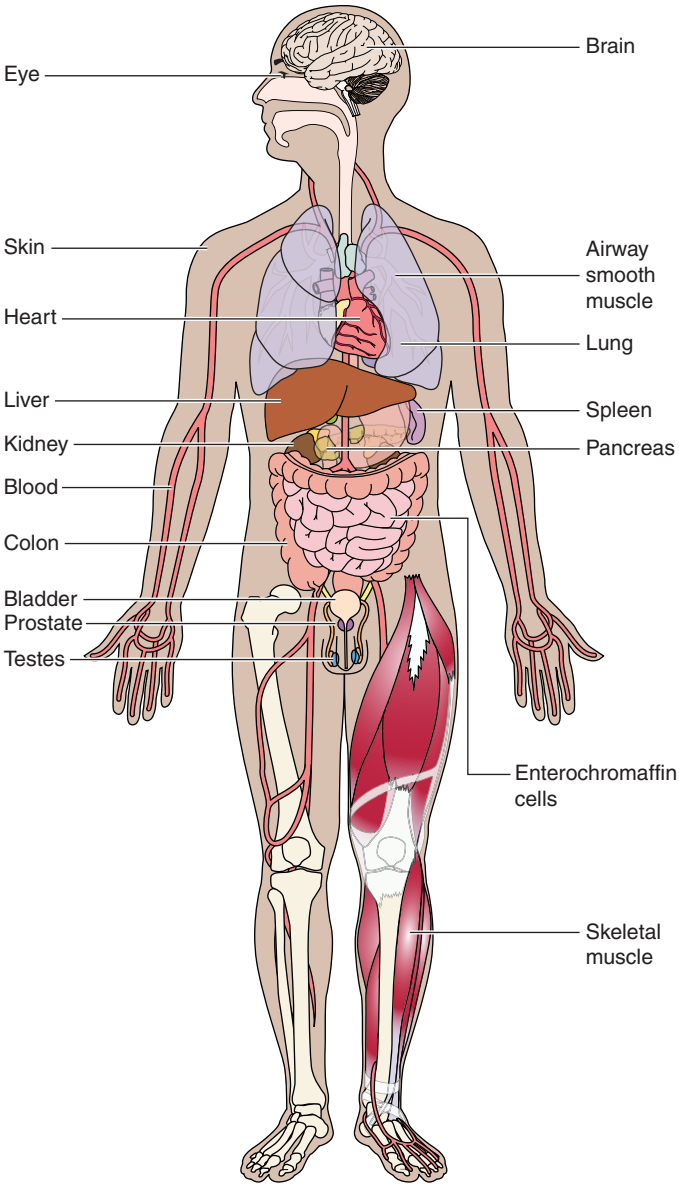

FIGURE 2. Functional OR expression in the human body. This illustration indicates all human tissues and corresponding cell lines in which OR functionality has been demonstrated. [Modified from Laskowski and Balicki (101).]

A. Cardiovascular System

The functional analysis of ectopic ORs in the cardiovascular system is of particular interest because they have an enormous potential to operate as the main carrier of endogenously and exogenously derived odorants throughout the entire human body.

OR10J5 is expressed in the human aorta, coronary arteries, and umbilical vein endothelial cells (HUVECs). Its activating odorant, lyral, evokes an intracellular Ca^{2+} influx and the phosphorylation of protein kinase B (AKT), which results in enhanced migration and angiogenesis (93).

Another function has been proposed in the human heart: the "motor" for the blood circulation. In this study, next-generation sequencing analysis indicated the expression pattern of ~10 different ORs in adult and fetal human heart muscle cells and identified the fatty acid-sensing OR51E1 as the most highly expressed OR in both cardiac developmental stages. Nonanoic acid and structurally related medium-chain fatty acids were identified as powerful agonists, and 2-ethylhexanoic acid was identified as a receptor antagonist. Several agonists were detected at receptor-activating concentrations in the plasma and epicardial adipose tissue, particularly in patients suffering from diabetes. The application of OR51E1 agonists induced negative chronotropic (reduced heart frequency) and inotropic (reduced contraction force) effects in cardiac trabeculae and slice preparations of human explanted ventricles, as well as human stem cell-derived cardiomyocytes. In the presence of the antagonist, the effect was reversed, which indicates a potential clinical use. These findings indicate that OR51E1 may play a role as a metabolic regulator of cardiac function (82).

B. ORs in the Cellular Immune System

OR transcripts have been identified in various human blood cells, e.g., erythrocytes, peripheral blood mononuclear cells (PBMCs), natural killer cells, B and T cells, and polymorphonuclear neutrophil granulocytes (11, 43, 47, 114, 117, 211). Aroma compounds from butter, known ligands for a variety of class I ORs that are expressed in various blood cell types (114), induce chemotactic behavior in human neutrophils (57). Odorants also act on immune cells in the murine immune system, where they can inhibit chemokine-driven chemotaxis in $CD4^+$ T cells (30) or can regulate macrophage function (104).

Furthermore, OR function has been implicated in myelogenous leukemia. The Sandalore-dependent activation of OR2AT4 leads to reduced proliferation and enhanced ap-

Table 1. *Physiological functions of ectopically expressed ORs*

System	Tissue	Cell Type	Olfactory Receptor	Odorants	Detection Technique	Function	Signaling	Reference
Cardiovascular system	Blood	PBMC-derived CD8+-T cells, PCa cell line PC-3 and LNCaP	OR51E2 (PSGR)	—	PSGR peptide synthesis, RT-PCR cytokine ELISA, IFN-γ ELISPOT assay, cytotoxicity assay	PSGR-derived peptides as tumor-associated antigen recognized by CD8+-T cells	—	(121)
	Blood/brain	Peripheral blood mononuclear cells (PBMC), mouse primary cortico-hippocampal neurons	OR52N5, OR11H1, OR4M1	Acetophenone (OR4M1)	Microarray, qRT-PCR, cAMP assay, WB	ORs as biomarkers for traumatic brain injury (decreased expression in PBMC) activation of overexpressed OR4M1 leads to reduced tau phosphorylation	cAMP ↑ JNK ↓	(211)
	Heart	Aorta, coronary artery, umbilical vein endothelial cells (HUVEC cell line)	OR1OJ5	Lyral	WB, calcium assay, migration assay, Matrigel plug assay, siRNA	Enhanced migration enhanced angiogenesis in vivo	Ca^{2+} ↑ AKT ↑	(93)
	Blood	Acute myeloid leukemia cells (K562 cell line), primary blood cells of acute myeloid leukemia patients	OR2AT4	Sandalore, brahmanol antagonist: phenirat	RT-PCR, IF, calcium imaging (fura 2-AM), WB, cell proliferation assay, annexin-V/PI staining	Inhibited cell proliferation enhanced cell apoptosis, cell cycle arrest ($G_{0/1}$, G_2/M) and differentiation to hemoglobin carrying cells	Ca^{2+} ↑ (AC) cAMP ↑ PKA ↑ AKT ↑ ERK ↑ p38 MAPK ↓ VGCC (L-type)	(115)
	Blood	Acute myeloid leukemia cells (K562 cell line)	OR51B5	Isononylalcohol (Iso)	RT-PCR, IF, calcium imaging (fura 2-AM), WB, cell proliferation assay	Iso-dependent receptor downregulation inhibited cell proliferation	Ca^{2+} ↑ (AC) PKA ↑ VGCC (L-type) ERK ↑ p38 MAPK ↑ Bcr-Abl ↓	(116)
	Heart	Stem cell-derived cardiomyocytes, human myocardial tissue culture	OR51E1 (PSGR2/ Dresden-GPCR)	Nonanoic acid, decanoic acid, further MCFS, antagonist: 2-ethylhexanoic acid	CRE-luciferase assay, calcium imaging (fura 2-AM), siRNA, RT-PCR, WB, IHC, contractile force measurements	Negative chronotropic and inotropic effects reduction of contraction force of explanted heart	Gβγ Ca^{2+} ↓ (AC/PLC?)	(82)

Continued

Table 1.—*Continued*

System	Tissue	Cell Type	Olfactory Receptor	Odorants	Detection Technique	Function	Signaling	Reference
Gastrointestinal system	GI	EC cells (BON cell line), primary mucosal human EC cells (ileum)	OR1A1, OR1G1, OR3A1	Thymol, geraniol (OR1G1) bourgeonal, helional (mouse orthologous of OR1A1, OR3A1)	RT-PCR, calcium imaging (fluo 4-AM), serotonin enzyme immunoassay, amperome try	Serotonin release	Ca^{2+} ↑ (intracellular, PLC, IP_3R) VGCC (L-type)	(17)
	GI	Primary EC cells, neoplastic EC cells (KRJ-I)	OR1G1 (?)	Thymol, eugenol	qRT-PCR, microarray, ERK ELISA, flow cytometry Ca^{2+} flux, (fluo 3-AM)	Serotonin release, inhibited by somatostatin analog	Ca^{2+} ↑	(92)
	Liver	Hepatocellular carcinoma cell line HepG2	OR1A1	(-)-Carvone	RT-PCR, IF, calcium imaging (fluo 4-AM), cAMP/PKA assay, lipid analysis, siRNA	Reduced mitochondrial glycerol-3-phosphate acyltransferase (GPAM) gene expression involved in triglyceride synthesis	cAMP ↑ PKA ↑ CREB ↑ HES-1 ↑ PPAR-γ ↓	(203)
	Liver	Hepatocellular carcinoma cell line Huh7	OR1A2	(-)-Citronellal, citronellol	RT-PCR, IF, calcium imaging (fura 2-AM), cAMP assay, cell proliferation assay, propidium iodide staining, WB, siRNA	Inhibited cell proliferation	Ca^{2+} ↑ (extracellular, AC) cAMP ↑ p38 MAPK ↑ CNG	(119)
	Pancreas	Pancreatic EC cell line QGP-1	OR2J3	Helional	RT-PCR, IF, calcium imaging (fura 2-AM), WB, serotonin ELISA	Serotonin release	Ca^{2+} ↓ (PKG)	(86)
	Gut	Colorectal cancer cell line HCT116, colon cancer tissue	OR51B4	Troenan	RNA-Seq, RT-PCR, IHC, CRE-luciferase assay, calcium imaging, WB, siRNA, proliferation assay, caspase-3/7 assay (apoptose), phalloidin staining (cytoskeleton)	Inhibited cell proliferation and migration, promoted apoptosis	Ca^{2+} ↑ (intracellular, PLC) ORAI p38 MAPK ↑ mTor ↓ Akt ↓	(191)
Genito-urinary system	Testis	Spermatozoa, HEK293 cell line	OR1D2	Bourgeonal	RT-PCR, IF, recombinant expression, calcium imaging, microcapillary bioassay, acrosome reaction assay	Chemotaxis (faster swim speed and flagellar beat rate)	Ca^{2+} ↑ (extracellular, AC) PK A ↑ p38 MAPK ↑ ERK 1/2 ↑	(130, 173, 174)

Continued

Table 1.—*Continued*

System	Tissue	Cell Type	Olfactory Receptor	Odorants	Detection Technique	Function	Signaling	Reference
	Prostate	PCa cell lines LNCaP and PC-3, HEK293 cell line, primary prostate epithelial cells	OR51E2	β-Ionone, androstenone derivatives, antagonist: α-ionone	RT-PCR, IF, calcium imaging (fura 2-AM), patch clamp, WB, siRNA, cell proliferation assay	Inhibited cell proliferation	Ca^{2+} ↑ Src TRPV6 p38 MAPK ↑ JNK/SAPK ↑	(132, 172)
	Testis	Spermatozoa, HEK293 cell line	OR7A5, OR4D1	Myrac (OR7A5), PI-23472 (OR4D1)	RT-PCR, recombinant expression, calcium imaging, cAMP ELISA, motility assay, microcapillary bioassay, acrosome reaction assay	Increased flagellar beating frequency	Ca^{2+} ↑ (extracellular, AC)	(182)
	Uterus	Cervical epithelial cancer cell line HeLa	OR2A4, OR1A2	—	qRT-PCR, IF, siRNA, live cell imaging, flow cytometry	Knockdown caused cytokinesis failure	GIPC1	(209)
	Prostate	PSGR transgenic mouse model, in vivo, PCa cell lines LNCaP and MDA PCa2a	OR51E2	—	q-RT-PCR, IHC, WB, reportergen assay, xenograft, transgenic mice	Overexpression promotes inflammation and low-grade PIN in transgenic mice enhance d tumor development in LNCaP	NF-κB/RELA ↑ (PI3K/AKT ↑)	(150)
	Prostate	LNCaP cell line, in vivo	OR51E2	β-Ionone/ α-ionone	Nested-PCR, cell invasion assay, xenograft (LNCaP), in vivo imaging and postmortem IHC	Promoted cell invasiveness in vitro metastasis spreading in vivo	Gβγ PI3Kγ	(158)
	Testis	Spermatozoa, HEK293 cell line	OR2W3, OR2H1, OR1OJ1	Nerol (OR2W3), methional (OR2H1), dimetol (OR1OJ1)	RNA-Seq, IF, calcium imaging	Odorant-dependent activation of ORs induces Ca^{2+} transients	Ca^{2+} ↑ (extracellular) CatSper/VGCC (T-type) (?)	(49)
	Prostate	PCa tissue, PIN tissue, PCa cell lines LNCaP, PC3, and C4–2	OR51E2	β-Ionone/ α-ionone	IHC (tissue microarray), WB, cell invasion, MTT cell proliferation assay	Inhibited cell proliferation and promoted cell invasion (C4–2 high protein expression in PIN, low expression in advanced PCa	p70 S6 kinase ↓	(26)
	Prostate	LNCaP cell line	OR51E2	β-Ionone	Phosphoproteomics, mass spectrometry	Advanced analysis of proteins involved in the signaling pathway	NHE1 ↑ Pyk2 ↑ NDRG1 ↓	(200)

Continued

Table 1.—*Continued*

System	Tissue	Cell Type	Olfactory Receptor	Odorants	Detection Technique	Function	Signaling	Reference
	Prostate	Benign prostatic tissue, PCa tissue, PCa metastases tissue, LNCaP cell line	OR51E1, (OR51E2, OR2A4/7)	Nonanoic acid	NGS, qRT-PCR, WB, IHC, IF, MTT cell proliferation assay, crystal violet staining, SA-β-GAL staining, PSA assay	Inh ibited cell proliferation induction of cellular senescence interference with AR-mediated signaling	Src p38 MAPK ↑ E2F1 ↓	(118)
	Kidney	Kidney tissue, proximal tubule HK-2 cells cell line	OR51E1, OR11H7	Isovaleric acid, 4-methylvaleric acid	RT-PCR, IF, calcium imaging	Increased Ca^{2+} transients	Ca^{2+} ↑ (extracellular, AC)	(87)
Respiratory system	Lung	Pulmonary neuroendocrine cells (PNECs), human tracheobronchial epithelial cells (hTECs)	OR2F1, OR2W1, OR2H3	Bourgeonal, bergamot oil, citronellal, nonanal, hexadecanol	Microarray, IF, WB, CRGP ELISA	Decreased secretion of serotonin, release of neuropeptide CGRP	—	(70)
	Lung	Adenocarcinoma	OR2J3	Helional, coumarin, 3-*cis*-hexen-1-ol, eugenol-methyl ester	RT-PCR, IF, WB, IHC, calcium imaging (fura 2-AM), TUNNEL assay, live imaging microscopy	Inhibited cell proliferation, apoptosis and migration	Ca^{2+} ↑ PI3K\ua rr\ERK1/2 ↑ MEK1/2 ↑ cRAF1/2 ↑ RSK1/2/3 ↑	(88)
	Lung	Human airway smooth muscle cells (HASMC)	OR1D2, OR2AG1	Bourgeonal/undecanal (OR1D2), amylbutyrate (OR2AG1)	RT-PCR, IF, IHC, calcium imaging (fura 2-AM), cAMP assay, WB, contraction assay, cytokine ELISA	OR2AG1: Inhibited histamine-induced contraction OR1D2: Increase in cell contractility, secretion of IL-8 and GM-CSF	Ca^{2+} ↑ (extracellular, AC) Ca^{2+} (Hist.) ↓ cAMP ↑ CNG	(85)

Continued

Table 1.—*Continued*

System	Tissue	Cell Type	Olfactory Receptor	Odorants	Detection Technique	Function	Signaling	Reference
Skin	Skin	HaCaT cell line, mouse trigeminal neurons	OR2AT4	Sandalore, javanol	Coculture, calcium imaging (fura 2-AM), patch clamp, ATP assay, propidium iodide staining	Odorant-induced communication between skin cells and trigeminal ganglia via ATP which is mediated by pannexins	Ca^{2+} ↑ ATP ↑	(171)
	Skin	Primary keratinocytes, HaCaT cell line, HEK293 cell line	OR2AT4	Sandalore, brahmanol, antagonists: oxyphenylon, phenirat	Microarray, RT-PCR, IF, calcium imaging (fura 2-AM), cAMP Assay, WB, siRNA, propidium iodide staining, cell proliferation assay, migration assay, skin organ culture	Enhanced cell proliferation, migration and wound healing	Ca^{2+} ↑ (extracellular, AC) cAMP ↑ CNG ERK1/2 ↑ p38 MAPK ↑	(24)
	Skin	Primary melanocytes	OR51E2	β-Ionone, antagonist: α-ionone	qRT-PCR, IF, calcium imaging (fura 2-AM), cAMP assay, WB, caspase-3/7 assay, cell proliferation assay, melanin content assay, differentiation assay	Inhibited cell proliferation, enhanced melanogenesis and dendritogenesis	Ca^{2+} ↑ (intracellular/ extracellular, AC) cAMP ↑ p38 MAPK ↑	(60)
	Skin	Primary keratinocytes, HaCaT cell line, HEK293	OR2A4/7, OR51B5	Cyclohexyl-salicylate (OR2A4), isononyl-alcohol (OR51B5)	NGS, RT-PCR, IHC, IF, calcium imaging, IL ELISA, phospho kinase array, WB, caspase-3/7 assay, cell proliferation assay, skin organ culture, migration assay, siRNA	OR2A4/7: Influences cytokinesis, increased cell proliferation, IL-1 secretion secretion	OR2A4/7: Ca^{2+} ↑ (extracellular, AC) CNG cAMP ↑ AKT ↑ CHK-2 ↓	(179)
						OR51B5: Enhanced migration, regeneration of keratinocyte monolayers, IL-6 secretion	OR51B5: Ca^{2+} ↑ (extracellular, AC) CNG cAMP ↑ Hsp27 ↑ AMPK1 ↑ p38 MAPK ↑	
	Skin	Primary melanoma cells derived from metastatic and vertical-growth phase	OR51E2	β-Ionone	qRT-PCR, IF, calcium imaging (fura 2-AM), ISH, siRNA, cell proliferation assay, migration assay	Inhibited cell proliferation and migration, apoptosis	Ca^{2+} ↑	(59)

AMACR, alpha-methylacyl-CoA racemase; CD, cluster of differentiation; EC, enterochromaffin; (F)ISH, (fluorescence) in situ hybridization; GI, gastrointestinal tract; IHC, immunohistochemistry; IFN, interferon; MA, microarray; MCFS, medium-chain fatty acids; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromid; PBMCs, peripheral blood mononuclear cells; PCa, prostate cancer; PIN, intraepithelial neoplasia; PLC, phospholipase C; PSA, prostate-specific antigen; qRT-PCR, quantitative reverse transcriptase polymerase chain reaction; SA-β-GAL, senescence-associated beta-galactosidase; SI-NEC, small intestine neuroendocrine carcinoma; TMA, tissue microarray; WB, Western blot.

optosis of acute myeloid leukemia cells through an increased cell cycle arrest in the $G_{0/1}$ and G_2/M phases (115). Furthermore, in the presence of an agonist, growth inhibition is accompanied by an increased number of hemoglobin-carrying erythroid cells that originate from immature precursor myeloblasts. The inhibition of myeloid leukemia cell proliferation is also mediated by a further OR, the isononylalcohol-activated OR51B5 (116). Both receptors initiate diverse and complex signaling pathways, including the elicitation of intracellular Ca^{2+} transients and the activation of further downstream effectors, e.g., kinases. This discovery provides novel opportunities for the development of therapeutic approaches for acute myeloid leukemia treatment.

C. Gastrointestinal System and Accessory Organs of Digestion

The identification of ectopic ORs in the human gastrointestinal system (GI) and digestion accessory organs is an intriguing discovery regarding the accessibility of external stimulants from the environment, e.g., via food ingestion. In addition, there are odorous chemicals also internally produced by the microbiome (145). In the enterochromaffin (EC) cells of the GI, known OR ligands cause intracellular Ca^{2+} increases, which result in enhanced serotonin release (17, 92), an important regulator of gut peristalsis and secretion. Thus ORs may significantly contribute to abnormal bowel functions, such as diarrhea or constipation. Sensing via ORs was demonstrated in further regions along the human GI tract. In addition to its potential function as a tissue biomarker in small intestine neuroendocrine carcinomas (34), the activation of the newly identified and deorphanized OR51B4 affects colorectal cancer cell physiology. The agonist Troenan causes inhibition of cell proliferation and migration, which is accompanied by proapoptotic properties (191). The negative effect on cellular growth was initiated by a phospholipase C (PLC)-dependent signaling pathway, including Ca^{2+} influx through calcium release-activated (CRAC) channels, increased p38 mitogen-activated protein kinase (MAPK) phosphorylation, and decreased mTor and Akt kinase phosphorylation. It may be hypothesized that these findings contribute to novel future concepts for colon carcinoma therapies. Because colon tumors are often accessible from the lumen, oral or rectal application of Troenan in effective concentrations is conceivable (191).

The liver harbors a smaller number of ORs compared with the GI and other tissues (47); however, the two paralogous related receptors OR1A1 and OR1A2 have been shown to exert important functions in hepatocyte physiology (119, 203). In general, the liver plays a central role in metabolic processes; it is responsible for the detoxification of substances that enter via the blood circulation, and it provides bile for digestion. Thus the liver is in close contact with the outer environment. The activation of OR1A1 by the terpene (-)-carvone leads to reduced mitochondrial glycerol-3-phosphate acyltransferase (GPAM) gene expression, which is involved in triglyceride synthesis (203), suggesting that the receptor may intervene in hepatic metabolism. In hepatocellular carcinoma cells, OR1A2 activation by (-)-citronellal leads to reduced proliferation via the initiation of a cAMP-dependent signaling pathway, similar to that in OSNs, and p38 MAPK phosphorylation (119). These findings are consistent with various studies that have described the anti-carcinogenic properties of terpenes (66, 76), which indicates that terpene-activated ORs represent promising targets for the development of cancer therapeutics.

Recently, a functionally important OR was identified in the human pancreas. In pancreatic EC cells, the helional-activated OR2J3 was shown to be involved in serotonin secretion, similar to ORs in EC cells present in the human GI. In contrast, OR2J3 activation causes a decrease in intracellular Ca^{2+}, which is mediated through a cGMP-dependent protein kinase (PKG) (86). In addition to its function as a neurotransmitter in the central nervous system, serotonin fulfills various functions in nonneuronal tissues. In the pancreas, its molecular targets are intracellular GTPases. Serotonin gets covalently linked to these enzymes by a transglutaminase. This serotonylation of proteins subsequently regulates insulin secretion, and the absence of serotonin cause signs of diabetes (149). In summary, the OR-mediated regulation of Ca^{2+} homeostasis has a significant impact on the functional units of the GI tract.

The identification of ectopically expressed members of the TASR1 and TASR2 families of sweet, umami, or bitter taste receptors highlights another class of chemoreceptors expressed in the GI tract in addition to ORs (25, 37, 103). These receptors serve as chemical sensors analyzing, for example, the luminal contents of the gut and regulate a variety of physiological functions, such as energy and glucose homeostasis, by releasing gut hormones and neurotransmitters (37). These receptors are present in enterochromaffin and brush cells (157) and thus may be coexpressed with the ORs present in enterochromaffin cells of the GI tract (17). Coexpression of these different receptor types with ORs could substantially broaden the number of detected chemical cues, as each receptor family is restricted to a subclass of ligands.

D. Genito-urinary System

Following the initial discovery of ectopic OR expression in the testes (140), efforts to determine their location and physiological function substantially increased. Spermatozoa have been shown to possess distinct chemosensory capacities, which enable chemical communication during egg fertilization. Recently, the complete testicular and spermatozoal OR transcript repertoire has been demonstrated,

highlighting the testes as the richest OR transcript-expressing tissue outside of the nose (47, 49). Multiple functions of ORs have been presumed based on their different protein localization in human spermatozoa (49). Localized in the midpiece (130), OR1D2 (OR17–4) was the first ectopic OR identified. Activation by its synthetic agonist bourgeonal leads to a faster swimming speed and enhanced flagellar beating frequency, which demonstrates a functional role in spermatozoal chemotaxis (173). The participation of OR1D2 in the regulation of swimming behavior and speed was confirmed using its specific antagonist undecanal (173). Recently, a reduced odor perception sensitivity towards bourgeonal was correlated with idiopathic infertility (137, 170). The activation of OR1D2 initiates the translocation of cytosolic β-arrestin2 to the nucleus, which may result in regulated gene expression required for fertilization or early embryogenesis (130). The activation of further ORs, OR7A5 and OR4D1, has been shown to influence the motility of spermatozoa through the odorants Myrac and PI-23472, respectively (182). It was also demonstrated, using specific antibodies and antagonists for the different ORs, that different ORs are expressed in the same sperm cell, albeit predominantly in distinct compartments (49, 182). Interestingly, the investigation of the occurrence of odor compounds in vaginal secretions and follicular fluid using gas chromatography-olfactometry yielded ~20 different odorants, including established activators of OR1D2. The other candidate ligands for ORs were further tested for the induction of sperm Ca^{2+} signals. Using this approach, two novel odorant receptor-ligand pairs have been reported (5α-androst-16-en-3-one for OR4D1 and 4-hydroxy-2,5-dimethyl-3[2*H*]-furanone for OR7A5), which induce elevated human sperm Ca^{2+} levels in response to both naturally occurring odorous substances (74). The majority of the ORs functionally characterized in spermatozoa elicited Ca^{2+} transients (7 of 10) following stimulation with their activating odorants (49, 173, 182), although not every OR signaling activation causes an increase in Ca^{2+}. There might also be Ca^{2+}-independent signaling components that were not tested. In spermatozoa, odorants do not activate the canonical signal transduction cascade and instead act independently on adenylyl cyclase activation and the second messenger cAMP (18, 182). Furthermore, several odorants, including bourgeonal, may also directly act on the CatSper calcium channel in human spermatozoa (18), and odorant-induced Ca^{2+} signals require a calcium-permeable channel and extracellular calcium. Mibefradil, which inhibits a variety of calcium channels in sperm, including CatSper (14, 41, 175, 197), also blocks Ca^{2+} signals induced by odorants (49). In conclusion, the exact mechanism underlying how odorants induce Ca^{2+} signals in spermatozoa, as well as the roles of ORs and the CatSper channels in particular, has yet to be examined in greater detail.

As a part of the urinary system, the human kidney also harbors functionally active ORs. The structurally related agonists of both OR51E1 and OR11H7 elicit intracellular Ca^{2+} flux in renal proximal tubule cells via adenylyl cyclase (AC) activity (87). The murine ortholog of OR51E2, the paralogous OR51E1, has previously been shown to mediate renin secretion upon short-chain fatty acid (SCFA) stimulation in the murine kidney, as well as influence blood pressure regulation (144, 164). These data strengthen the potential for human ORs to act in the physiological processes of the kidney.

Another function of ORs has been proposed for the human prostate. The broadly expressed class I receptors OR51E1 and OR51E2 were initially assumed to be GPCRs highly restricted to prostate tissue and were therefore deceptively named as prostate-specific G protein-coupled receptors (PSGR1/PSGR2). To date, it has been established that both ORs are ubiquitously expressed in various human tissues (47), albeit at significantly lower levels. Initially, OR51E2 was identified as the first hormone-activated membrane-bound rhodopsin-like GPCR. Activation by its agonist β-ionone, a synthetic terpenoid, and the steroid hormone 1,4,6-androstatriene-3,17-dione (ADT) leads to reduced proliferation of prostate cancer epithelial cells (PCa) in vitro and in LNCaP cells (132). The apoptotic effect exerted by β-ionone accompanied by an initiation of prostate cancer cell cycle arrest has been shown in subsequent studies (81), which supports the idea that OR51E2 may also act as a key mediator in these processes. OR51E2 activation leads to growth inhibition of both androgen-dependent and castration-resistant prostate cancer cells (26, 132); however, β-ionone stimulation enhances cell invasion (26, 158).

OR51E1 activation has also been suggested to influence prostate cancer cell growth. Stimulation with nonanoic acid and decanoic acid, both of which specifically activate OR51E1 (82, 155), significantly reduced proliferation and induced cellular senescence in the prostate cancer cell line LNCaP in vitro (118). Furthermore, this receptor appears to interfere with androgen receptor (AR)-mediated signaling, because the levels of the androgen-regulated target gene prostate-specific antigen (PSA) and the prostate homeobox protein coding tumor suppressor gene NKX3–1 are decreased (118). This led to the assumption that OR51E1 significantly contributes to prostate cancer (PCa) pathogenesis and progression.

In cervical cancer cells (HeLa), OR1A2 and OR2A4 have been shown to participate in cytokinesis. siRNA-mediated knockdown of both receptors resulted in incomplete cell separation (209). Furthermore, OR2A4 and OR1A2 knockdown promoted cytokinesis failure at early and late stages, respectively. Thus both receptors represent promising targets for the development of therapeutic strategies. The diverse physiological and pathophysiological functions of ectopic ORs underline their important features in the human genito-urinary system.

E. Nervous System

Beyond the association of ORs and neuropathological disorders, there is limited knowledge regarding their odorant-induced impact on physiological or pathophysiological processes in neuronal systems. However, it has been suggested that ORs adopt functions in the central nervous system. The activation of overexpressed human OR4M1 in mouse primary cortico-hippocampal neurons by acetophenone leads to reduced phosphorylation of abnormal microtubule-associated tau protein via a cAMP-dependent pathway and decreased c-Jun NH_2-terminal kinase (JNK) activity (211). This phenomenon leads to the assumption that OR4M1 may interfere with aberrant tau hyperphosphorylation, which is involved in the pathogenesis of neurodegenerative disorders. These assumptions were confirmed by findings in which olfactory receptor dysregulation was documented in the brains of patients who suffer from neurodegenerative diseases (7). In the human nervous system, the orphan OR OR6B3 was determined to be highly selectively expressed in the trigeminus and dorsal root ganglia. Its activating ligands and function remain unknown (48). Novel data describe the first evaluation of the mRNA expression of ORs and the distinct localization of OR proteins in the human retina. Transcriptome analyses detected an average of 14 OR transcripts in the neural retina; of these, OR6B3 was the most highly expressed OR. Immunohistochemical staining of retinal sections showed that OR2W3 localized to the photosensitive outer segment membranes of cones, whereas OR6B3 was identified in various cell types. OR5P3 and OR10AD1 were detected at the base of the photoreceptor-connecting cilium, and OR10AD1 was localized to the nuclear envelope of all retinal nuclei. The cell type-specific expression of the ORs in the retina suggests that there are unique biological functions for these receptors (83).

F. Respiratory System

Like the GI and cardiovascular systems, the respiratory system is in perpetual contact with the environment and thus with volatile substances through inhalation. Different functional relevancies of ectopic ORs have been reported in the human lung. In pulmonary NEC cells, the activation of ORs has been shown to influence serotonin release. In this case, however, the odorant stimulation provoked decreased serotonin levels (69, 70). Amyl butyrate and bourgeonal, OR2AG1 and OR1D2 agonists, respectively, influence the contractility of human airway smooth muscle cells (HASMCs) (85). Amyl butyrate inhibited histamine-induced cell contraction, whereas bourgeonal enhanced the contractility of HASMCs. Both processes are mediated via a cAMP-dependent intracellular Ca^{2+} increase (85). Thus it may be possible in the future to use ORs as novel therapeutic targets for asthma and other chronic inflammatory lung diseases.

Non-small-cell lung cancer (NSCLC) has a high prevalence and a high mortality rate and is difficult to treat. NSCLC cells are nearly resistant to common chemotherapeutic approaches, and surgical resection provides the only possibility of cure for most patients. The expression of OR2J3 has been demonstrated in the NSCLC A549 cell line. The OR2J3 agonist helional triggers the release of intracellular Ca^{2+} and ERK phosphorylation via phosphatidylinositol 3-kinase (PI3K) signaling. This induces apoptosis and inhibits cell proliferation and migration in long-term stimulus experiments (88). This study provided the first evidence of the functional expression of an OR in NSCLC cells, as well as its putative therapeutic impact.

G. Skin

The skin is the outer barrier of the human body. Therefore, it is in uninterrupted contact with the environment and is exposed to multiple external factors of chemical origin. The expression of a diversity of cutaneous chemosensitive receptors facilitates the processing of these environmental cues by the skin. Several ORs have been identified in distinct cell types of the epidermal skin layer and human skin tissue (24, 44, 60, 179). In contrast to myeloid leukemia cells, the sandalore-activated receptor OR2AT4 promotes human keratinocyte proliferation and migration, which results in accelerated cutaneous wound healing in an ex vivo system (24). Furthermore, sandalore induced pannexin-mediated cell-cell communication between keratinocytes and trigeminal neurons via ATP in a coculture system (171), which demonstrates that OR2AT4 can fulfill a chemosensory role as the decisive intermediary between the environment and the trigeminal sensory system. Additional ORs have been proposed to be involved in keratinocyte growth and migration processes. Similar to its impact on HeLa cells, OR2A4/7 participate in keratinocyte cytokinesis (179). Furthermore, the activation of the receptor by cyclohexylsalicylate increases cell proliferation and interleukin (IL)-1 production. The isononylalcohol-dependent activation of OR51B5, in turn, enhances the migration and regeneration of keratinocytes accompanied by IL-6 secretion (179). Recent studies have indicated that OR51E2 also functions in human melanocyte homeostasis (60). Melanocytes are the pigment-bearing cells of the epidermis and protect the skin from excessive sunlight. The results of this study indicated that the activation of OR51E2 by β-ionone leads to enhanced melanogenesis and dendritogenesis, as well as reduced cell proliferation (60). In primary cell cultures of melanoma cells derived from metastatic and vertical-growth phases, the β-ionone-dependent activation of OR51E2 resulted in inhibited cell proliferation and migration. These results are useful for understanding the involvement of OR51E2 in pathological pigmentation disorders and cancer progression. They may also provide novel therapeutic development directions for melanoma treatment (59).

IV. EXPRESSION PATTERNS OF OLFACTORY RECEPTORS ARE ASSOCIATED WITH DISEASES: POTENTIAL UTILITY AS BIOMARKERS?

The link between OR expression levels and pathological alterations is one of the most urgent issues that must be clarified, because it provides the basis for the identification of valuable and early disease biomarkers for diagnostic approaches. Several studies have shown that differentially expressed ORs are associated with pathological alterations, predominantly in cancer and neuropathological diseases. The human prostate was the earliest and most studied tissue with regard to analyses of differential OR expression. In addition to a low occurrence in healthy and benign prostatic tissue, the transcript expression levels of both OR51E1 and OR51E2 are increased in high-grade intraepithelial neoplasia (PIN) and PCa, and their abundance has been suggested to be consistent with the pathological stage and tumor grade (52, 192, 195, 196, 206). Therefore, both receptors have been suggested to represent useful clinical PCa biomarkers. The protein expression of both receptors has also been evaluated in the majority of examined advanced PCa and spreading metastases specimens (26, 118). These studies have suggested that both ORs have diagnostic potential not only for early detection but also for tumor classification and progression, as well as metastasis identification. Furthermore, OR51E2 and/or OR51E1 expression has been associated with the PCa biomarker alpha-methylacyl-CoA racemase (AMACR), as well as higher levels of preoperative PSA (189, 206). The presence of OR51E2 in human urine sediment simplifies its accessibility and raises the potential for the use of this receptor in "liquid biopsy" tests as a urinary PCa tumor marker (148). Furthermore, novel chimerical fusion of PSGR with the erythroblast transformation-specific (ETS) transcription factor ETV1 was identified as being involved in prostate carcinogenesis, which retains one of the regulatory active OR51E2 promoters (12, 194). Together, these studies strengthen the functional importance of OR51E1 and OR51E2 in benign and malignant prostatic tissue physiology. However, a minor number of investigated PCa specimens exhibited a contradictory transcript expression pattern, as well as keen interindividual variations (65, 118, 205), which has led to doubt regarding its reliability as a single tumor marker. Other studies have suggested that the protein expression of OR51E2 is negatively associated with advanced PCa and decreased from PIN to advanced PCa (26), which indicates that its mRNA expression level is apparently, in this case, not predictive for the total protein amount. Giandomenico and co-workers (34, 62, 102) subsequently postulated that OR51E1 is a tissue biomarker for small intestinal neuroendocrine carcinomas (SI-NEC) and somatostatin receptor-negative lung carcinoids. Using microarray and qRT-PCR analyses, this OR exhibited increased expression compared with normal tissues and the adjacent tumor microenvironment. Increased expression of multiple ORs has also been associated with CHEK2 1100delC breast tumors, as well as an increased risk of salivary gland carcinoma (127, 204). Another strategy has been elaborated that may enable systematic targeting of OR51E2-expressing tumor cells. This study reported OR51E2-derived peptides that acted as tumor-associated antigens, which were recognized by $CD8^+$-T cells (121). This could be of particular interest for the expression of OR51E2 in melanoma cells, recently shown to be quite high (59).

OR7C1 plays a crucial role in the physiology of cancer-initiating cells in the colon. OR7C1 expression correlates with higher tumorigenicity. OR7C1 overexpression in a SW480 CRC model led to an increase in cancer-initiating cells in nude mice. OR7C1 is not only a potential biomarker but also a promising target of cancer-initiating cells (CIC)-targeting cancer immunotherapy, where there are indications that immunotherapy that targets only CIC via CIC antigen-specific cytotoxic T lymphocytes (CTL) is more successful than targeting all cancer cells using shared antigens (126).

Dysregulated OR gene expression has been linked to several neurodegenerative and neuropsychiatric disorders and has been evaluated in recent research studies (45). In cortical brain regions and the *Substantia nigra* of Parkinson's disease (PD) patients, different ORs (OR2L13, OR1E1, OR2J3, OR52L1, and OR11H1) have been determined to be downregulated in the early stages of PD pathogenesis, which may support their important role in the progression of the disease (56, 68). Differentially regulated OR gene expression has also been identified in patients with Alzheimer's disease (AD), Creutzfeldt-Jakob disease, and progressive supranuclear palsy (7). In AD patients, half of the ORs verified in cortical regions exhibited altered gene expression. OR11H1 appears to be upregulated, whereas OR4F4, OR10G8, and OR52L1 expression levels are decreased (7) and correlate with disease progression. Moreover, downregulation of a chronic schizophrenia-associated OR was ascertained by the same working group (8). The mechanism that controls the dysregulation of the OR gene expression and the function of the ORs remains elusive. Therefore, this concern must be clarified in detail. In addition to their localization in cerebral regions, ORs that are downregulated in PBMCs have been implicated in traumatic brain injury (211). The dual detection of both OR4M1 and OR11H1 is believed to have diagnostic potential for biomarker analysis.

Specific mutations in the OR2W3 gene have been suggested to be associated with the ocular disease retinitis pigmentosa (111). However, two commentaries based on whole-exome sequencing have refuted the assertion that

the rarely occurring OR2W3 variant causes this autosomal dominant retinal disease (163, 208a). Recent studies have demonstrated that OR2W3 does not form fusion transcripts with Trim58, and the protein is specifically localized to the photosensitive outer segment membranes of cones (83), which indicates potential cell physiological functions in the human retina. In addition to their prevalent roles in diseases, a common null variant in the OR1B1 gene has been associated with decreased serum cholinesterase activity, which suggests a potential influence on liver cell metabolism (97).

V. SIGNAL TRANSDUCTION PATHWAYS INITIATED BY ECTOPICALLY EXPRESSED ORs AND THEIR MODULATION

The processing of chemical cues following the activation of ectopically expressed ORs is based on a complex interplay of various signaling molecules, which greatly depends on the participating OR and the cellular system (**TABLE 1, FIGURE 3**). The functional versatility of ORs is related to their substantial plasticity in the activation of different molecular

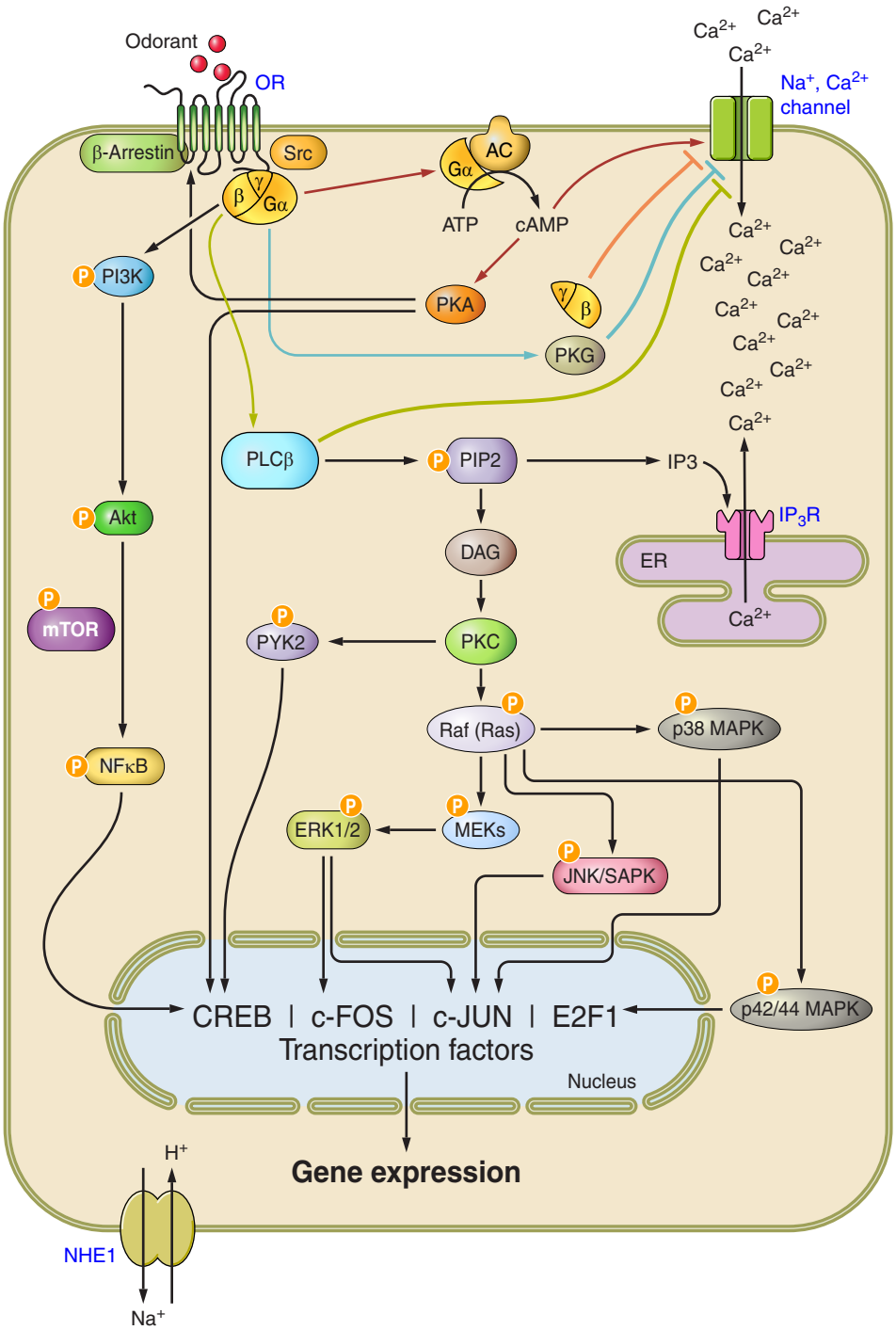

FIGURE 3. Schematic model of the most important signal transduction pathways initiated by ectopically expressed ORs. Involved cellular functions: proliferation, cell growth, differentiation, apoptosis, migration, and secretion (4, 17, 24, 49, 60, 82, 88, 115, 116, 118, 119, 132, 150, 158, 164, 173, 179, 182, 191, 209); senescence (118); dendritogenesis (60); chemotaxis (130, 173, 182); angiogenesis (93); wound healing (24); muscle contraction (82); hepatic metabolism (119); cytokinesis (179, 209); melanogenesis (60); and invasiveness (158).

and cellular mechanisms. For odorant detection, ORs elicit distinct signaling pathways in olfactory neurons, which leads to the production of electrical signals. Based on current knowledge, expressed ORs in somatic cells do not generate action potentials the way they do in olfactory neurons. In nonolfactory tissues, ORs can activate various signaling pathways. The specific pathway depends on the cellular phenotype regarding the expression of signaling components. Most likely, the most important decisive component is the type of involved heterotrimeric G protein.

The G_{olf} protein is widely expressed in peripheral human tissues (24, 47, 48, 85, 119). However, to date, there is no information regarding its actual functional participation. In cardiomyocytes and prostate cancer cells, $G\beta\gamma$ has been proposed as an alternatively active subunit (82, 158). Additionally, there are limited data regarding G_q activation in enterochromaffin and colorectal cancer cells (17, 191). In addition to the sparse knowledge of the participating G protein, several studies have demonstrated the presence and functional involvement of adenylyl cyclase and/or intracellular increases of the second messenger cAMP in skin cells (24, 60, 179), hepatocytes (119, 203), blood cells (115, 116), enterochromaffin cells (86), kidney cells (145), and many other human tissues (47, 85, 174). The partial involvement of cAMP in the signal transduction of ectopic ORs strengthens the hypothesis, suggesting at least a stimulatory G protein ($G\alpha_s$) (24, 85, 119) that is strongly expressed throughout the human body (47). Interestingly, a specific alternate signaling pathway is present in Olfr73-expressing OSNs in mice. Methylisoeugenol (MIEG), a weak Olfr73 agonist, triggers a signaling cascade independent of the canonical cAMP pathway, which leads to cell depolarization. This pathway is mediated by $G\alpha_o$ activation, and this newly identified pathway coexists with the canonical olfactory cAMP pathway in the same OSN and is triggered by the same OR in a ligand-selective manner (162).

The activation of the majority of ectopic ORs further leads to a cAMP-induced calcium flux from outside the cells, which represents a cascade reminiscent of the canonical pathway in OSNs (24, 47, 60, 85, 115, 116, 119, 174, 179). The expression of the required subunits that form the canonical heterotetrameric CNG channel (CNGA2, CNGA4, and CNGB1), particularly CNGA2, has not been detected in the majority of human tissues (47). However, the native rod protein CNGA1 is able to form functional homomeric channels (90) and is mainly activated by cGMP, in addition to cAMP (181). CNGA1 is the most prominent channel in peripheral cells and tissues (47) and is therefore likely able to function as a potential CNG channel (24, 119). The native cone photoreceptor CNGA3 channel is functionally expressed in sperm cells (199). This channel, together with the CatSper channel, may be involved in the OR-mediated chemotaxis of sperm by controlling Ca^{2+}. Interestingly, a decrease in intracellular Ca^{2+} levels through the helional-activated OR OR2J3 was observed in pancreatic enterochromaffin cells (QGP-1) activated via PKG, as the specific pharmacological inhibition of PKG with Rp-8-pCPT-cGMPS abolished the helional-induced Ca^{2+} response (86). Moreover, other results from pharmacological studies suggest that OR-dependent intracellular Ca^{2+} elevation may be induced via PLC and inositol trisphosphate (IP_3) receptor-dependent depletion of internal Ca^{2+} stores in colorectal cancer cells (191) or Ca^{2+} channel activation in enterochromaffin cells (17, 86). In general, the type of Ca^{2+} channel by which Ca^{2+} enters remains unknown in most cases. Using more or less specific blockers, other studies have provided evidence for the participation of TRP channels, CRAC channels, voltage-gated L-type Ca^{2+} channels, or spermatozoa-specific CatSper channels (24, 49, 60, 86, 115, 116, 119, 191). In melanocytes, the OR51E2-triggered Ca^{2+} signal is constituted by Ca^{2+} release from intracellular stores and an additive Ca^{2+} influx from the extracellular space. With the use of specific channel blockers (2-APB), members of the TRPM family that mediate the observed Ca^{2+} influx could be identified. The β-ionone-induced Ca^{2+} signal was significantly reduced (60). The paradigm that ectopic ORs exclusively initiate the canonical pathway was further rebutted for individual cases. The well-examined β-ionone-activated OR51E2, for example, induces a pathway in prostate cancer cells that is completely different from the pathway in OSNs. This type of signaling involves the activation of the tyrosine kinase Src (sarcoma), independent of an activated G protein, and a transient receptor potential channel V6 (TRPV6)-mediated intracellular Ca^{2+} increase in vitro (172). β-Ionone evokes the downstream phosphorylation of tyrosine kinase 2 (PYK2), p38 MAPK, and JNK/SAPK, which in turn inhibits the tumor suppressor N-myc downstream regulated gene 1 (NDRG1) (132, 172, 200). Moreover, in advanced castration-resistant prostate cancer cells, β-ionone reduces the phosphorylation of ribosomal protein S6 kinase (p70S6K) (26). For lower concentrations of β-ionone, it has been suggested that a signaling pathway mediated by $G\beta\gamma$ and the downstream PI3K/AKT signaling is induced, which may mediate different physiological processes in vitro and in vivo (150, 158). The paralogous receptor OR51E1, which is also expressed in prostate cancer cells, has been shown to interfere in AR-mediated signaling via Src kinase and different downstream kinases, without inducing elevated cAMP and intracellular Ca^{2+} levels (118). The absence of intracellular Ca^{2+} signals, but an increase in the cAMP levels and CREB phosphorylation, have also been identified for OR1A1 in hepatocytes following odorant stimulation (203). This, in turn, leads to upregulated hairy and enhancer of split 1 (HES1) gene expression and repression of peroxisome proliferator-activated receptor-γ (PPAR-γ), which are involved in triglyceride synthesis (203).

The modulation of various downstream protein kinases-following ectopic OR activation, mainly MAPK, has been identified in several cellular systems, independent of

whether a canonical-like or alternative pathway is initiated (24, 26, 60, 93, 115, 116, 118, 150, 158, 179, 191, 200, 203). These protein kinases appear to be the key downstream regulators of various physiological and pathophysiological processes. In summary, different mechanisms exist by which ORs mediate intracellular signaling transduction following odorant stimulation **(FIGURE 3)**. In addition to the participating OR and cellular systems, these processes are highly dependent on the odorant structure and concentration, the heterotrimeric G protein type or subunit, and the participation of other and/or less modulatory active scaffold proteins/cofactors, as well as the molecular features of the cellular system.

VI. AGONISTS OF ECTOPICALLY EXPRESSED HUMAN OLFACTORY RECEPTORS

Thus far, it has generally been accepted that humans can discriminate ~10,000 different odorants. In a recently published study, however, it was proposed that there may be even more than one trillion different odors that can be discriminated by the combinatorial activation of different ORs (23). However, the authors postulated this conclusion after making just 260 comparisons of 2 smells, of which only half could be discriminated. Reanalysis of the experiments by another group showed controversial data arguing for errors in the mathematical logic (123). At the molecular level, however, only ~10% of the ~400 intact human ORs have been deorphanized to date (3, 24, 49, 53, 58, 64, 75, 79, 91, 105, 112, 113, 120, 132, 134, 155, 159, 161, 168, 173, 178, 179, 182, 191, 198). Because of the potential of exogenous chemicals to activate ectopically expressed ORs, it will be interesting to elucidate how tissue accessibility is guaranteed. Moreover, the question arises as to whether endogenous ingredients may be recognized by specific tissue-expressed ORs.

Many naturally occurring odorants that can activate ORs are contained in essential plant oils, which can enter our body through the skin (80) and lung (42, 183) or can be ingested with our daily food. Essential oils are mainly composed of volatile terpenes and terpenoids, as well as aromatic molecules (143). Several of these volatiles have been shown to activate ectopically expressed ORs and thus influence physiological processes in various human cells; several examples include β-ionone (roses and berries), citronellal (citrus species), citronellol (pelargonium), thymol (thyme), and geraniol (rose oil and citronella oil) (3, 17, 70, 112, 119, 132, 155, 159, 161, 203, 211). The functional unit of terpenes, the isoprene, is synthesized in the mevalonate pathway during cholesterol biosynthesis in animals (40, 63). Several metabolic intermediates of the mevalonate pathway share structural similarities with OR-activating terpenes or terpenoids, e.g., farnesol and geranylgeraniol (40). Other terpenes, e.g., thymol and D-limonene (linalool and linalyl acetate) and their metabolites, have been detected in plasma within several minutes after cutaneous or oral application, partially at micromolar concentrations, and demonstrate a half-life of up to 12–24 h in mammals before they are excreted in urine, which implies that terpenes possess high bioavailability (19, 20, 78, 94–96, 183). A substantially higher affinity has been identified for lipid-rich tissues as a result of the lipophilic nature of terpenes (33).

Another major group of exogenous and endogenous activators of ORs belongs to fatty acids, particularly short- and medium-chain fatty acids (SCFA/MCFA). The SFCA propionic acid and its conjugated base, propionate, have been shown to activate recombinant and endogenous human OR51E2, respectively (144, 146, 155). Interestingly, propionic acid is endogenously produced by mammalian gut microbiota fermentation in sufficient concentrations to activate OR51E2 (128, 145, 152, 155).

The paralogous receptor OR51E1 is also activated by SCFAs but is more sensitive for MCFAs of 5–14 carbon chain lengths, such as nonanoic acid and the more potent decanoic acid, as well as valeric acid derivatives (53, 82, 118, 155). Isovaleric acid has been further shown to activate OR11H7 in human kidney cells (87). Free MCFAs that activate OR51E1 have been identified in human plasma and epicardial adipose tissue (32, 82). Therefore, it is likely that MCFAs are not only derived from dietary intake but are also released by adipose tissue. These findings provide the first hints of an involvement of ORs in the regulation of heart functions by circulating natural ligands released into the plasma from epicardial adipose tissues.

The previously identified human sperm chemoattractants and OR agonists bourgeonal, myrac, and PI-23472 (OR1D2, OR4D1, and OR7A5) are of synthetic origin (173, 182). Interestingly, endogenous odorants have also been identified in the female reproductive system. With the use of gas chromatography-olfactometry, compounds in the follicular fluid and vaginal secretion were extracted {5α-androst-16-en-3-one (androstenone) and 4-hydroxy-2,5-dimethyl-3[2H]-furanone}, which represent endogenous OR-activating agonists and are capable of inducing Ca^{2+} transients in spermatozoa (74). Furthermore, 5α-androst-16-en-3-one is contained in human breast milk, urine, and axillary sweat (9, 73) and has been demonstrated to activate OR7D4 (91), which is expressed in the testis and olfactory epithelium (109, 135).

VII. FUNCTIONAL CHARACTERIZATION OF HUMAN OLFACTORY RECEPTORS: A MAJOR CHALLENGE

After a comprehensive study was published (44) in which the widespread expression of OR transcripts in many hu-

man tissues was demonstrated, an intensive discussion began regarding the functional roles of ectopically expressed ORs. In this study, a neutral or nearly neutral evolution model of OR transcription control was discussed "whereby functionality is rendered less likely" (44). However, the data could not exclude the possibility that a subset of ORs play functional roles in different tissues. By comparison of OR expression levels in nonolfactory tissues in humans and chimpanzees, it was also shown that a subset of orthologous OR genes with conserved ectopic expression evolved under stronger evolutionary pressure than OR genes exclusively expressed in OSNs (35a). These findings provide no direct functional data, but additionally support the hypothesis that at least a subpopulation of OR genes has functions in nonolfactory tissues. In the past decades, numerous experimental designs have been developed to directly study the effects of OR activation in primary cell culture or cell lines of nonolfactory tissues.

Therefore, the extent of knowledge regarding OR-dependent (patho)physiological cellular functions has continuously increased. Despite the broad tissue expression distribution, the functions in human tissues have been deciphered for only a small number of ORs. A major obstacle in discovering the physiological function is the limited knowledge regarding their activating agonists. The deorphanization of the molecular receptive field of an OR is a prerequisite for its functional characterization. One problem limiting agonist identification is the relatively sparse composite odorant blends that exist, which are far from reflecting the chemical diversity of naturally occurring odorous molecules. Furthermore, several OR-activating odorants can in turn act as antagonists for other ORs (169, 173). This is accompanied by the finding that some ORs possess high odorant selectivity and respond only to closely structurally related odorants, whereas other ORs are more broadly tuned (46, 155, 177), which enables high odor coding variability. These findings therefore indicate that the identification of new receptor agonists is immensely challenging. Furthermore, the composition of odorant blends is subjectively influenced by hedonic properties, as unpleasant odors are often reluctantly used by researchers within deorphanization experiments. This issue may explain why most of the currently deciphered receptors react to pleasant odorants. To reduce the complexity of the odor landscape, a focus on ecologically relevant (food) odors has been suggested, an approach that has led to the identification of new OR ligands (57, 58, 134, 178).

In addition to the substantial difficulties with heterologous OR expression as a result of poor cell-surface expression (122, 198), the activation efficiency of recombinantly expressed ORs may not reflect the responsiveness achieved by endogenously expressed ORs in vivo. This may have several underlying reasons.

First, deorphanization using heterologously expressed ORs is an easily controlled system which enables for the guidance of the signaling pathway by the overexpression of corresponding accessory proteins (156, 212), e.g., $G\alpha_{olf}$, guanine nucleotide exchange factor B (Ric8b) (185, 186), and/or the CNGA2 channel (169). Other techniques have been presented based on the recombinant expression of GPCRs in combination with IP_3 signaling-triggering $G\alpha_q$ subunits, including the murine $G\alpha_{15}$ or human $G\alpha_{16}$, or chimeras of $G\alpha_{olf}$ and murine $G\alpha_{15}$ (84, 98, 212). It has been suggested that the type of G protein is decisive if an odorant acts as a receptor agonist or antagonist in a heterologous expression system (169). Despite the involvement of the same G protein, the OR sensitivity depends on the technical procedure of the readout, whether via Ca^{2+} flux or determination of the cAMP levels (e.g., OR1A1/nonanal) (82, 155, 161). In addition to the participation of varying cellular signal transduction components, the signal processing is influenced by a complex network of scaffolding proteins, phosphorylation events, and additional potential interacting proteins, such as nonolfactory GPCRs (13, 22). Therefore, it is not surprising that different cells exhibit divergent or contradictory physiological responses to one and the same OR/odorant pair, as indicated for ectopic OR2AT4; however, this issue complicates the exploration of ectopic OR function.

Second, "artificial" OR expression systems can only partially mimic ORN functionality by coexpressing auxiliary proteins for enhanced OR expression and activation efficiency, such as receptor transporting protein 1 long and short (RTP1l/s), RTP2, and receptor expression enhancing protein 1 (REEP1) (2, 71, 98, 106, 131, 142, 156, 165). Further modifications, such as NH_2-terminal tags on the OR (e.g., rho and lucy) (98, 165, 198) or coexpressed proteins (2), such as the heat shock protein 70t (Hsc70t) (131), M3 muscarinic acetylcholine receptor (M3) (106), and β2 adrenergic receptor (71), are not comparable to endogenously expressed ORs. However, significant progress was made by the development of the MouSensor assay system, which uses transgenic mice that express human ORs in murine ORNs (38).

Third, as previously discussed, the question remains whether more potent (endogenous) agonists exist. Most studies are related to the characterization of ectopic ORs based on the utilization of odorant concentrations at supraphysiological levels.

Fourth, the tissue accessibility of exogenously derived odorants varies substantially. Tissues that are not in direct contact with the outer environment, e.g., the kidney and prostate, may not be easily reached by exogenous chemical substances at appropriate concentrations. Therefore, the identification of more potent activating agonists that occur endogenously in the human body, such as hormones or

metabolites, would considerably enrich this research topic. A prerequisite for very potent ligand identification is the structural investigation of the ligand binding niche. The correlation between structure and odorant selectivity has been investigated by site-directed mutagenesis and computational modeling to improve the ligand identification of ORs (6, 28, 61, 100, 160, 161, 201, 202). The prediction of ligand binding of ectopically expressed ORs using in silico approaches in the future may facilitate the expansion of knowledge regarding their receptive field and accelerate the identification of more potent (endogenous) OR agonists.

Analysis of the protein expression of ORs remains a major challenge. Because of the high sequence homology and the difficulties in finding suitable accessible epitopes in highly hydrophobic membrane proteins, the development of specific OR antibodies is intensively hampered. However, in previous years, various studies have demonstrated specific OR protein expression by antibodies of high quality, specificity, and variable technical applicability (24, 26, 34, 45, 48, 49, 60, 70, 82, 83, 85–88, 93, 115, 116, 118, 119, 130, 132, 147, 179, 180, 191, 209). This provides at least the opportunity to define the function of ectopic ORs based on their subcellular localization.

Whether the diverse physiological responses after odor application are definitively based on OR activation is another challenge that must be solved. Few studies have definitively indicated, e.g., via RNAi knockdown, that the physiological effects induced by odorants depend on specific OR activation (24, 59, 85–88, 93, 119, 132, 179, 203, 209). These experiments highly depend on good transfection efficiencies; however, in most cell systems, the rate of transient transfection is $<5\%$, and the effects are too small to enable sufficiently precise quantification to detect differences. Additionally, the RNAi effect is mostly incomplete, which makes the evaluation even more complicated. Therefore, the establishment of more effective knockdown strategies (e.g., gene editing via CRISPR/Cas) would be beneficial in future experiments.

Another powerful strategy to demonstrate the involvement of a particular OR in cellular reaction is the use of specific antagonists. However, only a few antagonists for human ORs have been identified, namely, undecanal (OR1D2), α-ionone (OR51E2), oxyphenylon and phenirat (OR2AT4), methyl cinnamaldehyde, hydrocinamaldehyde and bourgeonal (OR3A1), which exhibit general structural similarities to OR agonists (24, 79, 132, 173).

Common knockout studies are difficult to implement because most human ORs have no clear ortholog in mice. Ectopic receptors may also vary in function between species, which complicates the transfer of the physiological function of human ORs to that of other mammals.

Thus the identification of novel OR functions is quite challenging, and technical improvements are required to address the scientific knowledge gaps of OR function outside of the nose in its entirety.

VIII. PERIPHERAL TISSUE EXPRESSION OF OTHER MEMBERS OF THE OLFACTORY SYSTEM

Another class of odorant-sensing GPCRs in the nasal mucosa includes trace-amine-associated receptors (TAARs) (11). TAARs are specifically activated by biogenic trace amines and have been suggested to function in pheromone sensing in mice (107). The human TAAR family comprises six gene members, of which four members have been identified at trace levels in the OE (27). However, substantial evidence exists that TAARs are expressed in peripheral human tissues outside of the OE (11, 47). In addition to the initial identification in the mammalian brain (15), murine and human TAAR1 is absent in the OE; however, it is broadly expressed in different tissues, e.g., blood, lung, ovary, testis, and brain tissues (10, 15, 47). In contrast, human TAAR5 is more abundant in the human OE (135) and is also ectopically expressed at low levels in the human brain (47). Whether tissue expression is really "ectopic" appears to be uncertain (11) and may depend on the respective receptor. It was recently shown that human TAARs expressed in the OE are functional. Human TAAR5 can be specifically activated by TMA, a highly volatile aminic compound and the prototype of "fishy" odor (187). It may be, as indicated for mice, a molecular sensor for the detection of volatile amines in humans. An advantage of both TAAR1 and TAAR5 is that their specific antagonists, EPPTB [*N*-(3-ethoxyphenyl)-4-(pyrrolidin-1-yl)-3-trifluoromethylbenzamide] and Timberol, respectively, have been elucidated (16, 188). Moreover, TMA occurs in bodily secretions (167); thus human TAAR5 receptors could revive the olfactory research of human social cues. However, there is limited knowledge regarding their physiological functions in human tissues beyond the cellular immune system (5, 117). TAARs have been detected in blood lymphocytes (10, 129), and TAAR1 and TAAR2 were shown to be involved in immune functions of blood leukocytes of humans (10) and primates (139). TAAR1 is functionally expressed in normal and malignant B cells and in a Burkitt's lymphoma cell line, in which its receptor agonists were proposed to induce apoptosis (190).

IX. CONCLUSIONS AND FUTURE PERSPECTIVES

ORs are characterized by high structural variety and are thus broadly sensitive to diverse chemicals. Furthermore, ORs form the largest gene family in the mammalian genome. The finding that ORs are expressed in the entire human body at individually noteworthy levels provides suf-

ficient justification to exert every effort to decode their importance. Their potential to be important regulators in the versatile processing of chemical cues beyond the nose has been proven for many tissues. Substantial challenges remain regarding agonist and antagonist elucidation, odorant tissue accessibility, and mechanisms of decoding OR function; nevertheless, scientific interest and technical capabilities are rapidly progressing. Furthermore, unraveling endogenous ligands for tissue-expressed ORs may expand our knowledge regarding receptor functions at physiological levels. Examples of the pronounced expression of non-deorphanized receptors are OR6B3 in the retina and TG, as well as OR4N4 in spermatozoa (48, 49, 83). Furthermore, the augmentation of ligand prediction using in silico approaches would help accelerate the identification of the entire OR binding spectra (201). As species-overlapping studies are inconclusive because of their previously described differences, the development of alternative approaches using human settings is mandatory. Moreover, advances in bioartificial materials (tissue engineering) have made it possible to characterize ectopic ORs while more closely simulating their real physiological conditions in the future. Studies at the mRNA level are undoubtedly valuable to obtain an overview of the molecular basis of ORs; nevertheless, large-scale proteomics would facilitate the identification of potential interacting partners (13) to definitively understand the complex signal transduction following odorant-dependent activation, which has only been comprehensively investigated for OR51E2 to date (200).

The functional importance of ectopic ORs remains insufficiently understood. As presented here, however, their impact on carcinogenesis has been widely demonstrated for various human cancer types using in vitro and murine in vivo technologies (1, 26, 50, 59, 88, 89, 115, 116, 118, 119, 132, 150, 158, 179, 191). In nearly all cases examined to date, the activation of ORs in tumor cells induces a significant decrease in proliferation or a complete termination of tumor cell growth. Accordingly, the idea of clinically benefitting from the use of ORs as biomarkers, which has been suggested for several ORs (34, 45, 62, 102, 132, 196, 205), must be expanded to develop promising clinical strategies in the future. It will also be interesting to decipher disease-associated OR functions following ligand-dependent activation. Therefore, the idea of targeting ORs for diagnostic and therapeutic approaches is feasible because ~30% of the currently used pharmaceuticals function via rhodopsin-like GPCRs (138), and ORs are the largest GPCR subfamily. Most ORs can be detected in tissues outside of the olfactory epithelium via transcriptome analysis. This suggests an interesting and substantial new group of important membrane proteins that are involved in cell biological processes. The deorphanization of additional ORs will certainly increase the possibility of analyzing their detailed functions and the identification of further potential targets that contribute to cancer development and progression.

Targeting ORs is conceivable not only for the treatment of cancer or other disorders but also for the pharmacological control of healthy cells because they positively influence cellular processes, as previously indicated for skin keratinocytes (24), melanocytes (60), and airway cells (85) and in the heart (82), kidney (87), gut (17), and spermatozoa (173).

The data provided here indicate the extranasal expression and functionality of ORs. One obvious conclusion from the fact that ORs have been identified outside the nose is that one can no longer consider ORs to be purely olfactory receptors, but rather general chemoreceptors involved in physiological and pathophysiological processes throughout the human body. Furthermore, with ~400 members, ORs make up nearly half of the GPCR proteins in humans, which represent ~30% of the targets of all pharmaceuticals used. In the future, several of the ORs will probably be of similar importance as structurally closely related GPCRs, such as the adrenergic or serotonergic receptors.

However, at present, numerous questions remain to be solved, and more research is needed before the role of ORs, which they can play in different human tissues and in cancer pathology, is fully enumerated.

Several of the most important directions for current OR research include *1*) the identification of endogenous, physiological relevant ligands; *2*) the identification of particular signaling pathways; *3*) the characterization of the function of ORs in vivo; and *4*) the application of active chemical compounds to ORs for clinical use (translational approach).

To solve these demanding problems, the following steps are required:

- the establishment of chemical libraries for identifying agonists and antagonists, especially by extracting possible endogenous ligands from natural sources (blood, body fluid);
- the generation of an antibody library against specific OR peptides to achieve better and broader profiling of OR expression and localization in extranasal cells;
- the establishment of in vitro systems for functional assays, such as a three-dimensional model of human skin or animal models, which include the possibility of gene editing;
- more detailed analysis of the regulation of OR expression in disorders and diseases by deep NGS sequencing; and
- the study of homo- and heterodimerization for activation of novel signaling pathways, resulting in different cellular processes and functions.

The extranasal expression of ORs is a new and exciting area of science that should attract young scientists because of the exciting recent breakthrough discoveries. As scientists have

matched only a handful of extranasal receptors (<10%) to the specific effects of activating compounds on human nonolfactory cells, there is an enormous potential within unexamined ORs that are awaiting further characterization. This may include new and exciting information regarding important functions in physiological and pathophysiological processes. Using odors to help with serious health issues may currently be a distant dream facing significant challenges, but it represents a promising and widely unexplored therapeutic area.

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Address for reprint requests and other correspondence: H. Hatt, Ruhr-University Bochum, Dept. of Cell Physiology, Universitätsstraße 150, D-44780 Bochum, Germany (e-mail: hanns.hatt@rub.de).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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