Ectopic olfactory receptors in human: New therapeutic possibilities

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Abstract

The distributions of olfactory receptors (ORs) are widely available throughout our body, not compartmentalized in nasal parts, which are known as Ectopic olfactory receptors (EORs). Their functions are diverse but the majority of them are yet to be determined. ORs in non-olfactory tissues transduce their signals via different pathways that vary depending on their placements. As they are G-protein coupled receptors (GPCR), they stimulate Golf protein following the activation with specific ligands. They are involved in several cellular processes like chemotaxis, tissue repairing, hair growth, cell proliferation, energy metabolism, inflammation, apoptosis, etc. All these functions make them prospective therapeutic targets. The transformed expression level of ORs in the healthy and cancerous cells might open a new door to detect and diagnose cancer in the early stages. Ligand-based activation can also block the cancer pathway. This review summarizes the therapeutic potential of the EORs including their manifold functions outlined till date.

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Abstract

The distributions of olfactory receptors (ORs) are widely available throughout our body, not compartmentalized in nasal parts, which are known as Ectopic olfactory receptors (EORs). Their functions are diverse but the majority of them are yet to be determined. ORs in non-olfactory tissues transduce their signals via different pathways that vary depending on their placements. As they are G-protein coupled receptors (GPCR), they stimulate Golf protein following the activation with specific ligands. They are involved in several cellular processes like chemotaxis, tissue repairing, hair growth, cell proliferation, energy metabolism, inflammation, apoptosis, etc. All these functions make them prospective therapeutic targets. The transformed expression level of ORs in the healthy and cancerous cells might open a new door to detect and diagnose cancer in the early stages. Ligand-based activation can also block the cancer pathway. This review summarizes the therapeutic potential of the EORs including their manifold functions outlined till date.

Keywords: Olfactory system, Odorants, Ligands, Essential oil, Health benefits, Cancer, Biomarker, Transcript, Aromatherapy

Introduction

The odor is a very common trait surrounding us that generally is a mixture of various chemical substances known as odorants (Hetherington-Rauth & Ramirez., 2016; Locatelli, Fernandez & Smith, 2016; Chan et al*.,* 2018). Odorants are generally small and hydrophobic organic molecules with diverse chemical structures and characters (Pick et al*.,* 2009; Chan et al*.,* 2018). Commonly, odorants can be either came from external environments or formed by internal metabolisms of living beings (Lee, Depoortere & Hatt, 2019). Most of the living entities can use olfactory receptors (ORs) to recognize and differentiate odorants for chemical communications and finding food, making territories, identifying mates and avoiding dangers, etc. (Breer*,* 2003; Luu et al.,2005). Apart from chromosome 20 and the Y, OR genes are present in a cluster in the telomeric regions of other human chromosomes (Glusman et al*.,* 2000; Glusman et al*.,* 2001). ORs are classified as 7 transmembrane G-protein coupled receptors (GPCR) which are the major drug targets and 40% market-available pharmaceutical drugs target GPCR proteins (Firestein, 2001; Glusman et al*.,* 2001; Hutchings et al*.,* 2017). Except for nasal epithelium, ORs could be also found everywhere in the human body, such as testis, lungs, intestine, skin, heart, and blood, which are known as "Ectopic olfactory receptors" (EORs) (Flegel et al*.,* 2013). EORs show no connection to the olfaction, but they represent attractive potential novel therapeutic chances with variety of biological functions like sperm chemotaxis, wound healing, hair growth, muscle regeneration, cancer cell inhibition (Feldmesser et al*.,* 2006; Spehr et al*.,* 2013; Busse et al*.,* 2014; Cheret et al*.,* 2018; Lee, Depoortere & Hatt, 2019). For instance, cyclohexyl salicylate activates OR2A4/OR2A7 which transduces p38MAPK signaling. This leads to the reduction of melanocyte by slowing down p42MAPK signaling and increasing the growth of melanin (Tsai et al*.,* 2017). Receptor based signaling biology eludes the mechanism for binding of odorants to the EORs (Kaupp, 2010, Maßberg & Hatt, 2018). Recently, using high-throughput screening, scientists showed that 304 human ORs can respond to 89 odorants after analyzing 535 interacting pairs of odorants and ORs (Mainland et al*.,* 2015). Some ORs activated by specific odorants can have a huge change in expression level according to their presence in healthy or cancerous tissues. These ORs can be considered as early detectors for cancerous tissues (Weber et al*.,* 2018a, b). As many ORs are still orphans, their functions are yet to be determined (Maßberg & Hatt, 2018). This review intends to focus on their expressions and possible mechanisms in different tissues and functions in healthy and diseased tissues. Another aim is to enlist their known ligands which may lead us to a therapeutic possibility.

2. Olfactory system

After Buck and Axel (1991) found the ORs in rats, olfaction research began at molecular level (Buck & Axel, 1991). OR genes are discovered as the largest GPCR family in nasal epithelium with about 900 genes, among which only 370 genes are functional, and the others are pseudogenes (Rouquier et al., 1998; Glusman et al., 2001; Firestein, 2001; Wiese et al., 2015). Since 1992, the first EOR was identified in mammalian testis, more and more EORs were found in the other non-sense tissue with potential bio-functions need to be confirmed (Parmentier et al., 1992; Braun et al., 2007; Garcia-Esparcia et al., 2013; Xu et al., 2015; Wu et al., 2015). As ORs exist in non-sense tissues, they have no connection with olfaction termed EORs.

EORs have the same structures as ORs, so only odorants can be their ligands to activate biological functions (Kim et al., 2015; Ferrer et al., 2016; Maßberg & Hatt, 2018). Until now, 6% of total ORs have been identified with specific odorants as ligands to activate the functions (Buck, 2000; Dalton & Lomvardas, 2015; Tham et al., 2019). Normally Odorants bind with ORs and transduce a signal cascade which produces chemical signals by amplifying the chemical information (Jones & Reed, 1989). The initiation of that signaling cascade based on the activation of Golf protein. Following the binding of GTP, Golf protein activates adenylyl cyclase III (ACIII, also known as ADCY3) which later on raises the amount of cyclic adenosine monophosphate (cAMP) in the cytoplasm. This increase facilitates the opening of nonspecific cation-selective cyclic nucleotide-gated (CNG) channels resulting in external calcium and sodium influx (Firestein, 2001).

Some EORs have different effects on cell biological functions owing to their versatility in activating different molecular and cellular signaling mechanisms which depend on the cell types and the signaling components involved (Lee, Depoortere & Hatt, 2019). All the above discussion directs us towards the fact that EORs might have some good potentials for future therapeutics.

3. Ectopically expressed olfactory receptors in human

After activating by ligands, ORs in the nasal epithelium are responsible for creating smell perception through hormones, neural networks, and neurotransmitters. EORs have no business with smelling and neural sensation, but they are capable of triggering different responses through ligand-receptor bonding, such as promoting muscle regeneration, wound healing, cell proliferation and alleviating oxidative stress, reducing arthritis (Ferrer et al*.,* 2016).

Nowadays, EOR transcripts identification is generally carried out depending on qRT-PCR, microarray or next-generation sequencing (NGS) of mRNA (Maßberg & Hatt, 2018). Since the identification of first EOR in the testis in 1992 by RT-PCR (Parmentier et al*.,* 1992), many EORs were found in different non-sense tissues until today: placenta (Itakura et al*.,* 2006), gut (Braun et al*.,* 2007), colon (Kaji, Karaki & Kuwahara, 2011), brain (Garcia- Esparcia et al*.,* 2013), lung (Gu et al*.,* 2014), liver (Wu et al*.,* 2015), heart (Kim et al*.,* 2015), pancreases (Munakata et al., 2018), salivary glands (Xu et al*.,* 2015), kidney (Kelbe et al*.,* 2016c), leukemia cells (Menteniotis et al*.,* 2016 a,b), cardiac and skeletal muscle (Jovancevic et al*.,* 2017a), airway and adipose tissues (Wu et al*.,*2017), retina (Jovancevic et al*.,* 2017b), skin (Tham et al*.,* 2019), tongue (Malik et al*.,* 2019). The highest number of EOR genes was identified in testis (more than 60) and the lowest is in the liver (2) (Flagel et al*.,* 2013). Substantially, the expressions of EOR transcripts are not very strong as nasal ORs and distribution of some EORs is very comprehensive while some are tissue-specific (table 1) (Fledmesser et al*.,* 2006; Olender et al*.,* 2016). Most of the evidences show that EORs express at the mRNA level, not as proteins because they do not own specific antibodies.

3.1 Reproductive organs

Following the first human EOR discovered in testis mid-piece, efforts to determine their location and function substantially increased (Parmentier et al*.,* 1992). OR1D2 was the first EOR identified in humans. Activation by odorant bourgeonal triggers spermatozoal chemotaxis by increasing the swimming speed and direction of spermatozoa by enhancing the beating frequency of flagella (Neuheus et al*.,*2006). OR1D2 activated by undecanal regulates the behavior of spermatozoa by fastening swimming speed (Spehr et al*.,* 2003). The

activation of OR1D2 can regulate some fertilization or early embryogenesis gene expression by initiating the transfer of cytosolic β-arrestin2 to the nucleus (Neuhaus et al., 2006). Reduced bourgeonal perception sensitivity may be correlated with idiopathic infertility (Ottaviano et al., 2013; Sinding et al.,2013). The effect of OR7A5 and OR4D1 activated by Myrac and PI-23472 respectively on spermatozoal mobility were found later in testis (Veitinger et al., 2011). OR4N4 is another OR that expresses highly in spermatozoa which is not found in other tissues (Flagel et al., 2016).

After activated by specific ligands, most EORs characterized in testis show implications on Ca^{2+} transients (Spehr et al., 2003; Veitinger et al., 2011). Through testing the induction of sperm Ca^{2+} elevated level, two novel ligands 5α-androst-16-en-3-one for OR4D1 and 4-hydroxy-2, 5dimethyl-[$2H$]-furanone for OR7A5 were found (Hartmann et al., 2013). Instead of activating EORs to initiate the canonical signal transduction cascade and cause elicited Ca^{2+}transients, some odorants act on adenylyl cyclase activation, the second messenger cAMP and even the (cataion channel of sperm)CatSper calcium channel directly in human spermatozoa (Veitinger et al., 2011; Brenker et al., 2012). Calcium channels and extracellular Ca^{2+} are the prerequisites for Ca^{2+}signaling. Mibefradil, a blocker, could inhibit different calcium channels located in sperm, including CatSper and Ca^{2+}signals activated by odorants (Bezprozvanny, Scheller & Tsien, 1995; Wennemuth et al., 2003; Strünker et al., 2011; Flegel et al., 2016).

Until now, there were a few EORs discovered in the female reproductive system, but more than 20 different odorants including established activators of OR1D2 were found in vaginal secretions and follicular fluid by gas chromatography-olfactometry(GC-O) (Hartmann et al., 2013).

3.2 Prostate

The prostate is the most important endocrine gland of the male reproductive system. OR51E1 (PSGR1) and OR51E2 (PSGR2) are the two definite EORs expressed in this tissue stimulated by β-ionone and steroid hormone 1,4,6-androstatriene-3,17-dione (ADT) respectively (Neuhaus et al., 2009; Maßberg & Hatt, 2018). Up-to-date researches showed that these two EORs can be expressed widely in various tissues of the human body, such as the human tongue, heart, skin, etc. (Flagel et al., 2016; Gelis et al., 2017; Jovancevic et al., 2017a; Malik et al., 2019).

3.3 Respiratory system

As breathing is the most primary trait for being alive, the respiratory system is the prominent system in our body. Inhalation is the way to contact the environment for the respiratory system. Different EORs activated by different odorants control serotonin release in pulmonary neuroendocrine (NEC) cells (Gu et al., 2013; Gu et al., 2014). A study on Non-small cell lung cancer (NSCLC) A549 cell line shows the expression of OR2J3 triggered by helional and prompts PI3K signaling by secreting intracellular Ca^{2+}flux (Kalbe et al., 2017). Long-term exposure of stimulus, the activation of OR2J3 could provoke apoptosis and block cell migration and proliferation. The most important function of this EOR in the respiratory system is to control serotonin release and airway flexibility (Gu & Ben-Shahar, 2013; Gu et al., 2014). OR2AG1 stimulated by amyl butyrate can inhibit histamine and induced human airway smooth muscle cell contraction. Paired with Bourgeonal, the OR1D1 activation causes increased contraction of the airway muscle cell in the lungs (Kalbe et al., 2016a).

3.4 Kidney

The kidney plays a very important role in the urinary system. OR1A1 and OR1A2 are the most important ORs found in the liver (Flegel et al., 2013). They may be responsible for detoxification and hepatic metabolism (Maßberg et al., 2015; Wu et al.,2015). OR51E1 and OR11H7 in the kidney stimulated by isovaleric acid and 4-methylvaleric acid could control the secretion of renin and blood pressure by regulating the intracellular Ca^{2+} flux via cAMP-mediated pathway (Pluznick, 2013; Shepard et al., 2016).

3.5 Skin

Skin is the largest organ of the human body that maintains direct contact with the external environment.

Various sensory receptors presented in skin tissues (Maßberg & Hatt , 2018). So far, more than 5 ORs are found in skin tissues and epidermal skin layers (Oh, 2018). Basal keratinocytes express a high mRNA level of OR2AT4 paired with sandalore. An ex-vivo experiment showed that this activation speeds up keratinocyte migration and proliferation and results in wound healing via cAMP-dependent pathway. The wound healing process can be blocked by antagonist oxyphenylon (Busse et al., 2014). In the co-culture system, ATP based pannexin-mediated cell-cell communication between trigeminal neurons and keratinocytes may be induced by OR2AT4 activation (Sondersorg et al., 2014). Upon activation with sandalore or brahmanol, OR2AT4 can also increase the growth of hair follicles (Cheret et al., 2018). Studies on HeLA cells showed that OR51B5, depending on its agonist isononyl alcohol, may cause an increase in the migration and proliferation of keratinocytes with cytokine secretion such as IL-6. The expression of OR2A4/7 in keratinocytes stimulated by cyclohexyl-salicylate leads to the production of IL-1 and cell proliferation (Tsai et al., 2017). OR2A4/7 activation can persuade p38MAPK signaling by reducing intracellular Ca^{2+} and cAMP levels in melanocytes (Wojcik et al., 2018)

3.6 Heart

The heart is the most important of the circulatory system, which provides blood throughout our body by rhythmic pumping. Different odorant can enter our body through blood circulation. Through next-generation sequencing, almost 10 different ORs have been identified in adult and fetal cardiovascular systems (Lee, Depoortere & Hatt, 2019). OR51E1 shows a huge expression and can sense fatty acids. The strongest two stimulators are Nonanoic acids and structurally related medium-chain fatty acids (MCFAs) (Jovancevic et al., 2017a). OR51E1 may regulate our heart rate as its activation by MCFAs negatively affects chronotropic affects human stem cell-derived cardiomyocytes and reversely induce inotropic effects human explanted heart preparations (Jovancevic et al., 2017a). Odorant lyral can activate OR10J5 present in the human aorta, coronary arteries, and umbilical vein endothelial cells. This activation results in increased migration and angiogenesis by inhibiting Ca^{2+} influx and protein kinase B (AKT) phosphorylation (Kim et al., 2015)

3.7 Gut

The gut is the most important part that expressed ORs because it has to tackle the odorants from the outside world and from inside as gut microbiota produces many metabolites (Lee, Depoortere & Hatt, 2019). Different odorants from spices can activate several ORs present in gut enterochromaffin (EC) cells and increase Ca^{2+} level which leads to the regulation of serotonin secretion (Braun et al., 2007). On the contrary, OR2J3 in pancreatic EC cells is stimulated by helional may increase serotonin secretion but reduce intracellular calcium level (Kalbe et al., 2016b).

(-)-citronellal induced OR1A2 in hepatocellular cells activates the cAMP-dependent signaling pathway and decreases cell proliferation (Maßberg et al., 2015). In liver cells, OR1A1 takes part in the synthesis of triglyceride by reducing mitochondrial glycerol-3-phosphate acyltransferase (GPAM) gene expression (Wu et al., 2015).

3.8 Other tissues

By adenylyl cyclase signaling, another OR, OR11H7, present in renal proximal tubular cells, can evoke Ca^{2+} influx intracellularly (Kalbe et al., 2016b). RNA-seq analysis identifies an orphan OR, OR6B3. It is highly expressed particularly in trigeminus and dorsal root ganglia of the human nervous system (Flagel et al., 2015). OR2W3, OR5P3, and OR10AD1 showed cell type-specific expression for retina in immunohistochemical staining of the retinal section (Jovancevic et al., 2017b). OR1A1 and OR1A2 are the most important ORs found in the liver (Flegel et al.,2013). They may be responsible for detoxification and hepatic metabolism (Maßberg et al., 2015; Wu et al., 2015). Serotonin secretion can also be regulated by helional-stimulated OR2J3 available in pancreatic EC cells (Kalbe et al., 2017). Several ORs are also found in the tongue and immune tissues for which functions need to be specified. OR2W1, OR5A1, OR5P3, and OR51E1 present in the human tongue can have a good impact on our taste perception (Malik et al.,2019). Erythrocytes, peripheral blood mononuclear cells, natural killer cells, B and T cells, and poly-morpho-nuclear neutrophil granulocytes are subjected to research with food aroma compounds. This means a various class I OR trans-

cripts are expressed in those human body defense cells (Geithe et al., 2015; Clark et al., 2016; Manteniotis et al., 2016a, b). Volatile amines can target trace amine-associated receptors (TAAR) genes in human which can act as ORs (Gainetdinov, Hoener & Berry, 2018).

4. Odorants as therapeutic ligands with EORs

Odorants with therapeutic potentials play a very crucial role in human life (Denda et al., 2000; Kako et al., 2008; Lee, Depoortere & Hatt, 2019). Several investigations have presented EORs activations by odorants administration may have some help on a physiological and psychological process in humans (Table 2), for example, odorants can encourage skin barrier recovery by reducing the stress responsible for homeostasis (Denda et al., 2000; Angelucci et al., 2014).

From the literature review, we summarize the EORs activating odorants (ligands) into three main groups. In this section, these three groups have been elaborated with examples.

4.1 Fatty Acids

According to the research to date, fatty acids are a large group of ligands that can activate EORs, mainly short-chain fatty acids (SCFAs) and medium-chain fatty acids (MCFAs). In the human body, about 500–600 mmol of SCFAs are formed in the gut per day, but the amount of SCFAs production depends on the fiber intake dose and sources. Some good sources of dietary fiber are apples, apricots, milk, yogurt, see-weeds, etc. (Dhingra et al., 2012; Dalile et al., 2019). Acetate (C2) and propionate (C3) are the prominent SCFAs in the human body (Macfarlane & Macfarlane, 2003). Acetate stimulates OR51E2 in the kidney and induces renin secretion (Pluznick , 2013). Propionate activates OR51E2 to mitigate airway contraction (Aisenberg et al., 2016). Propionic acid, an SCFA metabolite generated from gut microbiota fermentation can trigger OR51E2 and reduce anabolic and proliferative signals in the prostate (Natarajan & Pluznick, 2016; Pluznick, 2016; Rooks & Garrett, 2016; Abaffy et al., 2018). Another receptor OR51E1, paralogous to OR51E2, can also be stimulated by SCFA, but most prone to be activated by MCFA like nonanoic acid, decanoic acid and valeric acid derivatives (Fujita et al., 2007; Jovancevic et al., 2017a). MCFA can be released by the metabolism of adipose tissue as well as direct dietary intake (Costa et al.,1998). MCFA is present in human plasma and epicardial adipose tissue, which is a case in point to indicate the participation of ORs in heart function. Because MCFA-activated OR51E1 can negatively induce cardiac trabeculae in human explanted heart and results in chronotropic negativity in human stem cell-derived cardiomyocytes (Jovancevic et al., 2017a).

4.2 Essential oil oriented flavor compounds

EORs activating odorants are naturally found in plant essential oils (EOs) (Lahlou, 2004). EOs are colorless smelling liquids consisting of saturated and unsaturated hydrocarbons, alcohol, aldehydes, esters, ethers, ketones, oxides phenols, and terpenes, which can be considered a mixture of fragrance compounds (Schiller, & Schiller, 1994; Wildwood , 1996). The human body could intake these odorants through the skin and lungs by absorption and inhalation (Maßberg & Hatt, 2018). Furthermore, Some of EOs can also be taken with drinks or foods as additives.

With small molecular weight, they are highly refractive. EOs are the main therapeutic agents in aromatherapy, an age-old treatment system that still possesses a very strong position in medical science (Ali et al., 2015). As EOs are highly concentrated with fragrance elements, they can work very effectively on pressure points even by inhalation (Alok, Rakesh & Sushil, 2000). Besides relieving the stress, rejuvenating and regenerating the individuals, EOs also has antimicrobial and antioxidant characteristics (Guleria et al.,2013). For centuries, EOs are used by folklore professionals as powerful treatment materials for diseases like Alzheimer's, cardiovascular, cancer and labor pain in pregnancy in different parts of the world (Perry & Perry, 2006; Shiina et al., 2008; Jimbo et al.,2009; Smith, Collins & Crowther, 2011). Even recent medical science has found that EOs can have a good effect on cancer treatment (Blowman et al., 2018).

Volatile terpenes and terpenoids are the main components of EO (Pichersky, Noel & Dudareva, 2006). Some of these volatiles viz. citronellal (pelargonium), thymol (thyme), ionone (roses and berries), geraniol (rose oil and citronella oil) and citronellal (citrus species) can trigger ORs in non-chemosensory tissues and affect the

cellular process (Sanz et al., 2005; Braun et al., 2007; Saito et al., 2009; Adipietro, Mainland & Matsunami, 2012; Gu & Ben-Shahar, 2013; Wu et al., 2015; Zhao et al., 2013).

β-ionone, an endogenous ligand for OR51E2, is a very available component of cosmetics because it has a good impact on melanogenesis and dendritogenesis. It can also cut off the proliferation of melanocytes in cell culture. OR51E2, formerly believed to be native in the prostate, has shown its presence and effects on skin tissues too (Gelis et al., 2016). In prostate cancer cells, β-ionone triggers OR51E2 and activates tyrosine kinase Src and increases Ca^{2+}via transient receptor potential channel (TRVP6) (Spehr et al.,2011). This ligand retards the tumor suppressor N-myc downstream-regulated gene 1 (NDRG1) by evoking the downstream phosphorylation of tyrosine kinase 2 (PYK2), p38 MAPK, and JNK/SAPK. It can also suppress the phosphorylation of ribosomal protein S6 kinase (p70S6K) (Wiese et al., 2015).

Sandalore stimulates OR2AT4 and triggers cAMP-dependentt pathway following Ca^{2+} increment and protein kinases phosphorylation. This results in the proliferation and migration of human keratinocytes. Keratinocyte proliferation and migration by sandalore mediated OR2AT4 can develop healing in wounded human cells by *ex vivo* system (Busse et al., 2014; Sondersorg et al., 2014). Activation of OR2AT4 in human scalp hair follicles by sandalore promotes hair growth by boosting the formation of anagen-prolonging growth factor IGF-1 and reducing the amount of apoptosis (Cheret et al., 2018). Italy has planned to use sandalore clinically by making it an ingredient for shampoo and lotions (Di Pizio, Behrens & Krautwurst, 2019).

Activation of OR2AT4 by Brahmanol and also by sandalore can induce a strong reduction of hair matrix keratinocyte apoptosis by inhibiting catagen development. OR2AT4 activation promotes anagen improvement (active growth phase) of the hair follicle by boosting the production of IGF1. That means OR2AT4-induced signaling has a significant role in the hair growth cycle (Chéret et al., 2018).

OLFR16 activated by Lyral has a great impact on the regeneration of muscle tissues (Griffin, Kafadar & Pavlath, 2009). This activation causes a rise of intracellular cAMP leading to myocyte migration, myofibre branching, and myogenesis. OLFR16 also modulates cell-cell adhesion and myotube formation (Pichavant, Burkholder & Pavlath, 2015).

Troenan (5-methyl-2-pentan-2-yl-5-propyl-1, 3-dioxane) stimulates OR51B4 in colorectal cancer cells which results in apoptosis and inhibition of cell proliferation (Weber et al., 2017). In German clinics, suppository capsules with troenan have already been used to treat colon cancer patients (Di Pizio, Behrens & Krautwurst, 2019).

Activation of OR2AG1 using amyl butyrate might inhibit the histamine-inducedd contraction of human airway smooth muscle cells, resulting in muscle relaxation. By contrast, stimulation of OR1D2 using bourgeonal increased cell contractility and elicited the secretion of interleukin-8 (IL-8) and granulocyte– macrophage colony-stimulating factor (Kalbe et al., 2016a).

Eugenol and thymol from spices increase gut motility by activating some ORs, e.g. OR1G1, OR1A1, OR3A1 (Braun et al., 2007). Thymol can also induce angiogenesis via hOR17-7/11(Kim et al., 2015).

OR1A1 stimulated by the ligand (–)-carvone, a supreme compound in spearmint essential oil, triggers PKA signaling pathway without influencing intracellular Ca^{2+} levels. This transduction helps in hepatic metabolism by reducing intracellular triglyceride concentrations. α-cedrene activates OR10J5 and decreases hepatic lipid concentrations (Wu et al., 2015).

Cyclohexyl salicylate can reduce intracellular cAMP (cyclic adenosine monophosphate) and Ca^{2+} levels by activating OR2A4/OR2A7. It can inhibit the growth of melanocyte and induce melanin biosynthesis by reducing p42 MAPK (also known as MAPK1) and/or p44 MAPK (also known as MAPK3) phosphorylation and promoting p38 MAPK signaling (Tsai et al., 2017).

4.3 Metabolites

In animal cholesterol biosynthesis, terpenes are degraded into their functional unit isoprene through mevalonate pathway (Goldstein & Brown, 1990). In addition, lots of metabolic intermediates of this pathway

generally contain similarities with OR activating terpenes in their structure (Edwards & Ericsson, 1999). 19-Hydroxyandrostenedione is a testosterone metabolite, which can activate OR51E2 and transduce Neuroendocrine Trans-Differentiation of prostate cancer cells (Abaffy et al., 2018)

5. EORs involved in diseases

Some EORs may show no or very low expression in healthy tissues. Nevertheless, they can show high expression in cancer and diseased tissues, which might represent such kinds of EORs as potential biomarkers for pathogenesis.

5.1 Breast Cancer

OR2B6, a tissue-specific EOR in breast cancer, has been found 73% and 80% expression of OR2B6 in breast carcinoma cell lines and carcinoma tissues respectively. The upregulated expression of OR2B6 was found in blood platelets of tumors from breast cancer patients. OR2B6 can also express mutually with a histone gene HIST1H2BO and build a fusion transcript together in carcinoma tissues. However, healthy tissues hardly show any expression of OR2B6 that makes it to be a probable biomarker for breast cancer. OR2B6 can also express in several carcinoma tissues, but not as remarkable as breast carcinoma tissues (Weber et al., 2018a). OR2W3 and OR2T8 are also highly up-regulated. These three EOR genes are "over-expressed" in breast cancer tissues (Masjedi, Zwiebel & Giorgio, 2019).

5.2 Bladder Cancer

Bladder cancer tissues show a significant expression of OR10H1 compared to the normal bladder. The triggering of this receptor can change the morphology of cytoskeletons that can be identified β-Catenin, T-cadherin, and β-actin staining. Stimulation by sandranol blocks cell migration and proliferation, implies cell cycle arrest and leads to a limited extent- apoptosis. Sandranol inhibits adenylyl cyclase and thus reduces cAMP levels which evoke an increase of intracellular Ca^{2+} concentration (Weber et al., 2018b).

5.3 Lung cancer

RSK1 silencing increases tumor metastasis in non-small-cell lung cancer (NSCLC) tissues in humans. This cell shows very strong positivity about the expression of OR2J3. This receptor also can start the release of Ca^{2+} from intracellular Ca^{2+} stores (Kalbe et al., 2017). Functional imaging and immunohistochemical studies show quite stable and high expression of OR51E1 in lung cancer cells. Due to the extensive membrane localization, OR51E1 can be considered as a novel therapeutic target against available Somatostatin receptors (SSTRs). Moreover, some tumor patients do not respond to SSTRs based diagnosis (Giandomenico et al., 2013)

5.4 Colorectal Cancer

In 2017, Weber et al. found extraordinarily over-expression of OR51B4 in colorectal cancer tissues confirmed by shRNA mediated knockdown. In HCT116 cells, Troenan can stimulate anti-proliferation, anti-migration, and pro-apoptosis by PLC activation and intracellular calcium level changes. This results in phosphorylation levels changes of p38, mTOR and Akt kinases (Weber et al., 2017). Cancer initiating cells (CICs) in colon expresses OR7C1, which results in higher tumorigenicity. Peptide specific cytotoxic T lymphocyte (CTL) antigen for OR7C1 is toxic to CICs (Morita et al., 2016).

5.5 Myelogenous leukemia

By next-generation sequencing, a recent study shows that chronic myelogenous leukemia (CML) cell express OR at a high rate, specifically OR51B5. Isononyl alcohol activates OR51B5 and increase intracellular Ca^{2+} level in acute myelogenous leukemia (AML) patients. OR51B5 can inhibit cell proliferation in both AML and CML patients by reducing the phosphorylation of p38MAPK (Manteniotis et al., 2016b).

OR2AT4 can increase the phosphorylation of p38-MAPK that leads to leukemia. This receptor expresses highly in human myelogenous leukemia (Manteniotis et al., 2016a)

5.6 Hepatic diseases

OR1A2, which is paralogous to OR1A1, is a potentially expressed olfactory receptor in hepatic cancer cells. (-)citronellal activates OR1A2 which increases cytosolic Ca^{2+} level via the cAMP-dependent pathway and reduces cell proliferation by p38MAP phosphorylation (Meβberg et al., 2015). As a null variant, OR1B1 gene influences liver cell metabolism by reducing serum cholinesterase activity. It aids to effect significantly in liver autoimmune disease (Koyano et al., 2008).

5.7 Retinitis Pigmentosa

Definite mutation in OR2W3 gene is highly related to an ocular disease called Retinitis pigmentosa (RP) (Ma et al., 2015). RP is an inherited autosomal dominant retinal disease, which is rare, reported only one of 3000 to 5000 peoples (Zhang & Huang, 2015). OR2W3 is located in the photosensitive outer membrane of cone cells. As it does not fuse with Trim58 transcript, it can be concluded that it possibly has a physiological function in the human retina (Sharon, Kimchi & Rivolta, 2016).

5.8 Neurological Disorders

Neurodegenerative and neuropsychiatric disorders evaluation in recent days proves the relation with dysregulated OR gene expression. Several ORs (OR2L13, OR1E1, OR2J3, OR52L1, and OR11H1) have been identified to be down-regulated in the early stages of Parkinson's disease pathogenesis (Garcia-Esparcia et al., 2013; Grison et al.,2014), which may lead to their undeniable importance in the development of the disease. Patients samples with Alzheimer's disease (AD), Creutzfeldt-Jakob disease, and progressive supra-nuclear palsy present differentially regulated OR gene expression (Ansoleaga et al.,2013). Among the verified ORs in AD patients, half showed altered expression in the cortical region. OR11H1 supposed to be up-regulated, while OR4F4, OR52L1, and OR10G8 expression are reduced and linked up with disease development (Ansoleaga et al., 2013; Woodward et al., 2017).

Downregulated ORs in cerebral regions leads to chronic schizophrenia (Ansoleaga et al., 2015) and traumatic brain injury (Zhao et al., 2013). For biomarker analysis, the detection of both OR4M1 and OR11H1 can have a potential diagnostic feature in the near future (Maßberg & Hatt, 2018). Down-regulation of OR2L13, OR2T33, OR2J3, OR52L1, OR10G8, OR11H1 and OR4F4 in frontal cortex has been detected in the early stages in Parkinson's disease (Grison et al., 2014). Olfactory receptor gene cluster on 14q11.2 region containing OR4M1, OR4N2, OR4K2, OR4K5, and OR4K1 shows modifications in their expression at the earlier age of Alzheimer's disease (Ansoleaga et al.,2013).

5.9 Urological disorders

OR51E1 and OR51E2 are the most distributed and expressed ectopic OR. They make themselves noble biomarkers by expressing higher in cancer tissues than healthy tissues. They were first introduced as a significant OR, expression restricted to prostate adenocarcinoma and named as PSGR (OR51E2) and PSGR2 (OR51E1) (Xia et al., 2001; Xu et al., 2006). PSGR locates in chromosome 11p15 encoding 320 amino acid-containing proteins (Xu et al., 2000). Its mRNA level, correlated with prostate-specific antigen (PSA), raises remarkably prostate intraepithelial neoplasia (PIN) and Prostate cancer (PCa) (Xu et al., 2006). As it is available in human urine sediment, it can be used as an alternative biopsy for prostate cancer (Rigau et al., 2010). According to Cao et al., PSGR can boost up cell proliferation invasion and later on metastasis in prostate cancer (Cao et al., 2015). The elevated expression refers to an early alteration of PCa while low expression reveals poor prognosis. Both OR51E1 and OR51E2 can be linked with PCa marker alpha-methyl-CoA racemase (AMACR) (Wang et al., 2006). Therefore, a dual marker can be a good identifier to ensure the development of prostate cancer. Besides, PSGR can be fused up with erythroblast transformation specific (ETS) transcription factor (ETV-1) chimerically and show important positive effects on the elevation of prostate cancer (Weng et al., 2005; Barros-Silva et al., 2013).

5.10 Others

OR51E1 can also be a potential biomarker for the detection of somatostatin receptor-negative lung carcinoids

(Giandomenico et al., 2013) and small intestinal neuroendocrine carcinomas (Leja et al., 2009; Cui et al., 2013). A recent study mentioned that peptide derived from OR51E2 can behave as tumor-associated antigen (TSA), detected by CD8+ T-cells, in various cancer cells including melanoma (Gelis et al., 2017).

6. Possible mechanisms of EORs

Even EORs are not involved in smell and neural perception; they share the same structure with ORs in the nasal epithelium as well as their mechanisms. The signaling of EORs is hypothesized by the fragmentary involvement of cAMP, recommending heterotrimeric G-protein (Golf protein) as a strong stimulatory that widely expressed in human tissues (Flegel et al., 2013; Busse et al., 2014).

6.1 The initial process for EORs activation

When a ligand binds to the OR, the 7 transmembrane receptor initiates and converts its conformation based on the interaction between GPCR and G-protein. The Gα subunit presumes a triggered conformation upon GTP-binding and dissociates from receptor and Gβγ. When GPCR activates, Gα releases from GDP. "Empty pocket" of G-protein and the receptor bridges with a high-affinity complex, which can be described with "action at a distance" hypothesis elaborated by Oldham & Hamm (2008). The conversion of GTP from GDP results in dissociation of Gβγ dimer from Gα that further starts intracellular signaling as "second messenger" (Sprang, 2007). This second messenger can initiate or inhibit other elements of cell mechanisms. For instance, Phospholipase C enzyme can hydrolyze phosphatidylinositol 4,5-bisphosphate (PIP2) to 1,2-diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). DAG can actuate protein kinase C isoforms. IP3 can connect with receptors which lead to calcium release in the cytosol. A large number of the second messenger including cyclic AMP, cyclic GMP, calmodulin, and kinases can be modulated by G proteins. When GTP hydrolyzes into GDP by GTPase activity of the Gα subunit, inactive Gαβγ is formed by the re-association of Gα-GDP and Gβγ. Evidence implicates that there is no physical disassociation of G-protein from the complex (Frank et al., 2005; Digby et al., 2006).

An activated G-protein can co-localize with regulatory factor Resistance to inhibitors of cholinesterase 8B (Ric8B) in olfactory sensory neurons. Although there is no solid information for specific functional appearance, there are some limited proof and proposed data of G-protein subunit activation in cancer cells (Sanz et al., 2014). ORs require definite cofactors to develop membrane localization of receptors. The important co-factors are Receptor transporter proteins 1 and 2 (RTP1 and RTP2) and receptor expression enhancing protein (REEP1). They are found in neurons cytoplasm doing down-regulation of brain's signaling molecules (Krautwurst, Yau, & Reed, 1998; Abaffy, Matsunami, & Luetje, 2006; Li & Matsunami, 2011; Peterlin, Firestein & Rogers, 2014)

6.2 cAMP-induced calcium flux

Most of the ectopic ORs trigger a cAMP-induced calcium influx. It generally happens from outside the cells representing the canonical pathway cascade in olfactory sensory neurons (OSNs). The necessary subunits expressions to build the canonical heterotetrameric cyclic nucleotide-gated (CNG) channel (CNGA2, CNGA4, and CNGB1), particularly CNGA2, has not been identified in most tissues of the human body. CNG channel is a very important channel in peripheral human tissues and cells (Flegel et al., 2013). CNGA1, mainly activated by cGMP along with cAMP, is the native rod protein capable of forming functional homomeric channels. CNGA1 can perform as a CNG channel (Kaupp et al., 1989). CNGA3 channel is a cone photoreceptor native to sperm cells. Along with the CatSper channel, CNGA3 expressed functionally indicating its possible involvement in OR-mediated sperm chemotaxis (Busse et al., 2014; Maßberg et al., 2015)

Though the Ca^{2+} entering channels are still mostly unidentified, some researches have shown the involvement of TRP channels, CRAC channels, voltage-gated L-type Ca^{2+}channels, or spermatozoa-specific CatSper channels (Brown et al.,2019). There is a possibility of determining Ca^{2+}influx through TRPM family members by using particular channel blockers 2-APB (Kalbe et al., 2016b; Flegel et al., 2016; Manteniotis et al., 2016b).

Intracellular Ca^{2+} increment in human airway smooth cell is induced by OR1D2 and OR2AG1 through a cAMP-dependent pathway. OR1A1 induces cAMP response element-binding protein (CREB) without cAMP induction and intracellular Ca^{2+}.

6.3 MAPK downstream cascade

Ectopic OR activation can lead to regulate downstream protein kinase cascades, precisely MAPK, in various cellular signaling dependent or independent of the canonical pathway. These protein kinases presume to be the main downstream modulators of several cellular processes (Kim et al., 2015; Gelis et al., 2016)

These ORs mediated signaling in physiological systems are distinctly relied on the OR ligands structure and concentration, morphology and biochemistry of the regarding cellular systems, the heterotrimeric G protein subunits, and the involvement of other less regulatory scaffold proteins(Rodriguez et al., 2014; Wiese et al., 2015; Wu et al., 2015). By reducing early phosphorylation of p38 mitogen-activated protein kinases (p38-MAPK), OR2AT4 can hinder cell growth and through the phosphorylation of p44/42-MAPK can decrease cell apoptosis in acute myelogenous leukemia (AML) patient (Manteniotis et al., 2016a).

6.4 Others

Some ORs can activate the tyrosine kinase Src (sarcoma) signaling pathway. Without activating any G-protein, this cascade can raise the Ca^{2+} level in the cell via transient receptor potential channel V6 (TRPV6). Some evidences show that some specific ligands such as β-ionone can trigger PI3K/AKT downstream signaling via Gβγ stimulation. OR51E1 shows involvement in AR-mediated signaling through Src kinase (Spehr et al., 2011; Maßberg et al.,2016).

In essence, ORs activated by their specific odorants can transduce intracellular signal cascade by several mechanisms.

7. Conclusions

As extra-nasally expressed ORs show their prominent involvement in diseases, undoubtedly they can be promising therapeutic targets. The characteristics of EORs can be categorized as "chemosensors" as they show no connection to olfaction (Lee, Depoortere & Hatt, 2019). As the EORs are categorized as chemosensors in the human body, undoubtedly they might be promising therapeutic targets.

It is quite practical to consider ORs as therapeutic targets, as approximately 30% of pharmaceuticals work through rhodopsin-like GPCRs (Overington, Al-Lazikani & Hopkins, 2006). Some ORs have also been suggested as biomarkers (Kalbe et al., 2017; Weber et al., 2018a). These biomarkers can be a noble clinical holy grail to detect diseases in the embryonic stage and to start the diagnosis of cancer. Although a lion's share of the ectopic ORs is orphan, some of them with stimulants can actually inhibit several biosynthesis that leads to the betterment of human health.

EO can be a good source to continue the search for EORs activation mechanisms. EO is naturally full of fragrant compounds and frequently used by local doctors and aroma-therapists. It can balance physiological and psychological responses in the human body. We can use EO to deorphanize the orphan EORs and that may bring out the possible therapeutic effects of EORs.The most dynamic and significant future research should be the identification of ORs, their agonist or antagonist, and their functions. No doubt, mRNA expression level research can encourage the possibilities of ORs as therapeutic targets.

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9. Conflicts of Interest

The authors declare no conflicts of interest.

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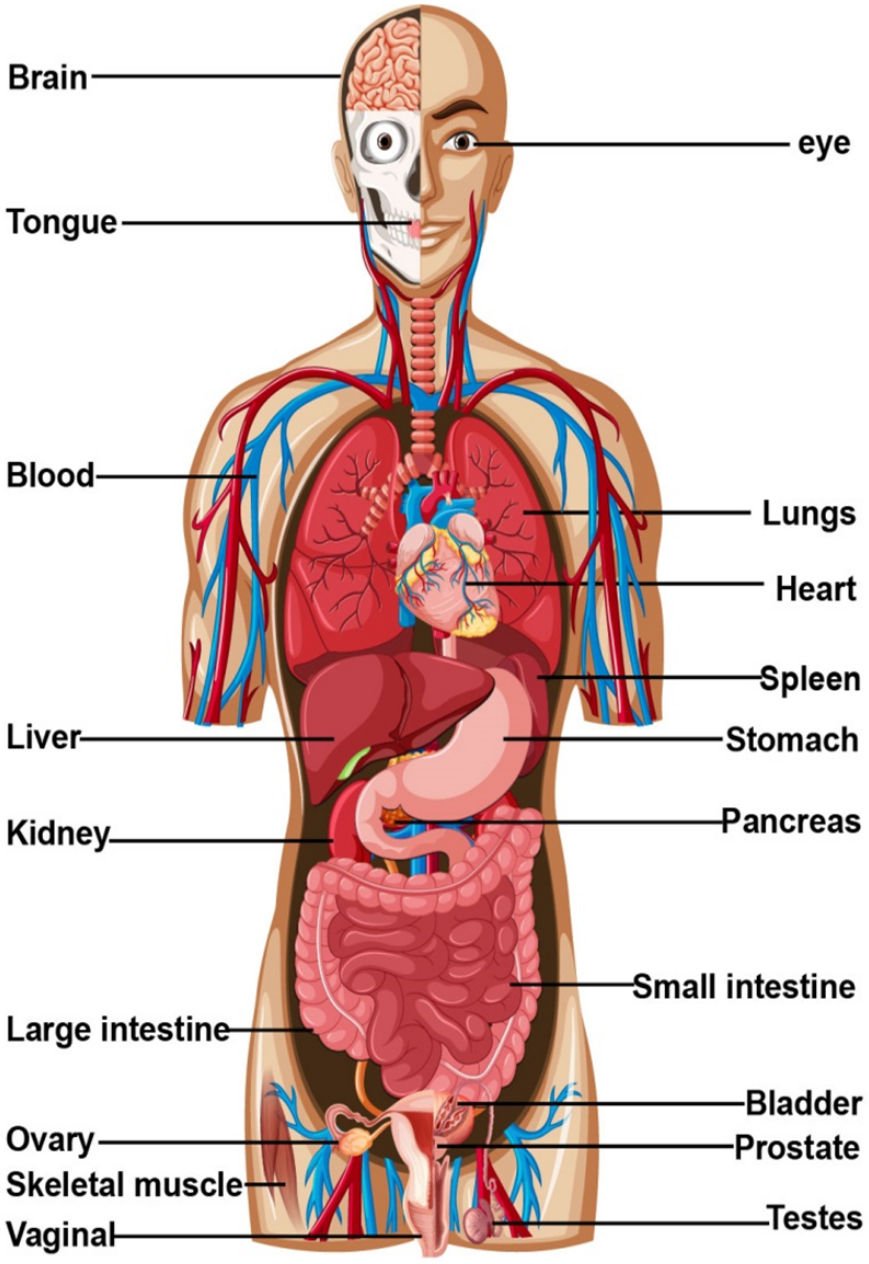

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