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Invited Mini Review

Odorant receptors in cancer

Chan Chung[1,2,#,*], *Hee Jin Cho*[3,4,#], *ChaeEun Lee*[1,2] *& JaeHyung Koo*[1,2,5,*]

[1]Department of New Biology, DGIST, Daegu 42988, [2]New Biology Research Center (NBRC), DGIST, Daegu 42988, [3]Department of Biomedical Convergence Science and Technology, Kyungpook National University, Daegu 41566, [4]Cell and Matrix Research Institute, Kyungpook National University, Daegu 41944, [5]Korea Brain Research Institute (KBRI), Daegu 41062, Korea

Odorant receptors (ORs), the largest subfamily of G protein-coupled receptors, detect odorants in the nose. In addition, ORs were recently shown to be expressed in many nonolfactory tissues and cells, indicating that these receptors have physiological and pathophysiological roles beyond olfaction. Many ORs are expressed by tumor cells and tissues, suggesting that they may be associated with cancer progression or may be cancer biomarkers. This review describes OR expression in various types of cancer and the association of these receptors with various types of signaling mechanisms. In addition, the clinical relevance and significance of the levels of OR expression were evaluated. Namely, levels of OR expression in cancer were analyzed based on RNA-sequencing data reported in the Cancer Genome Atlas; OR expression patterns were visualized using t-distributed stochastic neighbor embedding (t-SNE); and the associations between patient survival and levels of OR expression were analyzed. These analyses of the relationships between patient survival and expression patterns obtained from an open mRNA database in cancer patients indicate that ORs may be cancer biomarkers and therapeutic targets. [BMB Reports 2022; 55(2): 72-80]

INTRODUCTION

Odorant receptors (ORs) are G protein-coupled receptors (GPCRs) that are essential for detecting and distinguishing among odorants. ORs were originally detected by analyses of the extent of receptor diversity and their expression pattern in the olfactory system (1). Since the first ORs were discovered in rats, approximately 400 of more than 800 human GPCRs and 1,000 of an estimated 1,700 mouse GPCRs have been identified (2, 3). Because of their intrinsic function, ORs were originally thought to be expressed only in olfactory epithelium, but they were later detected in dog ovaries and testes, including in germ cells (4). To date, ORs have been found to be expressed in various tissues and cells (5-8), including the bladder, thyroid, and thymus (9); the kidneys (10), skin (11), pancreas (12), liver (13), and brain (14-16); and cancer cells (6, 17, 18). This widespread expression of ORs in nonolfactory tissues and cells suggests that ORs are involved in various biological functions beyond sense of smell (5, 6).

Studies have shown that ORs are expressed in tumor cells and tissues, including hepatocarcinoma cells (19), breast carcinoma tissues (20), prostate cancer cells (21), enterochromaffin tumor cells (22), melanomas (23), and urinary bladder cancers (24). Functional evaluations have shown that ORs in these cancers regulate cancer cell invasiveness, metastasis, differentiation, and prognosis (25, 26), as well as being involved in cell signaling, proliferation, and apoptosis (5-7). This review describes current knowledge about the expression of distinct ORs in cancers, as well as the canonical and non-canonical signaling pathways induced by these ORs. In addition, OR expression pattern in various cancers were analyzed based on RNA-sequencing data reported in the Cancer Genome Atlas (TCGA), and the associations between patient survival outcomes and OR levels were analyzed to determine the clinical relevance and significances of OR expression in tumors.

OR EXPRESSION IN VARIOUS TYPES OF CANCER

Prostate cancer

The level of expression of OR51E2, also called PSGR and prostate-specific GPCR, was high in prostate cancer (21, 22, 27-32). The level of OR51E2 mRNA was found to be significantly higher in prostate tissue samples from patients with prostate intraepithelial neoplasia and prostate cancer than in normal prostate tissues and tissues from patients with benign prostatic hyperplasia (33). These results suggest that OR51E2 may play an important role in the development of early prostate cancer (26). In addition, the level of OR51E1 mRNA, also called PSGR2 and the paralogue of OR51E2, was higher in tissue samples of patients with high grade prostate intraepithelial neoplasia and prostate cancers (30, 34, 35). Although both

*Corresponding authors. Chan Chung, Tel: +82-53-785-1660; Fax: +82-53-785-1819; E-mail: chungc@dgist.ac.kr; JaeHyung Koo, Tel: +82-53-785-6112; Fax: +82-53-785-1819; E-mail: jkoo001@dgist.ac.kr
#These authors contributed equally to this work.

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ORs were thought to be useful and specific biomarkers for early prostate cancer, their expression patterns were found to be distinct at the cellular level and varied within tumor samples. Both ORs were detected in basal gland structures and were diffusely expressed throughout the cytoplasm of prostate epithelial cells. However, OR51E1 was mainly expressed in apical luminal cell structures, indicating a membrane localization pattern. OR51E1 protein was highly expressed in most lymph nodes and distant metastases of prostate cancers, indicating that OR51E1 may have a distinct physiological function in advanced prostate cancers (36). Also, OR1D2 mRNA is highly expressed in LNCaP prostate carcinoma cells (37). In our analysis, the expression of ORs was re-evaluated in cancer patients by cancer types by t-distributed stochastic neighbor embedding (t-SNE) clustering of OR genes using RNA-sequencing data from the TCGA database. These t-SNE analyses showed that OR expression patterns differed among types of cancer (Fig. 1A) and between tumor and normal tissue samples of the same tissue types (Fig. 1B). Detailed analysis of the expression of each OR gene across various cancer types (Fig. 1C-O) showed that the levels of OR51E1 and OR51E2 were also highest in prostate adenocarcinomas (PRAD), consistent with previous study showing that OR51E1, OR51E2, and OR1D2 expression were found in PRAD. Interestingly, they were expressed in many other types of cancers, such as kidney renal clear cell carcinoma (KIRC) and glioblastoma multiforme (GBM) (Fig. 1C, D). By contrast, the level of OR1D2 expression in PRAD was not noticeable in our t-SNE analysis (data not shown).

Breast cancer

Analysis of samples stored in the sequence read archive, the RNA-sequencing database (https://www.ncbi.nlm.nih.gov/sra), showed that OR2B6 was expressed in 73% of breast carcinoma cell lines and in over 80% of primary breast carcinoma tissues, but not in normal breast tissue, suggesting that OR2B6 may be a reliable marker for breast cancer (20, 38). An analysis of OR transcript abundance in patients with invasive breast carcinoma found that OR2W3, OR2T8, and OR2B6 mRNAs correlated with breast cancer progression (20, 39). In addition, OR2T6 was shown to be overexpressed in breast cancer tissue and to tightly correlate with lymph node metastasis as well as with higher tumor/node/metastasis staging. Patients with OR2T6-posi-

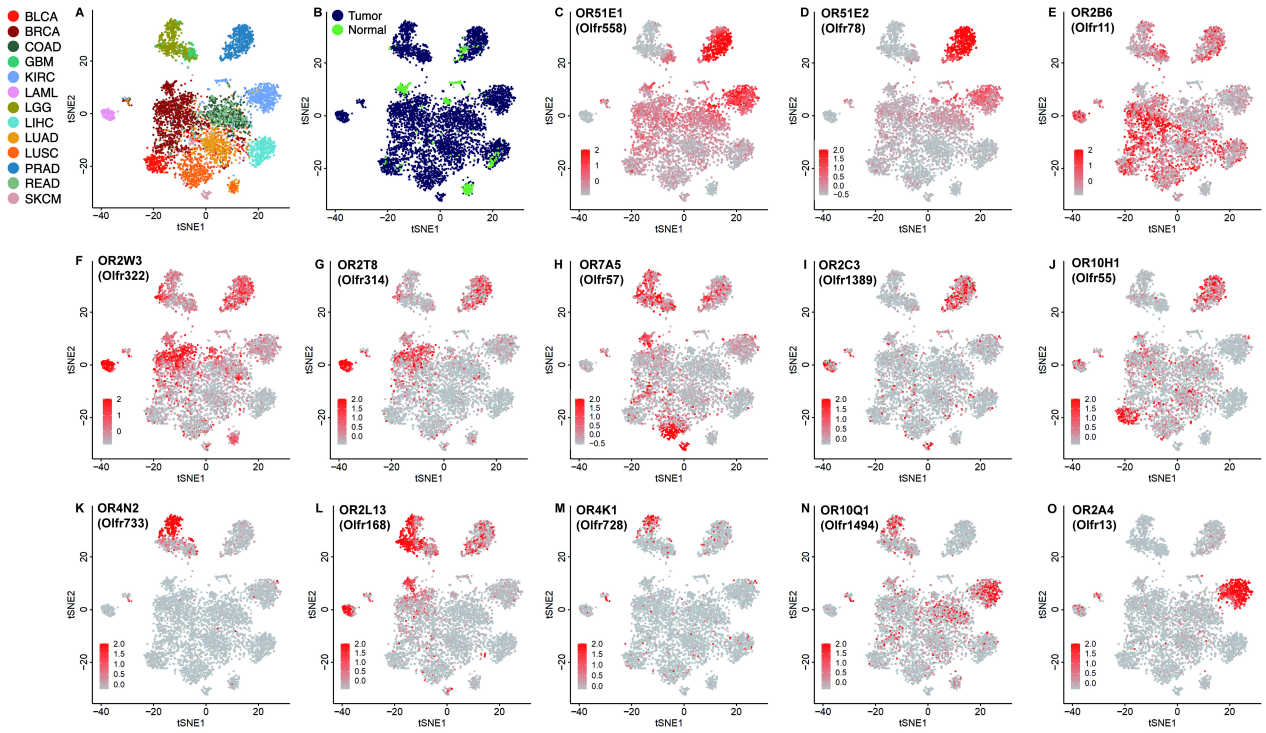

Fig. 1. Relationships between distinct human OR expression profiles and tumor types. (A-O) t-Stochastic nearest neighbor (t-SNE, perplexity = 50) plots of TCGA RNA-seq samples (tumor N = 5523, normal N = 471) for 842 OR genes, colored by tumor types (A), sample types (B), or the expression of OR genes (C-O). The color scale indicates Z-normalized log2(transcripts per million (TPM) + 1) values of each gene (C-O). The range of color scale is from -2 (gray) to 2 (red). BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; COAD, colon adenocarcinoma; GBM, glioblastoma multiforme; KIRC, kidney renal clear cell carcinoma; LAML, acute myeloid leukemia; LGG, lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SKCM, skin cutaneous melanoma. The mouse ortholog of each human OR is in parentheses.

tive breast cancer had a poor prognosis, as shown by reduced overall survival (OS) and disease-free survival (DFS) (40). Although our analysis of the TCGA database also found that OR2B6, OR2W3, and OR2T8 were expressed in breast invasive carcinoma (BRCA) samples, these ORs were also expressed in other types of cancer, including PRAD, GBM, lower grade glioma (LGG), and acute myeloid leukemia (LAML) (Fig. 1E-G). Previous studies and our analysis show that high levels of OR51E2 expression were also associated with poor prognosis in breast cancer patients (Fig. 2A) (25).

Melanoma

OR51E2 has been reported to influence melanocyte homeostasis, with activation of OR51E2 enhancing melanogenesis and dendritogenesis and reducing melanocyte proliferation, results indicating that OR51E2 regulates melanocyte differentiation (41). In addition, OR51E2 mRNA and protein levels were found to be upregulated in melanoma tissue sections and primary cells from melanoma tissues, and OR51E2 activation by β-ionone was shown to inhibit the proliferation and migration of primary melanoma cells (23). However, OR51E2 expression was relatively low in skin cutaneous melanoma (SKCM) samples in the TCGA database compared with other cancer types (Fig. 1D). By contrast, t-SNE visualization showed that OR7A5 and OR2C3 were highly expressed in SKCM (Fig. 1H, I).

Colon cancer

OR51B4 was found to be highly expressed in HCT116 colon

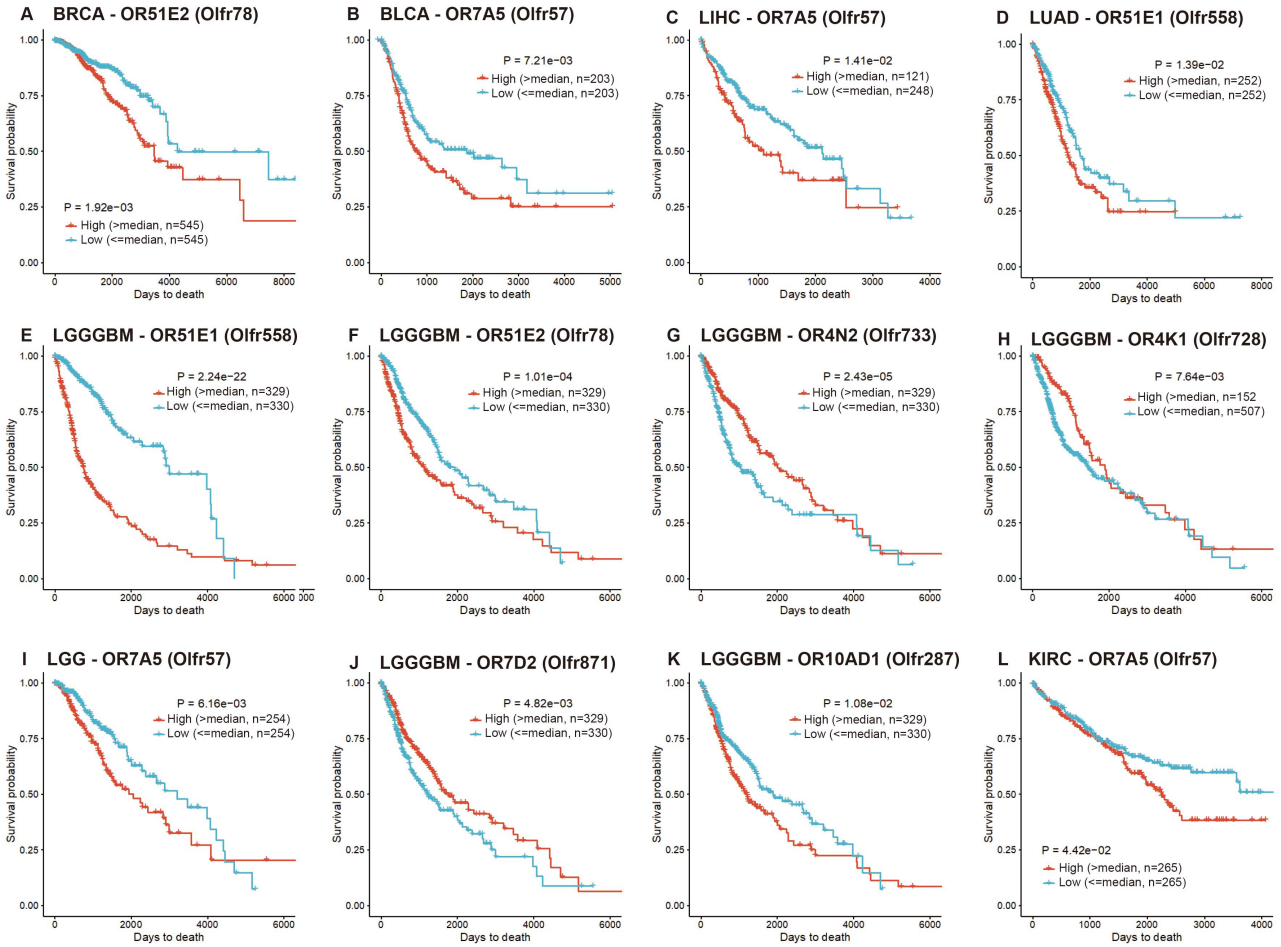

Fig. 2. Kaplan-Meier analysis of overall survival in patients with high and low levels of expression of human ORs. OR51E2 in BRCA (A), OR7A5 in BLCA (B), OR7A5 in LIHC (C), OR51E1 in LUAD (D), OR51E1 in all gliomas (E), OR51E2 in all gliomas (F), OR4N2 in all gliomas (G), OR4K1 in all gliomas (H), OR7A5 in LGG (I), OR7D2 in all gliomas (J), OR10AD1 in all gliomas (K), and OR7A5 in KIRC (L). BRCA, breast invasive carcinoma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; BLCA, bladder urothelial carcinoma; LGG, lower grade glioma; GBM, glioblastoma multiforme; KIRC, kidney renal clear cell carcinoma. The mouse ortholog of each human OR is in parentheses.

cancer cells. Troenan, its specific ligand, was shown to activate OR51B4, inducing the activation of phospholipase C (PLC) via Ca^{2+} influx. PLC was found to be involved in the increased phosphorylation of p38 and the decreased phosphorylation of Akt in colon cancer cells. This signal transduction led to the inhibition of cell proliferation and migration (42). OR7C1 may be another potential biomarker in colon cancer. OR7C1-positive patients showed higher tumorigenicity than OR7C1-negative patients (43). By contrast, our analysis showed that OR51B4 and OR7C1 expression was not detectable in colon adenocarcinoma (COAD) (data not shown), whereas OR51E1 was expressed in COAD (Fig. 1C).

Bladder cancer

OR10H1 mRNA and protein levels were found to be significantly higher in cancerous bladder tissue than in normal bladder (24). Our analysis of TCGA data also found that the OR10H1 was highly expressed in bladder urothelial carcinoma (BLCA) (Fig. 1J), suggesting that OR10H1 may be a potential biomarker for bladder cancer. To functionally characterize OR10H1, it was activated by the sandalwood-related compound, sandranol, in BFTC905 bladder cancer cells. Sandranol altered cell morphology; reduced cell viability, proliferation, and migration; and enhanced apoptosis (24). In addition, OR7A5 was found to be expressed in a subset of BLCA patients, with high OR7A5 expression associated with poor prognosis in patients with BLCA (Fig. 1H and 2B).

Neuroendocrine carcinomas

OR51E1 was identified from microarray analysis and from expressed sequence tag database analysis by comparisons of normal and tumor tissues. OR51E1 level was found to be higher in laser-captured small intestine neuroendocrine carcinomas than in cells from the adjacent microenvironment (44, 45).

Liver cancer

OR1A1 was found to be overexpressed in plasma membranes of hepatocarcinoma cells. OR1A1 activated by the ligand (−)-carvone induced the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA)-cAMP response element-binding (CREB) signaling pathway without altering the intracellular Ca^{2+} concentration. Activated OR1A1 reduced intracellular concentrations of triglycerides, but not of cholesterol (46). In addition, OR1A2, a paralogue of OR1A1, and OR8B3 were found to be expressed in a monoterpene-activated hepatocellular carcinoma (HCC) cell line. Activation of OR1A2 resulted not only in an increase in cytosolic Ca^{2+} level through the activation of a cAMP-dependent signaling pathway, but also induced the phosphorylation of p38-mitogen-activated protein kinase (MAPK) and a reduction in cell proliferation, showing that ORs affect HCC progression (19). However, analysis of patient data revealed that OR1A1 and OR1A2 were only slightly expressed in cancers including liver hepatocellular carcinoma (LIHC) (data not shown). We found that high OR7A5 expression in patients with HCC was associated with poor prognosis (Fig. 2C).

Lung cancer

OR2J3 was found to be expressed in cell membranes of the helional-activated non-small-cell lung cancer (NSCLC) cell line A549, increasing intracellular Ca^{2+} concentration. Activation of OR2J3 led to the phosphorylation of ERK and components of the ERK signaling pathway, including ERK1/2, RSK1/2/3, MEK1/2, and c-Raf. Helional-induced OR2J3 inhibited cell migration and decreased cell proliferation (47). Despite OR2J3 expression being confirmed in this NSCLC cell line, its expression levels in patients, as shown in the TCGA database, were negligible (data not shown). OR51E1 was found to be highly expressed in the lung carcinoid cell lines NCI-H727 and NCI-H720 and in frozen lung tumor specimens (48), consistent with previous results (Fig. 1C and 2D). Compared with xenografts of LLC murine Lewis lung carcinoma cell on wild-type mice, xenografts of these cells on mice with knockout of Olfr78, a mouse analog of OR51E2, showed reduced tumor growth and metastasis. In addition, TCGA analysis showed that lower OR51E2 expression correlated significantly with better survival (25). Solid-phase microextraction GC/MS identified a cancer-specific odorant, 2-ethyl-1-hexanol, in the SK-MES cancer cell line, and screening of human ORs found that OR4D11P was a sensitive and selective receptor of 2-ethyl-1-hexanol (49).

Brain cancer (Glioma)

Although ORs particular to glioma have not been identified, we recently suggested that several ORs (18), which had not been mentioned in a report on the importance of GPCR in glioma (50), were clinically relevant and significant in glioma. Evaluations of patient-derived specimens and primary cell cultures have identified several ORs associated with glioma. One study evaluating the transcriptional regulatory networks of mesenchymal-associated tumor-associated macrophages in glioblastoma identified 21 candidate transcriptional master regulators, including peroxisome proliferator-activated receptor gamma (PPAR-γ) and nuclear factor-kappa B (NF-κB). Interestingly, OR4N2 and OR7A5 were found to be involved in the transcriptional regulatory network (51), and OR51E2 was involved in glioblastoma progression. Analysis of glioblastoma patients in the TCGA database showed that high expression of OR51E2 was associated with poor prognosis (25). In addition, a four-gene signature (ASPM, CCNB1, EXO1, and KIF23) in patients with LGG correlated negatively with response to treatment with temozolomide (TMZ), which is frequently used as primary chemotherapy for LGG. A comparison of expression levels and DNA methylation profiles suggested that OR51F2 may act as a potential downstream effector in glioblastoma (52). Our t-SNE analysis showed that OR expression profiles in gliomas were distinct from those in other types of solid tumors. These analyses confirmed that OR4N2, OR2L13, and OR4K1 were expressed in gliomas (Fig. 1K-M), along with OR51E1, OR51E2, OR2B6, OR7A5, OR10Q1 (Fig. 1C-E, H, N), and OR2W3 (Fig. 1F). In addition, the differ-

ential expression of several other OR genes, including OR51E1, OR51E2, OR4N2, OR4K1, OR7A5, OR7D2, and OR10AD1, in GBM and LGG suggested that these ORs were associated with prognosis in patients with glioma (Fig. 1A, 2E-K, and (18)).

OR SIGNALING PATHWAY IN CANCERS

Canonical pathway

The canonical signal transduction of ORs involves the heterotrimeric G-protein, G_{olf}. ORs are initially activated by binding to specific odorant(s). The alpha subunit of G_{olf} ($G_{\alpha olf}$) facilitates an exchange of GDP with GTP. GTP-bound $G_{\alpha olf}$ dissociates $G_{\beta\gamma}$-heterodimer and binds to adenylyl cyclase III. This complex converts ATP to cAMP. Increased cAMP activates cyclic nucleotide-gated channels, which cause Ca^{2+} ion influx, leading to the generation of an action potential in the olfactory neuron axon (5, 6).

Non-canonical pathway

Unlike the classical pathway, ectopic ORs induce the non-canonical pathway in cancers. OR51E2 induces PI3 kinase-γ, leading to cell invasion and metastasis (22). OR51E2 also activates NF-κB via the phosphatidylinositol-3-kinase/Akt pathway, inducing chronic inflammation (26). We recently reported that lactate-activated Olfr78/OR51E2 induces the differentiation of bone marrow-derived macrophages into M2-tumor-associated macrophages. Depletion of Olfr78 reduces tumor progression and metastasis and increases antitumor immunity (25). OR51B5, which is activated by isononyl alcohol, increases intracellular Ca^{2+} levels in blood cells derived from a patient with acute myeloid leukemia (LAML) and in a human erythroleukemic cell line K562. Activated OR51B5 reduces p38-MAPK phosphorylation, reducing cell proliferation (53). Lyral-activated OR10J5 increases Ca^{2+} levels and the phosphorylation of AKT and ERK in human aorta, coronary artery, and umbilical vein endothelial cells (HUVEC). Lyral also induces the migration of HUVECs via OR10J5 and enhances angiogenesis *in vivo* (54). Following activation with (−)-citronellal, OR1A2 induces MAPK signaling, but not ERK1/2 and SAPK/JNK signaling, and reduces the proliferation of hepatocarcinoma cells (19). Not all pathways accompany the increase in cytosolic Ca^{2+} level at initial activation. For example, activation of OR1A1 by its ligand (−)-carvone increases cAMP, a step in the canonical pathway, but not intracellular Ca^{2+}, leading to PKA activation. PKA upregulates CREB-responsive genes, including hairy and enhancer of split (HES)-1 and PPAR-γ by phosphorylating CREB in hepatocytes (46). Analysis of single-cell transcriptomes in cancer cells revealed a complicated signaling network in response to OR expression. A metascape analysis of BRCA-associated ORs showed that prominent biological functions included regulation of the cell cycle, transcriptional or translational regulation, PTEN regulation, metabolic processes, and DNA repair (17). This approach confirmed previous findings of signal transduction by ORs, and suggested new and previously unknown pathways in OR-related cancers.

CONCLUSION

ORs are expressed in many nonolfactory tissues and cells (5, 6), although the levels of certain ORs in normal tissue are extremely low or undetectable. Many of these ORs, however, are detected during early stages of cancer, suggesting that ORs may be potential biomarkers for cancer and the need to identify target ORs in specific cancer types. Most studies of ORs in cancer have involved cancer cell lines, with few studies assessing OR expression in tissues derived from cancer patients. In particular, the functions of ORs in cancers have been generally assessed by treating cell lines with known OR ligands and detecting changes in intracellular Ca^{2+} or signaling mechanisms (Table 1). However, findings in cell lines may not reflect tumor processes in cancer patients, especially if stimulation of cell lines by known ligands does not involve the expected pathway. Table 1 summarizes *in vitro* results of cancer-related ORs, as well as their possible associations with results in patients, as determined by OR expression in RNA-seq samples of cancers in the TCGA database and visualization of expression patterns by t-SNE (Fig. 1A). These t-SNE analyses showed that OR expression profiles differed in tumor and matched normal tissue samples (Fig. 1B), indicating that tumor tissues show both tumor-specific and tissue-specific OR expression. Interestingly, OR51E1 and OR51E2, which were identified in prostate cancer, were also expressed in KIRC (Fig. 1C, D), consistent with reports showing that OR51E2/Olfr78 is expressed in the kidneys and is involved in the regulation of blood pressure (10). Moreover, OR51E1 was more highly expressed in GBM than in LGG, consistent with our recent findings (18). By contrast, OR4N2 and OR2L13 were expressed in LGG but not GBM, with t-SNE analysis confirming our previous findings (Fig. 1K, L). In addition to OR51E1/2, OR4N2, and OR2L13, we evaluated the levels of expression of additional OR genes described in Table 1 as well (Fig. 1E-J, M, N). Several of these OR genes were found to be tumor- and/or tissue-specific. For example, OR2A4 was expressed only in KIRC, suggesting that OR2A4 may be a potential therapeutic target or biomarker of KIRC (Fig. 1O). Kaplan-Meier survival analysis comparing survival in patients with low and high levels of each OR in Table 1 identified ORs that differed significantly (Fig. 2). For example, high expression of OR51E2 was associated with poor prognosis in patients with breast cancer and glioma, and high expression of OR7A5 was a risk factor for poorer outcomes in patients with liver, bladder, and kidney cancer and LGG. By contrast, high levels of OR4N2, OR7D2, and OR4K1 expression were associated with longer OS in patients with LGG.

Although the main function of ORs is sensing odorants in olfactory epithelium, ORs can also regulate cancer cell proliferation, apoptosis, migration, invasion, and senescence. However, the signaling pathways by which ORs act in cancers remain poorly understood. Several ORs have been shown to activate PKA and MAPK (21, 40, 53), and analysis of single-cell transcriptomes in cancer revealed that OR expression was

Table 1. Expression of odorant receptors in various human tumor types

Cancer type	Odorant receptor	Ligands/sample origin	Function	Ref
Prostate cancer	OR51E1 (PSGR2)	Nonanoic acid, medium-chain fatty acids	Senescence, growth suppression, cytostatic effects, cell death	(21, 30, 34-36, 55, 56) Fig. 1C
	OR51E2 (PSGR)	β-Ionone, acetate, propionate	Activation of the MAPK family and inhibition of cell proliferation	(21, 22, 26-33, 55, 57, 58) Fig. 1D
	OR1D2	Bourgeonal	Uptake of both bourgeonal conjugates *in vitro* and *in vivo*	(37)
Breast cancer	OR2B6	Unknown/patient specimens	Breast cancer proliferation and invasion	(17, 20, 38, 39) Fig. 1E
	OR6M1	Anthraquinone, rutin	AQ induced the death of MCF-7 cells, which was inhibited by rutin	(59)
	OR2W3	Unknown/patient specimens	Breast cancer proliferation and invasion	(20, 39) Fig. 1F
	OR2T8	Unknown/patient specimens	Breast cancer proliferation and invasion	(39) Fig. 1G
	OR2T6	Unknown/patient specimens	Increase in cell proliferation, invasion, and migration via EMT-MAPK signaling	(40)
	OR51E2	TCGA database	Poor prognosis	(25) Fig. 2A
	OR4F17	scRNA-seq	Metastasis (negative correlation)	(17)
	OR8B8 OR8H1	scRNA-Seq		(17)
Melanoma	OR51E2	β-Ionone	Inhibition of cell proliferation and migration	(23, 41)
	OR2C3	TCGA database		(60) Fig. 1I
	OR1A1	scRNA-Seq	Skin cutaneous melanoma	(17)
Colon cancer	OR51B4	Troenan	Apoptosis and inhibition of proliferation and migration	(42)
	OR7C1	Patient specimens	Correlation with tumorigenicity	(43)
Bladder cancer	OR10H1	Santalol and Sandranol	Decreased cell viability, proliferation and migration; increased apoptosis	(24) Fig. 1J
Neuroendocrine carcinomas	OR51E1	Tumor tissue	Increased expression	(44, 45)
Liver cancer	OR1A1	(−)-Carvone	Regulation of hepatic triglyceride metabolism	(46)
	OR1A2	Monoterpene (−)-citronellal	Decreased cell proliferation	(19)
	OR8B3	Monoterpene (−)-citronellal	No changes in intracellular Ca^{2+} levels in response to carvone, the activating ligand	(19)
Lung cancer	OR2J3	Helional	Inhibition of cell migration and decreased proliferation via the ERK pathway	(47)
	OR51E1	Patient specimens	High expression in lung carcinoids	(48)
	OR51E2	TCGA database	Poor prognosis	(25)
	OR4D11P	2-Ethyl-1-hexanol	Potential lung cancer biomarker	(49)
	OR6C75 OR5A1	scRNA-Seq	Invasion (negative correlation)	(17)
Brain cancer (Glioma)	OR4N2	Patient specimens and primary cell culture	MA-TAM target gene	(18, 51), Fig. 1K Fig. 2G
	OR7D2	scRNA-Seq	Astrocytoma	(17) Fig. 2J
	OR4F17	scRNA-Seq	Glioblastoma	(17)

Table 1. Continued

Cancer type	Odorant receptor	Ligands/sample origin	Function	Ref
	OR7A5	Patient specimens and primary cell culture	MA-TAM target gene	(51) Fig. 1H Fig. 2I
	OR51E2	TCGA database	Poor prognosis	(18, 25) Fig. 2F
	OR51F2	TCGA database treated with TMZ	Efficacy of TMZ therapy	(52)
	OR4Q3	TCGA database		(61)
	OR7E156P	TCGA database		(62)
	OR10Q1 OR4K1	COSMIC database	Astrocytoma	(63), Fig. 1N Fig. 1M, Fig. 2H
Kidney	OR2M3	scRNA-Seq	Renal cell carcinoma	(17)
Blood	OR10H1	scRNA-Seq	Chronic myeloid leukemia	(17)
	OR2AT4	Sandalore, antagonist Phenirat/acute myeloid leukemia (AML) patientshuman chronic myelogenous leukemia (CML) cell line	Reduced proliferation and induced apoptosis	(64)
	OR51B5	Isononyl alcohol/AML, CML	Reduced proliferation	(53)

COSMIC: catalogue of somatic mutations in cancer database, TCGA: the cancer genome atlas database.

associated with a complicated signaling network. Metascape analysis showed that breast cancer-associated ORs were involved in the cell cycle, transcriptional or translation regulation, metabolic processes, and DNA repair (17). Additional research on the mechanism of action of ORs in cancer may lead to the development of OR-targeting drugs.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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