Association between Olfactory Receptors and Skin Physiology

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Olfactory receptors are chemosensory receptors that detect odorants and function in the initial perception of a smell. Intriguingly, olfactory receptors are also expressed in cells other than olfaction sensory cells, an expression pattern termed ectopic expression. Ectopically expressed olfactory receptors have a distinct role depending on the type of tissues or cells in which they are expressed. This review introduces current research on the ectopic expression and function of olfactory receptors in skin and provides insight into directions for future research.

Keywords: Ectopic gene expression, Olfactory receptor, Skin, Skin physiology

INTRODUCTION

The olfactory receptor (OR) is a member of the G-protein coupled receptor (GPCR) family.1-6 ORs respond to a specific group of chemicals called odorants and transform them via intracellular cyclic adenosine monophosphate (cAMP) signaling.7 ORs thus function in the olfactory system to detect odorants. Since ORs are a chemoreceptor, they recognize specific odorants. As part of the olfactory system, ORs monitor chemical changes in the outer environment. The olfactory system has four subsystems: the main olfactory epithelium (MOE), vomeronasal organ (VNO), septal organ (SO), and Grueneberg ganglion (GG). ORs in the MOE and VNO sense odorants and pheromones, while ORs in GG sense alarm pheromones, resulting in freezing behavior. ORs in the olfactory system are generally located in the olfactory epithelium (OE).1-5,8

OLFATORY RECEPTOR-MEDIATED SIGNALING PATHWAYS

Odorant activation induces certain signal pathways downstream of the OR. As a GPCR family protein, OR activation is
associated with a conformational change that opens its binding site, leading to subsequent binding of G proteins to the intracellular portion of the OR. This activation results in an intracellular cAMP increase. Adenylate cyclase III is formed, followed by activation of cation-selective cyclic nucleotide-gate (CNG) ion channels. External Ca\(^{2+}\) influx activates Cl-channels, resulting in rapid depolarization of the plasma membrane. After a series of signaling cascades, the Ca\(^{2+}\) level returns to its original state through Na\(^+\)/Ca\(^{2+}\) exchanger (NCX), potassium-dependent Na\(^+\)/Ca\(^{2+}\) exchanger (NCKX5), and plasma membrane Ca\(^{2+}\)-ATPase (PMCA). This mechanism is shown in Fig. 1.

ECTOPIC EXPRESSION OF OLFACTORY RECEPTORS

Early studies on ORs revealed that they are specifically expressed in the OE. However, in the last 30 years, many studies found that ORs are also expressed in various non-olfactory tissues, like spermatozoa, prostate epithelial cells, enterochromaffin cells of the gut, hepatocarcinoma cells, and lung cells. Intriguingly, among the 396 types of human ORs discovered, 111 have been shown to function in other tissues throughout the body. The extranasal expression of ORs is called ‘ectopic expression’. Ectopic expression of ORs throughout the body suggests that these receptors might have roles in other biological functions. Many studies have reported that ORs are associated with the regulation of sperm chemotaxis, wound healing, muscle regeneration, hair growth, adiposity, and cancer cell inhibition. Although the function of ectopically expressed ORs remains unclear, there are ongoing studies about the physiological roles of these ectopically expressed ORs.

There are certain characteristics of ectopic OR expression. The first is the ‘one cell-one receptor rule,’ which suggests that a cell expresses only one type of OR gene. However, this rule might not apply in all tissues. For example, more than one type of OR is expressed in extra-nasal tissues require unique signaling factors. For instance, Ca\(^{2+}\) signaling pathway activation of ectopic ORs operates in a tissue-specific manner. The signaling requires CNGA2, CNGA4, and CNGB1, all of which are CNG channels, but these channels are not found in most extra-nasal tissues. Therefore, ectopic ORs need to be studied independently, without assumptions related to existing knowledge about conventional nasal ORs. Although there...
Roles of Olfactory Receptors in Skin

have been some recent discoveries on ectopic ORs, research on ORs within skin tissue is in the early stages. Therefore, this review briefly introduces several types of ORs that are expressed in skin tissue, their odorants, and signaling pathways, along with research on OR physiological functions and therapeutic potential (Table 1).

**OR2AT4 IN SKIN PHYSIOLOGY**

OR2AT4 is a receptor for the odorants sandalore, brahmanol, cyclohexylsalicylate (CHS), and isononyl alcohol (INA). Its antagonists include phenirat, javanol, and oxyphenylon. OR2AT4 is expressed in HaCaT cells, human primary keratinocytes, and basal melanocytes of the human epidermis. In HaCaT cells, activation of OR2AT4 is involved in the communication between skin cells and trigeminal ganglia. During long-term activation, OR2AT4 also increases proliferation, migration, and wound healing in keratinocytes. These cellular processes are induced by sandalore, resulting in increased Ca²⁺ signaling, activation of cAMP-dependent pathways, and phosphorylation of extracellular signal-regulated kinases (Erk1/2) and p38 mitogen-activated protein kinases (p38 MAPK), promoting human keratinocyte proliferation and migration. These pathways are shown in Fig. 2.

Basal keratinocytes are an essential cell type responsible for wound healing. A previous study showed that OR2AT4 is highly expressed in basal keratinocytes. Sandalore-induced keratinocyte proliferation and migration enhanced cutaneous wound healing ex vivo in a human system, while the antagonist oxyphenylon inhibited this effect. Furthermore, OR2A4

| Receptor | Odorant | Function | Cell type | Signaling | Reference |
|----------|---------|----------|-----------|-----------|-----------|
| OR2AT4   | Sandalore, Brahmanol, Cyclohexylsalicylate, Isononyl alcohol | - Communication between skin cell & trigeminal ganglia - Keratinocyte proliferation - Keratinocyte migration - Wound healing - Cell cycle arrest - Apoptosis - Hair growth | HaCaT Primary keratinocyte Basal melanocyte Hair follicle | Ca²⁺ signal cAMP pathway Erk1/2 & p38 MAPK phosphorylation | 16-18 |
| OR2A4/ OR2A7 | Cyclohexyl salicylate | - Melanogenesis - Melanocyte growth inhibition - Cytokinesis | HaCaT HEK293 Primary keratinocyte | Ca²⁺ signal cAMP pathway p38/p42/p44 MAPK AKT & CHK-2 phosphorylation | 16, 29 |
| OR51B5 | Isononyl alcohol | - Migration & regeneration - Cytokine (IL-6) release - Wound healing | Keratinocyte HaCaT HEK293 | CNG, cAMP pathway Hsp 27, AMPK1, p38 MAPK phosphorylation | 16 |
| OR10G7 | Acetophenone, Eugenol | - Associated with atopic dermatitis - Inflammatory response (IL-1β) | Primary human keratinocyte | cAMP pathway | 19 |
| OR51E2 | Beta-ionone, Androstenone, Propionate, Acetate | - Proliferation - Melanogenesis - Dendritogenesis - Apoptosis - Renin secretion | Primary melanocyte Melanoma | Ca²⁺ signal cAMP pathway p38 MAPK phosphorylation JNK/SAPK | 20-23 |

CNG: cyclic nucleotide-gate, IL: interleukin, cAMP: cyclic adenosine monophosphate, -: not available.
was shown to promote hair growth ex vivo in the human hair follicle. Human hair follicle epithelium, especially the outer root sheath, expresses OR2AT4, which induces hair growth via decreased apoptosis, increased growth factor expression, and delayed cell cycle when stimulated by sandalore or brahanol. Catagen development was retarded, along with prolonged anagen, in hair follicles ex vivo. Additionally, apoptosis was extremely decreased in hair matrix keratinocytes. In terms of molecular effects, OR2AT4 induced upregulation of PI3K, AKT, and NF-κB levels, along with downregulation of p53, a pro-apoptotic protein. CHS also initiates OR2A4 signaling, promoting cytokinesis, increasing interleukin (IL)-1 secretion, inducing phosphorylation of AKT and Chk-2, and promoting keratinocyte proliferation. While sandalore tends to sensitize the Ca²⁺ influx, desensitization induced by CHS is detected in HaCaT cells. Both CHS and INA activated the cAMP pathway. These pathways are shown in Fig. 3.

**OR2A4/OR2A7 IN SKIN PHYSIOLOGY**

OR2A4/7 is expressed in primary keratinocytes, HaCaT cells, and HEK293 cells. The specific odorant of OR2A4/7 is CHS. OR2A4/7 activated by CHS induces strong calcium ion signaling through the cAMP-dependent pathway. This might impact the activity of MAPKs, resulting in induced p38 MAPK

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**Fig. 2.** OR2AT4-mediated signaling pathway in keratinocytes. cAMP: cyclic adenosine monophosphate, ATP: adenosine triphosphate.

**Fig. 3.** OR2AT4-mediated signaling pathway in hair follicle. IL: interleukin.
phosphorylation, reduced p42 MAPK (MAPK1), and phosphorylated p44 MAPK (MAPK3). Moreover, this signaling is associated with increased melanogenesis accompanied by melanocyte growth inhibition\(^2\). Along with OR2A4, OR2A7 provokes cytokinesis and cell proliferation mediated by phosphorylation of AKT and CHK-2. Increased IL-1 secretion is also detected\(^2\).

**OR51B5 IN SKIN PHYSIOLOGY**

The odorant of OR51B5 is INA. OR51B5 is mainly expressed in suprabasal keratinocytes\(^2\). When activated, OR51B5 increases migration and regeneration in primary keratinocytes, HaCaT cells, and HEK293 cell. When activated by INA, OR51B5 increases migration and regeneration and produces cytokines. INA signaling strongly increases IL-2, IL-5, IL-6, and IL-13 in HaCaT cells, and IL-6 and IL-12 in primary keratinocytes.

Starting from CNG, via the cAMP pathway, OR51B5 phosphorylates Hsp27, AMPK1, and p38-MAPK. Although both OR2A4/7 and OR51B5 were suggested to be involved in the wound-healing process, OR51B5 has more pronounced effects on wound healing, according to *in vitro* and *in vivo* scratch assays\(^2\). In addition, both OR2A4/7 and OR51B5 increased expression of cytokines such as IL-2, IL-6, and IL-13, but OR51B5 promoted a stronger increase. When it comes to kinase regulation, both OR2A4/7 and OR51B5 caused Hsp60 upregulation; however, OR2A4/7 and OR51B5 seem to control phosphorylation of kinases in different directions, via different targets, and OR51B5 showed a relatively stronger effect than OR2A4/7.

**OR10G7 IN SKIN PHYSIOLOGY**

The human *OR10G7* gene is located on chromosome number 11 and the OR10G7 protein is highly expressed on the skin upper granular layer. The odorants of this receptor are acetophenone and eugenol. A recent study showed that OR10G7 is associated with atopic dermatitis (AD)\(^2\). According to the study, mRNA expression of the *OR10G7* gene was increased in primary human keratinocytes of AD patients. ATP level was increased when ORs were activated by acetophenone and eugenol. These results were further confirmed by experiments using OR10G7 small-interfering RNA that showed that the increase of ATP depends on the activation of OR10G7. In addition, CAMP production was increased in response to OR10G7, indicating an activation of the OR10G7-mediated cAMP pathway. OR10G7 might also trigger an inflammatory response, as the expression of IL-1β increased in odorant-treated keratinocytes. Therefore, OR10G7 in AD skin might induce ATP-dependent and inflammatory responses, worsening the symptoms of AD\(^2\).

**OR51E2 IN SKIN PHYSIOLOGY**

The odorants of OR51E2 are β-ionone, androstenone, and propionate, and the antagonist is α-ionone. OR51E2 is expressed in primary human melanocytes. OR51E2 signaling inhibits proliferation, enhances melanogenesis, and induces dendritogenesis of primary melanocytes. In response to OR51E2, melanocyte cell proliferation decreases, while differentiation and melanin content increases\(^2\). In melanocytes, OR51E2 increases Ca\(^{2+}\) concentration intracellularly and extracellularly, phosphorylating p38 and MAPK. In research on melanoma cells, β-ionone showed no effect on cell migration, while cell migration increased upon downregulation of lysophosphatidic acid-induced migration. Signals induced by β-ionone were reported to inhibit the proliferation and migration of primary melanoma in the vertical growth phase (VGP) via the apoptotic process. The anti-proliferative and pro-apoptotic effects of OR51E2 in melanoma suggest the therapeutic possibility for the use of OR51E2 against melanoma.

OR51E2 is also highly expressed in lung-resident cells. OR51E2 is activated by propionate, a kind of short-chain fatty acid (SCFA), as ligand, and OR51E2 activation alleviates airway obstruction by inhibiting human airway smooth muscle cell proliferation\(^2\). Moreover, OR51E2 can be activated by acetate, another SCFA, and this activation can upregulate renin secretion\(^2\). A previous study found that OR51E2 is specifically expressed in prostate tissue, especially in epithelial cells of the prostate gland. OR51E2 also exhibited overexpression in prostate tumors compared with normal prostate tissues. Therefore, OR51E2 may be a biomarker of prostate cancer and also complementary with α-methylacyl-CoA racemase, which is used to diagnose prostate cancer\(^2\). OR51E2 activation stimulated protein tyrosine kinase Pyk2 and tumor suppressor protein N-myc downstream-regulated gene 1 (NDRG1) (Pyk2-NDRG1 axis). OR51E2 also inhibited prostate cancer cell proliferation.
by upregulating phosphorylation of p38-MAPK and JNK/SAPK. In this case, OR51E2 was activated by ketone, especially androstenone. Stimulation decreased cell proliferation, and β-ionone inhibited cell proliferation. These pathways are shown in Fig. 4.

**THERAPEUTIC POTENTIAL OF OLFATORY RECEPTORS**

Several studies have suggested the possibility that odorants might have potential medical applications. Various odorant phytochemicals were found to have pharmacological activities. These effects may be attributed to activation of ectopic ORs. As described above, ectopic ORs in the skin have been shown to mediate wound healing and hair growth. Moreover, some ORs are also associated with various diseases such as AD, skin pigmentation disease, and even cancer.

OR2AT4, OR2A4/OR2A7, and OR51B5 expressed in keratinocytes promote wound-healing. Sandalore-activated OR2AT4 enhanced wound healing in keratinocytes by promoting proliferation and migration. In another study, OR51B5 and OR2A4/7 were shown to increase migration and regeneration in primary keratinocytes, HaCaT cells, and HEK293 cells. These effects were also confirmed through in vivo scratch assays. Furthermore, OR2AT4 has been shown to be effective in hair growth regulation. Sandalore- or brahmanol-activated OR2AT4 retarded catagen development of hair follicles and decreased apoptosis in hair matrix keratinocytes. It also maintained the anagen state of hair follicles through increased insulin-like growth factor-1 production. According to a hair pull test in a preliminary pilot clinical trial, applying a lotion containing sandalore for 12 weeks reduced hair loss by approximately 20% compared with a control group. These results suggest the potential of ORs as novel targets for hair growth regulation.

OR10G7 was recently suggested to be a novel target of AD. The receptor was highly expressed in AD patient keratinocytes compared with the control group. Induced activation of OR10G7 by odorants provokes an ATP-dependent response and allergic inflammatory response. Although the specific mechanism of OR10G7 in skin disease should be studied in further research, OR10G7 seems to be a reasonable target for treating AD.

In melanocytes, OR51E2 activated by β-ionone increased melanogenesis and dendritogenesis levels. Additionally, OR2A4/OR2A7 activated by CHS increased melanin synthesis and induced melanocyte growth inhibition. Together, these discoveries indicate that ORs have the potential to be used for treating pigmentation disorders by regulating melanogenesis.

Intriguingly, several types of cancer cells show upregulated OR expression, such as melanoma cells. OR51E2 activation in primary melanoma cells inhibited cell proliferation and migration, also inducing apoptosis. Furthermore, both acute and chronic myelogenous leukemia proliferation was reduced by the cAMP-dependent pathway of sandalore-activated OR2AT4, which also increased apoptosis. In the leukemia cell line K562, OR2AT4 induced cell cycle arrest in G0/1 and G2/M phases. From these results, ORs might be considered novel candidates for treating severe diseases such as cancer. However, while OR51E2 has been verified as a prostate tumor antigen and targeted for immunotherapy, there is still a lack of research on targeting or applying ORs expressed in skin tissue to other diseases. Therefore, the physiological role of ORs and their therapeutic effects should be further investigated.

**CONCLUSIONS**

There are some limitations to studying OR physiology in skin tissue. First, the rate of expression of OR transcripts is low. Second, due to the similarities among ORs, few antibodies...
with sufficient specificity are available. Therefore, studying ORs at the protein level is challenging. Finally, few ligands have been identified\(^1\). To examine ORs, especially in vitro, most experiments depend on ligand-induced activation of ORs. Therefore, the lack of knowledge of the ligands of ORs is an obstacle that needs to be overcome in future research.

ORs expressed in skin cells or skin tissues are involved in various skin diseases, including AD, pigmentation disorders, and even melanoma. Recent reports have shown that these functions in skin diseases result from ORs critical role in skin physiology. The observations that ORs, which were initially identified as membrane proteins in olfactory organs, are deeply involved in skin physiology suggest the possibility that ORs may be important molecular targets for improving skin diseases and skin impairments.

**CONFLICTS OF INTEREST**

The authors have nothing to disclose.

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