Olfactory Signaling Pathway

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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


Mammalian Olfactory Receptor (OR) genes were discovered in rats by Linda Buck and Richard Axel, who predicted that odorants would be detected by a large family of G protein-coupled receptors (GPCRs) that are selectively expressed in the olfactory epithelium. This prediction was based on previous biochemical evidence that cAMP levels increased in olfactory neurons upon odor stimulation. These predictions proved to be true, and Buck and Axel received a Nobel Prize for this and subsequent work (reviewed in Keller & Vosshall 2008).

Subsequent work in mice and other vertebrates has confirmed that OR genes are comprised of a very large family of G Protein-Coupled Receptors (GPCRs) that are selectively expressed in olfactory epithelium. Although some OR are also expressed selectively in one or a few other tissues, their expression in olfactory epithelium generally indicates a functional role in mediating olfaction, where they couple binding by odorant ligands with intracellular olfactory signaling. (Note: the other subclasses of GPCR signaling pathways are described under "GPCR Signaling").

The ligands for ORs are diverse, ranging from chemical compounds to peptides. Intracellular signaling by OR proteins in mice and other mammalian systems is known to be mediated via direct interactions of OR proteins with an olfactory specific heterotrimeric G Protein, that contains an olfactory-specific G alpha protein: G alpha S OLPH (also named "GNAL").

There are two models for GPCR-G Protein interactions: 1) ligand-GPCR binding first, then binding to G Proteins; 2) "Pre-coupling" of GPCRs and G Proteins before ligand binding (Oldham & Hamm 2008). Both models may be true for certain GPCRs in different contexts. Pre-coupling is likely to be functionally important, as pre-coupling of receptor and G Protein allows much more rapid kinetic response once ligand is bound, because the ligand-bound receptor is immediately able to transduce the signal, rather than having to diffuse around within the plasma membrane until it encounters a G Protein to interact with (Oldham & Hamm 2008).

The pre-coupling model is used here to characterise the reaction of the human ORs with G Proteins in the absence of ligand, because the ligands in humans are almost completely undocumented experimentally.
In model genetic systems such as mice, many candidate OR genes have been shown experimentally to function in olfactory signaling (reviewed in Keller & Vosshall 2008). For the human OR genes, experimental analysis has been much more limited, although some specific OR genes, such as OR7D4 and OR11H7P have been confirmed to mediate olfactory response and signaling in humans for specific chemical odorants (Keller et al. 2007, Abbafy 2007). Mice and other rodents are believed to have about 1000 functional OR genes, as well as many additional pseudogenes. Based on sequence similarities, there are 960 human OR genes, but approximately half of these are pseudogenes (Keller 2008). In mice, essentially all olfactory signaling requires G-alpha-S (OLF); mouse G-OLF knockouts have been shown to lack olfactory responses (Belluscio 1998). Bona fide human OR genes identified by sequence similarity (not pseudogenes with function-blocking mutations) that are expressed in olfactory epithelium are expected to interact with G alpha S OLF containing G Protein trimers.

Of the 960 human OR genes and pseudogenes, there is experimental evidence that indicates over 430 are expressed in human olfactory epithelium, including 80 expressed OR pseudogenes (Zhang 2007).

When expressed in model cell systems mammalian odorant receptors (OR) are typically retained in the ER and degraded by the proteasome (McClintock et al. 1997). A study using Caenorhabditis elegans showed that the transport of ORs to the cilia of olfactory neurons required the expression and association of ORs with a transmembrane protein, ODR4 (Dwyer et al. 1998). Co-transfection of rat ORs with ODR4 enhanced the transport and expression of ORs at the cell-surface (Gimelbrant et al. 2001). These studies suggested that olfactory neurons might have a selective molecular machinery that promotes expression of ORs at the cells surface. Two human protein families have been identified as potential accessory proteins involved in the trafficking of ORs to the plasma membrane (Saito et al. 2004). Receptor transporting proteins 1 and 2 (RTP1, RTP2) both strongly induced expression of several ORs at the cell-surface. To a lesser extent, the receptor expression enhancing protein 1 (REEP1) also promoted cell-surface expression. These proteins are specifically expressed in olfactory neurons with no expression in testis, where a subset of ORs are expressed (Parmentier et al. 1992, Spehr et al. 2003). Other members of the RTP and REEP families have a widespread distribution. RTP3 and RTP4 have been shown to promote cell-surface expression of the bitter taste receptors, TAS2Rs (Behrens et al. 2006). REEP1 and REEP5 (also known as DP1) are involved in shaping the ER by linking microtubule fibers to the ER (Park et al. 2010, Voeltz et al. 2006). A recent study looking at the role of REEP in the trafficking of Alpha2A- and Alpha2C-adrenergic receptors showed that REEP1-2 and 6 enhance the cell-surface expression of Alpha2C, but not Alpha2A, by increasing the capacity of ER cargo, thereby allowing more receptors to reach the cell-surface (Bjork et al. 2013). Unlike RTP1, REEP1-2 and 6 are only present in the ER, do not traffic to the plasma membrane and specifically interact with the minimal/non-glycosylated forms of Alpha2C via an interaction with its C-terminus (Saito et al. 2004, Bjork et al. 2013). REEPs may function as general modulators of the ER, rather than specifically interacting with GPCRs. Loss of association of REEP2 with membranes leads to hereditary spastic paraplegia (Esteves et al. 2014).

**Literature references**


https://www.reactome.org
G Protein trimer formation (olfactory)

Location: Olfactory Signaling Pathway

Stable identifier: R-HSA-381749

Type: binding

Compartments: plasma membrane