Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 82

This document contains 1 pathway and 4 reactions (see Table of Contents)

https://reactome.org
Expression and translocation of olfactory receptors

Stable identifier: R-HSA-9752946

Olfactory receptors (ORs) are 7-pass transmembrane G protein-coupled receptors (GPCRs) located on dendritic cilia of olfactory sensory neurons (OSNs) of the olfactory epithelium (reviewed in Persuy et al. 2015). ORs are also located on cells of some other tissues (reviewed in Oh 2015). ORs bind ligands, called odorants, and activate downstream signaling through a heterotrimeric G-protein leading to opening of olfactory cyclic nucleotide-gated channels (CNG channels) and depolarization of the OSN. The human genome contains about 857 OR genes of which about 394 appear to be capable of encoding a functional OR. The remaining putative OR genes appear to be pseudogenes functionally inactivated by mutations.

Each OR binds a particular odorant or family of odorants. In order to provide odor discrimination, each OSN expresses only one OR gene and connects to specific olfactory bulb glomeruli according to the specific OR expressed (reviewed in Monahan and Lomvardas 2015, McClintock et al. 2020, Sakano et al. 2020). The choice of which OR gene to express is made by an epigenetic mechanism (reviewed in Bashkirova and Lomvardas 2019). Initially during OSN development, OR genes are heterochromatic. A few OR genes become weakly expressed and one then becomes dominant while all other OR genes remain silenced by heterochromatin. During activation of an OR gene, LHX2, LDB1, and EBF1 bind several (~60) intergenic enhancers located between OR genes on 18 chromosomes. The LHX2:LDB1:EBF1:enhancer complexes assemble into an interchromosomal super-enhancer that associates with the expressed OR gene and drives transcription.

Accumulation of OR protein in the endoplasmic reticulum membrane activates the unfolded protein response (UPR) that activates translation of ADCY3, which downregulates the histone methyltransferase KDM1A (LSD1) thereby preventing activation of any other OR genes (Lyons et al. 2013, Dalton et al. 2013).

Most OR proteins are inefficiently translocated from the endoplasmic reticulum membrane to the plasma membrane when they are expressed in heterologous cells. OSNs contain specific proteins that act...
as chaperones to increase subcellular translocation of at least some ORs (reviewed in Mainland and Matsunami 2012). The short isoform of RTP1 (RTP1S) and RTP2 bind the OR in the endoplasmic reticulum, are translocated with the OR to the plasma membrane, and remain at the plasma membrane. REEP1 more weakly increases translocation of ORs by an uncharacterized mechanism.

**Literature references**


**Editions**

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LHX2, LDB1, and EBF1 bind Olfactory Receptor gene and intergenic olfactory enhancers

**Location:** Expression and translocation of olfactory receptors

**Stable identifier:** R-HSA-9752951

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Lhx2, Ldb1, and Eb1 bind Olfactory Receptor gene and intergenic olfactory enhancers (Mus musculus)

Transcription factors LHX2 and EBF1 and scaffold protein LDB1 bind enhancers located between olfactory receptor (OR) genes (inferred from mouse homologs). OR genes are initially heterochromatic during development of the olfactory sensory neuron (OSN) lineage (McClintock et al. 2020). A few OR genes become weakly active and then one of these genes becomes highly active while all other OR genes are repressed by heterochromatin. In this way each OSN expresses only one OR gene. The single expressed OR gene is activated by a suprachromosomal cluster of intergenic olfactory enhancers located on the same chromosome and on other chromosomes (inferred from mouse homologs). Three dimension analysis of chromatin indicates 8-12 intergenic enhancers are sufficient to activate an OR gene (inferred from mouse homologs). Each intergenic olfactory enhancer is bound by the transcription factors LHX2 and EBF1 and by the scaffold protein LDB1, which may mediate enhancer-enhancer interactions (inferred from mouse homologs). As the expressed OR protein accumulates in the endoplasmic reticulum membrane, it activates the unfolded protein response, which increases translation of ADCY3 that then downregulates KDM1A (LSD) histone methyltransferase. The downregulation of KDM1A prevents any other OR genes from becoming active.

**Followed by:** Expression of Olfactory Receptor

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An olfactory receptor (OR) gene is transcribed to yield mRNA and the mRNA is translated to yield OR protein initially located in the endoplasmic reticulum membrane and then translocated through the Golgi to the plasma membrane (Durante et al. 2020, Olender et al. 2016, and inferred from mouse homologs). Humans contain 857 possible OR genes, however the number of human OR genes that are expressed and functional is the subject of current research. Durante et al. (2020) found 143 ORs expressed in olfactory neurons by single cell sequencing. Olender et al. (2016) found 346 intact human OR genes were expressed in at least 1 of 14 individuals. (About 61% of 466 OR pseudogenes also showed some expression.) Verbeurgt et al. (2014) found 273 OR genes were expressed above 5 copies per ng RNA in at least 1 of 26 individuals. Each mature olfactory sensory neuron expresses only one olfactory receptor (OR) (inferred from mouse homologs). LHX2, LDB1, and EBF1 bind intergenic olfactory enhancers and activate transcription (inferred from mouse homologs). Deletion of LHX2 causes loss of OR expression (inferred from mouse homologs). Heterochromatic silencing governed by EHMT2 (KMT1C, G9a) and EHMT1 (KMT1D, GLP) is required for singular receptor expression and produces a diversity of OR gene expression (inferred from mouse homologs). Olfactory enhancers interact interchromosomally to activate transcription of an OR gene (inferred from mouse homologs).

**Preceded by:** LHX2, LDB1, and EBF1 bind Olfactory Receptor gene and intergenic olfactory enhancers

**Followed by:** RTP1S and RTP2 bind underrepresented Olfactory Receptors (uORs)

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RTP1S and RTP2 bind underrepresented Olfactory Receptors (uORs)

**Location:** Expression and translocation of olfactory receptors

**Stable identifier:** R-HSA-9752977

**Type:** binding

**Compartments:** endoplasmic reticulum membrane

**Inferred from:** Rtp1s and Rtp2 bind underrepresented Olfactory Receptor (Mus musculus)

The chaperone-like proteins RTP1S (the short isoform of RTP1) and RTP2 bind olfactory receptor (OR) proteins in the endoplasmic reticulum membrane (inferred from mouse homologs). In the absence of RTPs, most ORs are inefficiently translocated to the plasma membrane and accumulate in the Golgi and endoplasmic reticulum (inferred from mouse homologs). Some ORs are, however, translocated efficiently. Efficiently translocated ORs are called overrepresented ORs; inefficiently translocated ORs are called underrepresented ORs (inferred from mouse homologs). RTP2 inhibits translocation of some ORs (inferred from mouse homologs). The mechanism by which RTP1S and RTP2 facilitate translocation of ORs to the plasma membrane is not yet known.

**Preceded by:** Expression of Olfactory Receptor

**Followed by:** RTP1S:RTP2:underrepresented Olfactory Receptor translocates from the endoplasmic reticulum membrane to the plasma membrane

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Some olfactory receptors (ORs), designated underrepresented ORs, are bound to RTP1S (the short isoform of RTP1) and RTP2 and translocate from the endoplasmic reticulum membrane through the Golgi to the plasma membrane (Ikegami et al. 2020, and inferred from mouse homologs). RTP1S and RTP2 increase the efficiency of the translocation by an uncharacterized mechanism (inferred from mouse homologs) though RTP2 decreases translocation of some ORs (inferred from mouse homologs). Some ORs, designated overrepresented ORs, are translocated efficiently without RTP1S or RTP2 (inferred from mouse homologs). REEP1 more weakly enhances translocation (inferred from mouse homologs).

**Preceded by:** RTP1S and RTP2 bind underrepresented Olfactory Receptors (uORs)

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