

# Olfactory receptors in neural regeneration in the central nervous system

Rafael Franco<sup>1,2,3,\*</sup>, Claudia Garrigós<sup>1</sup>, Toni Capó<sup>4</sup>, Joan Serrano-Marín<sup>1</sup>, Rafael Rivas-Santisteban<sup>2,5,\*</sup>, Jaume Lillo<sup>1,2</sup>

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## Abstract

Olfactory receptors are crucial for detecting odors and play a vital role in our sense of smell, influencing behaviors from food choices to emotional memories. These receptors also contribute to our perception of flavor and have potential applications in medical diagnostics and environmental monitoring. The ability of the olfactory system to regenerate its sensory neurons provides a unique model to study neural regeneration, a phenomenon largely absent in the central nervous system. Insights gained from how olfactory neurons continuously replace themselves and reestablish functional connections can provide strategies to promote similar regenerative processes in the central nervous system, where damage often results in permanent deficits. Understanding the molecular and cellular mechanisms underpinning olfactory neuron regeneration could pave the way for developing therapeutic approaches to treat spinal cord injuries and neurodegenerative diseases like Alzheimer's disease. Olfactory receptors are found in almost any cell of every organ/tissue of the mammalian body. This ectopic expression provides insights into the chemical structures that can activate olfactory receptors. In addition to odors, olfactory receptors in ectopic expression may respond to endogenous compounds and molecules produced by mucosal colonizing microbiota. The analysis of the function of olfactory receptors in ectopic expression provides valuable information on the signaling pathway engaged upon receptor activation and the receptor's role in proliferation and cell differentiation mechanisms. This review explores the ectopic expression of olfactory receptors and the role they may play in neural regeneration within the central nervous system, with particular attention to compounds that can activate these receptors to initiate regenerative processes. Evidence suggests that olfactory receptors could serve as potential therapeutic targets for enhancing neural repair and recovery following central nervous system injuries.

**Key Words:** adenosine receptors; adrenergic receptors; ectopic expression; G protein-coupled receptors; glia; neurons

## Introduction

Ectopic expression of olfactory receptors represents a fascinating frontier in sensory biology and biomedicine, revealing complexities that transcend the traditional boundaries of olfactory science. Olfactory receptors, which belong to the largest family of proteins in the mammalian genome, the G protein-coupled receptors (GPCRs), are traditionally recognized for their role in detecting volatile compounds in the olfactory epithelium (Spehr and Munger, 2009). However, more recent discoveries have illuminated their presence and functional implications in numerous non-olfactory tissues, including the brain, skin, heart, and even tumors (Oh, 2018). This emergent paradigm of ectopic olfactory receptor (OR) expression not only challenges our conventional understanding of sensory and physiological processes but also opens new avenues for therapeutic interventions and diagnostic tools.

There has been much debate about the nomenclature "ectopic olfactory receptors" because "ectopic" is a medical term used to define events occurring in the wrong place, i.e., it is used for diseases in which an event takes place in the wrong organ/tissue. Di Pizio et al. (2019) proposed a few years ago the term "ecnomotopic," which means occurring in an unusual place. At present, this word is not used and, therefore, we will refer to odorant receptors that are in places that do not participate in smell perception as "ectopically expressed olfactory receptors" or "olfactory receptors in ectopic expression."

The significance of ectopic OR expression is underscored by the diverse roles these receptors play in various biological processes beyond olfaction, such as metabolism regulation, cell proliferation, and chemotaxis (Weber et al., 2018). Moreover, the ability of ORs to respond to a wide array of chemical ligands

<sup>1</sup>Molecular Neurobiology Laboratory, Department of Biochemistry and Molecular Biomedicine, Facultat de Biologia, Universitat de Barcelona, Barcelona, Spain; <sup>2</sup>CiberNed Network Center for Biomedical Research in Neurodegenerative Diseases, Spanish National Health Institute Carlos III, Madrid, Spain; <sup>3</sup>School of Chemistry, Universitat de Barcelona, Barcelona, Spain; <sup>4</sup>Department of Biochemistry and Physiology, School of Pharmacy and Food Sciences, Universitat de Barcelona, Barcelona, Spain; <sup>5</sup>Laboratory of Computational Medicine, Biostatistics Unit, Faculty of Medicine, Autonomous University of Barcelona, Campus Bellaterra, Barcelona, Spain

\*Correspondence to: Rafael Rivas-Santisteban, PhD, [rrivasbioq@gmail.com](mailto:rrivasbioq@gmail.com); Rafael Franco, PhD, [rfranco@ub.edu](mailto:rfranco@ub.edu) or [rfranco123@gmail.com](mailto:rfranco123@gmail.com).  
<https://orcid.org/0000-0002-2078-6819> (Rafael Rivas-Santisteban); <https://orcid.org/0000-0003-2549-4919> (Rafael Franco)

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can potentially be harnessed for bioengineering applications, including the development of novel biosensors and targeted therapies. This paper aims to provide a comprehensive overview of the mechanisms of ectopic expression of olfactory receptors, the biological and clinical relevance of these phenomena, and the potential for leveraging these receptors in medical and technological applications. By integrating insights from molecular biology, genetics, and clinical research, this review seeks to elucidate the multifaceted roles of ectopically expressed ORs and pave the way for future research in this intriguing domain.

From receptors for neurotransmitters such as serotonin (Chaumont-Dubel et al., 2020; Guo et al., 2023) to receptors for neuromodulators such as melatonin (Feng et al., 2023), GPCRs represent a critical link between extracellular signals and neurogenic processes, mediating complex intracellular cascades that govern the birth, phenotypical differentiation and integration of neurons in the brain (Doze and Perez, 2012; Mak et al., 2024). Further research into GPCR signaling pathways, their interaction with other cellular mechanisms during neurogenesis, and their modulation by pharmacological agents hold significant promise for understanding brain function and treating a plethora of neurological diseases. This burgeoning field continues to offer fascinating insights into the intersection of neurobiology, pharmacology, and molecular genetics, holding substantial potential for future therapeutic innovations.

During embryonic development, GPCRs regulate the proliferation, differentiation, and migration of neural progenitor cells. Specific GPCRs, including those binding to neurotransmitters like serotonin and dopamine, influence the patterning and structural organization of the developing brain (Leung and Wong, 2017). For instance, serotonin and dopamine receptors are known to impact neural progenitor cell proliferation and differentiation. These processes are tightly controlled by GPCR-mediated signaling, often involving the variation of the levels of second messengers such as cyclic AMP (cAMP) and calcium that in turn modulate gene expression and cellular behavior (Sassone-Corsi, 2012; El-Atawneh and Goldblum, 2023).

In the adult brain, neurogenesis is largely confined to specific regions, notably the hippocampus and the subventricular zone. GPCRs continue to play a vital role in this context by influencing the behavior of adult neural stem cells. Chemokine receptors like CXCR4 and cannabinoid receptors are examples of GPCRs that impact the survival and differentiation of progenitor cells in the adult brain (Bianchi and Mezzapelle, 2020). Their activity can affect not only physiological brain functions but also responses to brain injury and neurodegenerative diseases. For example, modulation of the endocannabinoid system through CB<sub>1</sub> receptors has shown promise in enhancing neurogenic responses in models of Alzheimer's disease (Manuel et al., 2014). There is evidence that olfactory receptors may be key in neuroregeneration, but the main issue relates to finding the molecules that, apart from odorants, can modulate their functionality either as agonists or as antagonists. For example, data resulting from measuring the activity of the CB<sub>1</sub> receptor measured in post-mortem hippocampal samples from Alzheimer's disease patients suggest that the endocannabinoid system initially becomes hyperactive in brain areas that do not yet exhibit classical histopathological markers, possibly to compensate for early synaptic damage disease (Manuel et al., 2014). These findings suggest that early stimulation of the CB<sub>1</sub> receptor could have therapeutic benefits in this neurodegenerative disease. Gene expression analysis in microglia suggests that olfactory receptors could play a crucial

role in the pathophysiology of neurodegeneration (Franco et al., 2024). However, the primary challenge lies in identifying molecules other than odorants that can modulate olfactory receptor functionality, acting either as agonists or antagonists.

Alterations in GPCR signaling are implicated in various neurodevelopmental and neurodegenerative conditions. Dysregulation of GPCR-mediated pathways can lead to abnormalities in neuron development and maturation, which may contribute to the pathology of disorders such as schizophrenia, autism, and Parkinson's disease (DelaCuesta-Barrutia et al., 2020; Boczek et al., 2021). Understanding how GPCRs influence neurogenesis under pathological conditions can reveal potential therapeutic strategies to modulate neural plasticity and recovery.

This paper reviews evidence supporting olfactory receptor involvement in neuroregeneration. This attractive possibility arises from two well-known facts: (i) neurons of the mammalian olfactory system can regenerate all along the life of the organism (Schwob, 2002) and (ii) some of the hundreds of olfactory receptors are ectopically expressed in almost any tissue/organ (Lee et al., 2019). Some olfactory receptors are expressed in the non-chemosensory regions of the central nervous system (CNS). Brain regions that express olfactory receptors include the dentate gyrus, in which there are more chances to find cells primed for neural regeneration (Whitman and Greer, 2009; Botterill et al., 2021).

## Search Strategy

The search strategy aimed to capture a broad spectrum of relevant studies, from molecular and cellular mechanisms to potential therapeutic applications of olfactory receptors in CNS injuries and neurodegenerative diseases. The databases searched included PubMed, Scopus, and Google Scholar. The search on PubMed, conducted via the NCBI platform between January and April of 2024, utilized search terms such as "olfactory receptors" AND "neural regeneration," OR "olfactory receptors" AND "ectopic expression," OR "olfactory receptors" AND "CNS repair," OR "olfactory receptors" AND "spinal cord injury," OR "olfactory receptors" AND "neurodegenerative diseases." Similarly, the search on Scopus and Google Scholar, performed in the same timeframe, included equivalent search queries. To ensure we captured the most recent advancements and the state of the art, an exhaustive analysis was done on papers published after 2020.

## Description of Olfactory Receptors

Despite our considerable comprehension of sensory pathways such as vision and tactile perception, our understanding of olfaction remains restricted. The transmission of olfactory information encompasses the conversion of a molecular signal into a neural signal, ultimately culminating in a perceptual indication of scent. This process commences when odorants bind to olfactory receptors situated in neurons responsible for olfactory sensing within the olfactory bulb. Subsequently, the signal of excitation from these neurons travels to the brain, where the information is assimilated, eventually prompting a specific perception of smell. However, each phase of this complex process introduces an additional layer of complexity (Pourmorady and Lomvardas, 2022).

It is assumed that each sensing neuron exclusively expresses a sole olfactory receptor, yet each olfactory receptor possesses the capability to bind to a wide array of odorants. Conversely, odorant molecules can bind to distinct olfactory receptors. Consequently, the perception of scent arises from the combined activity of numerous olfactory receptors, triggered by the binding

of individual odorant molecules to various receptors (Niimura, 2012; Rufenacht et al., 2024).

### G protein-coupled receptors: structure and function

Mammalian olfactory receptors belong to the superfamily of GPCRs. GPCRs stand as the largest cluster of transmembrane proteins encoded in the human genome (Alexander et al., 2023). Due to their expression on the surface of cells across various tissues, GPCRs serve as key players in cell signaling and overall homeostasis. About 500 of all drugs approved by the U.S. Food and Drug Administration target these receptors (Hauser et al., 2017).

The structure of GPCRs consists of an extracellularly oriented N-terminal domain, an intracellularly oriented C-terminal domain, and seven transmembrane segments (TM1–TM7) connected by three intracellular and three extracellular loops. In most cases, an additional amphipathic helix 8 appears after TM7, near the beginning of the C-terminal region (Kooistra et al., 2021).

The original taxonomy, established in 1994, organized GPCRs into classes A to F, with the absence of classes D and E in vertebrates. However, a more contemporary classification framework was suggested, GRAFS, which results from Glutamate, Rhodopsin, Adhesion, Frizzled/Taste, and Secretin (Fredriksson et al., 2003; Kotliar et al., 2023). The website of the International Union of Basic and Clinical Pharmacology (IUPHAR) provides in 2024 the following classification for GPCRs: class A, class B, class C, opsin receptors, taste 1 receptors, taste 2 receptors, and “other 7TM proteins.” About half of Class A receptors are expressed in the nose and detect odors, thus being known as odorant or olfactory receptors (Fredriksson et al., 2003).

GPCRs respond to a variety of chemical structures, whether they are exogenous, such as approximately one trillion olfactory molecules (Bushdid et al., 2014), or endogenous (Dagan-Wiener et al., 2019), ranging from ions and small molecules like glutamate to peptides like opioids and even proteins such as chemokines or glycoprotein hormones (Hauser et al., 2017). Thus, the main function of GPCRs is to sense the huge variety of molecules that impact cells in the different tissues and organs. Binding of molecules to GPCRs results in signal transduction and *ad hoc* cell responses.

### Mechanism of action of olfactory receptors

Various cell types reside in the olfactory epithelium (Bolz et al., 2017; Schmidt and Benton, 2020). The olfactory epithelium exhibits a pseudostratified structure with the apical layer containing the cell bodies of glial-like sustentacular cells, the middle layer housing the cell bodies of olfactory sensory neurons, which are responsible for detecting odors, and the basal layer accommodating stem cells that are crucial for neural regeneration (Hayoz et al., 2024).

Olfaction is an encoding-decoding process that detects and discriminates multiple volatile odorants (Baroody et al., 2009; Wang et al., 2024). Humans discern odorants because of their binding to olfactory receptors found on the plasma membrane of olfactory sensory neurons. Olfactory receptors and odorants are both promiscuous. Each olfactory receptor can be activated by different odorants and a single odorant can activate various olfactory receptors (Wu et al., 2024).

The olfactory sensory neurons send signals to glomeruli in the olfactory bulb which then passes the information to dendrites (Pinto, 2011). The axons of the olfactory sensory neurons conduct the signal into the olfactory cortex for the integration of the sense of smell. The olfactory cortex is linked with the amygdala

and the hippocampus, a component of the limbic system; these connections make it possible to establish relationships between olfaction and memories (Plotsky et al., 2005).

The propagation of the odorant signal is said to occur primarily through the activation of  $G_{olf}$  proteins coupled to olfactory receptors. Activation of  $G_{olf}$  leads to an increase in the intracellular levels of cAMP which in turn activates the cyclic nucleotide-gated channel, a nonselective cation channel, and initiates the influx of calcium and sodium ions. Consequently, calcium stimulates chloride efflux and, overall, the olfactory sensory neuron depolarizes (Leopold et al., 2000; Xu and Pluznick, 2022).

During the coronavirus disease 2019 (COVID) pandemic, discussions surrounding the loss of smell in various illnesses have persisted for a considerable time. It was suggested that SARS-CoV-2 infection disrupted the signal transmission within the olfactory system. Bryce et al. (2020) reported that two days after nasal instillation with SARS-CoV-2, a disruption of the olfactory epithelium of golden Syrian hamster takes place, thus, providing a possible explanation for the anosmia occurring in some COVID-19 patients. Extensive research in neurodegenerative diseases like Parkinson’s disease (He et al., 2020), and Alzheimer’s disease (Steffener et al., 2021), shows that some patients exhibit olfactory impairments even at prodromic phases. Further investigations have shown that, for instance in Parkinson’s disease, the expression of some olfactory receptors in epithelial cells isolated from the nasal fluid is decreased (Kim et al., 2020).

### Classification of olfactory receptors

In 1991, Linda Buck and Richard Axel made a groundbreaking discovery of both the family of transmembrane proteins believed to be odor receptors and some of the genes encoding them (Ngai et al., 2003). This discovery led in 2004 to the Nobel Prize in Physiology/Medicine.

The superfamily of olfactory receptor genes can be classified into 18 families scattered throughout the genome, indicating their ancient origin, and constituting a large part of the human genome, underscoring their critical role in mammalian physiology and evolution (Olender et al., 2008). The olfactory receptors belong to the class A GPCRs (Korsching, 2013; Wu et al., 2024). The olfactory receptors were first classified into Class I and Class II, which are hypothesized to detect specific groups of odorants (Freitag et al., 1995). In mammals, Class II genes represent approximately 90% of the olfactory gene repertoire (Olender et al., 2008; Hayden et al., 2010).

Analyses at a deeper level, have provided a list of 241 olfactory receptor subfamilies in the mouse and 172 in the human genome with at least 60% similarity in protein sequence (Godfrey et al., 2004; Malnic et al., 2004). It has been shown that both olfactory receptor classes can be further divided into 13 monophyletic families conserved among mammals (Hayden et al., 2010). Olfactory gene and receptor sequences are available in the Olfactory Receptor Database (Crasto et al., 2002).

### Evolution of Olfactory Receptors

All organisms, from prokaryotes to mammals, have the capability of detecting exogenous compounds. Organisms have developed devices capable of detecting compounds at concentrations as low as 10 ppm (Smeets et al., 2007). In mammals the detection of environmental chemicals is traditionally referred to as olfaction when the recognized substance is present in the air, and as taste when the exogenous molecule is recognized in solution (Mollo et al., 2022).

The emergence of olfactory receptors was obviously due to the need to detect exogenous substances; however, along evolution, these receptors have participated in delineating complex anatomical structures, including the nervous systems (Churcher and Taylor, 2011). Very relevant is the correlation between developing anatomical structures and biological functions such as proliferation, differentiation, migration, and intercellular adhesion.

Churcher and Taylor (2011) proposed that the appearance of olfactory receptors more than 700 million years ago played a key role in the evolution of cell diversity, particularly in increasing the complexity of nervous systems. This is because these genes chronologically overlap with the emergence of cells that migrate to and create connections with distant cells that could produce molecules serving as ligands for these receptors. Some of these receptors are involved in axon pathfinding, nerve cell projections, cell migration, and neurite growth, suggesting that the roles of these receptors early in evolution were different from odor sensing. This hypothesis becomes even more evident when considering bilaterians, which include a plethora of organisms expressing dozens or hundreds of olfactory-like receptors in different tissues; these receptors are involved in a variety of processes unrelated to olfaction.

### Olfaction across species

The sense of olfaction exists in all animals, from the most primitive metazoan phylum to the most modern, including all five lineages: Placozoa, Porifera, Ctenophora, Cnidaria, and Bilaterians. The group of GPCRs that function as olfactory receptors appeared more than 700 million years ago, before the divergence of Cnidarians (medusas) and Bilaterians (organisms with a longitudinal plane of symmetry) (Churcher and Taylor, 2011). One of the oldest animals with orthologues of olfactory GPCRs is the cnidarian *Nematostella vectensis*.

Placozoans are ancestral metazoans that lack anatomical organs and consist of a mass of aggregated cells that are interdependent. Despite not displaying evident orthologs to olfactory GPCRs, they possess an unexpectedly large, diverse, and evolutionarily dynamic family of homologs of the gamma-aminobutyric and glutamate receptors. This has led some authors to propose these receptors as functionally equivalent to the olfactory receptors found in more modern metazoans (Nikitin and Borman, 2024). Porifera and Ctenophora, which appeared later in evolutionary terms, also lack apparent orthologs of mammalian olfactory receptors (Krishnan et al., 2014). Nevertheless, the EnsemblMetazoa database provides a gene in Porifera species that shares sequence similarities with genes that have already been established as coding for olfactory receptors (olfactory receptor 7D2-like (Gene ID: LOC105316855)). However, evidence has not led studies aimed at confirming whether the gene in sponges (Porifera) is coding a protein able to act like olfactory receptors.

Ensembl Metazoa database provides genes in Cnidaria, the metazoan phylum that includes the oldest organism with functional olfactory receptors, with high homology with mammalian OR genes. Examples are LOC122949044 (2W1-like gene), LOC122953497 (4D1-like gene), and LOC114964426 (11A1-like gene).

Regarding *Caenorhabditis elegans*, there are transcriptome data in gonadal somatic cells (GEO ID: GSE243994), that identify the transcripts for the so-called olfactory receptor 10 (odr-10), and for the so-called odr-4, a protein that may be expressed in neurons. Odr-4 seems to be differentially expressed under

conditions required for regeneration (Dwyer et al., 1998; Xu and Chisholm, 2014; Branicky et al., 2022).

In the case of *Danio rerio*, some putative olfactory receptors are overexpressed in the larval stages or during cardiac regeneration; among others or103, or104, or106, or107, or108, or109, or116 and or134 (Weinberger et al., 2024). Similarly, transcriptomic data of genes differentially expressed upon a spinal cord injury (GEO ID: GSE213435) show that a putative ortholog of mammalian olfactory receptors, prokr1a, is expressed.

### Olfactory system in vertebrates

The capability to perceive chemical cues has been pivotal in the evolutionary journey of animals. Vertebrate chemoreception has witnessed specialized adaptation and diversification, closely intertwined with the ecological challenges encountered by animals throughout their development and evolutionary history. This process undergoes parallel processing of separate sets of molecules, each associated with unique behavioral contexts and distinct telencephalic connections (Ache and Young, 2005). As a result of this complex process, the prevailing perspective has implied that environmental odors are exclusively processed by the main olfactory system (MOS), while pheromones are handled by the vomeronasal system (VNS) (Suárez et al., 2012). The existence of an accessory olfactory system in lungfish implies that all sarcopterygians originally possessed such a dual system (González et al., 2010). However, the vomeronasal system is not retained in all tetrapod groups and is either absent or vestigial in certain lineages such as archosaurs (birds and crocodilians) and higher primates (Suárez et al., 2012). When a chemical stimulus flows into the MOS or VNS, it interacts with specialized GPCRs on the membrane of sensory cells. This interaction triggers a signaling pathway that, as above mentioned, ultimately induces the depolarization of olfactory sensory neurons (OSNs) (Buck, 1992). Each olfactory sensory neuron projects the axon to a glomerulus in the olfactory bulb via the olfactory nerve. The mammalian olfactory bulb is characterized as a six-layered structure consisting of “the nerve fiber, glomerular, external plexiform, mitral, internal plexiform, granule cell, and subventricular layers” (Shipley and Puche, 2003). Layer II, contains glomeruli, which are spherical structures that receive inputs from the olfactory epithelium, as well as from mitral and tufted cells located in layers IV and III, and periglomerular cells (Smith and Bhatnagar, 2019). In this manner, OSNs within the MOS transmit chemosensory signals through the olfactory bulb, which relates to the higher brain centers. Additionally, OSNs of the VNS direct their axons to the so-called accessory olfactory bulb, located in the rostral telencephalon. From there, projections extend to the amygdala and hypothalamus, regions associated with, among others, fight or flight and mating behaviors (Dulac and Torello, 2003).

The VNS encompasses a separate sensory epithelium characterized by OSNs bearing microvilli instead of cilia. Like ciliated OSNs in the MOS, these microvillous OSNs express GPCRs that are known as vomeronasal type 1 and type 2 receptors. In vertebrates, while both anatomical subsystems were believed to be specialized for the detection and processing of odorants and pheromones, more recent research indicated a convergence of these functions (Touhara and Vosshall, 2009). Common odorants are observed to be detectable by the VNS (Trinh and Storm, 2003), and pheromone-like molecules are perceivable by the MOS (Munger et al., 2009).

The number of genes encoding chemosensory GPCRs varies significantly among species (Nei et al., 2008). Specifically, the olfactory receptor repertoire in different species ranges from

155 olfactory receptor genes in zebrafish to 1152 olfactory receptor genes in cows; however, most vertebrate species typically have between 600 and 1300 olfactory receptor genes. A large proportion of olfactory receptor genes in the genome are pseudogenes, meaning they have lost functionality during evolution.

Intriguingly, the vertebrate olfactory receptor expression is spatially organized into multiple overlapping zones that are continuously distributed along the dorsoventral axis of the main olfactory epithelium (Miyamichi et al., 2005). In the nasal cavity, mature olfactory sensory neurons that express the same olfactory receptor gene exhibit stochastic distribution within spatially delimited regions of the olfactory epithelium referred to as “zones.” Earlier investigations delineated four distinct, non-overlapping zones of olfactory receptor expression; however, subsequent studies have identified as many as 9 to 12 zones that partially overlap. Moreover, recent RNA sequencing experiments have revealed that the majority of intact olfactory receptors are expressed within the olfactory epithelium over a broad dynamic range, with only a minority exhibiting high levels of expression (Bressel et al., 2016).

Immature OSNs appear to express multiple olfactory receptors at low levels, whereas it is believed that mature OSNs express a single olfactory receptor at high levels (Hanchate et al., 2015). These findings suggest that the switch to singular OR gene expression occurs during OSN differentiation (Kurian et al., 2021). During differentiation, precursor cells undergo a series of molecular and cellular events that ultimately lead to the formation of mature olfactory sensory neurons. This intricate process involves the activation of specific genetic patterns, migration of neuronal progenitors, and the establishment of precise connections within the olfactory epithelium and olfactory bulb (Schwob, 2002).

In zebrafish and mice, *Foxj1*, a transcription factor containing a forkhead domain and usually associated with the creation of moving cilia, is necessary for forming the olfactory epithelium. The transcriptional program controlled by *Foxj1* for creating moving cilia has been adapted for producing stationary olfactory cilia and for the development of olfactory sensory neurons (D’Gama et al., 2021).

Genetic studies have pinpointed a crucial period required for establishing the initial olfactory map in rodents. Neurons arising before the first week after birth play a vital role in this mapping process. Without these early “navigator” neurons, later-born neurons fail to come together properly. It is suggested that later-born OSNs use adhesion molecules to track the axons of navigator neurons to arrive at the correct glomerular location (Ma et al., 2014). A mutation in Protocadherin 19, a cell adhesion molecule belonging to the cadherin superfamily, leads to defects in OSN clustering during regeneration (Martinez et al., 2023). However, the role of adhesion molecules in regeneration has not been fully explored. Additionally, how these molecules might affect the projection patterns of neurons during regeneration remains unknown (Martinez et al., 2023).

The sense of smell relies on the continuous generation of sensory neurons from neurogenic stem cells expressing CXCR4. CXCR4 signaling is influenced by the levels of its main ligand, CXCL12. It should be noted that CXCL12 is produced by glial-like cells in the olfactory system (Dietz et al., 2023). Very relevant was the finding that olfactory neurons can undergo neurogenesis throughout life at a rate that may depend on olfactory experience (see Dietz et al., 2023 for review). Regulating gene expression in a

specific time and space is crucial for the development and proper functioning of the nervous system. One component that deserves a closer look in neuroregeneration is the heterogeneous nuclear ribonucleoprotein (hnRNP) A/B, which is present in developing olfactory sensory neurons. Knocking out hnRNP A/B leads to a decrease in mature olfactory sensory neurons and abnormal guidance of their axons to the olfactory bulb (Fukuda et al., 2023).

### Function of olfactory receptors in ectopic expression

Olfactory receptors are expressed in the nasal olfactory epithelium, where they perform the recognition of several molecules (odorants). However, the expression of several olfactory receptors has been detected in different tissues that are not involved in chemo-sensory functions.

The role of olfactory receptors in ectopic expression is far from being completely understood. However, there is scattered information that provides indications of a wide range of physiological functions that are regulated by olfactory receptors in different organs and tissues. Interestingly, the possibility of ectopically expressed olfactory receptors to heteromerize with other G protein-coupled receptors should be considered. In particular, it has been reported that olfactory receptor 51E2, the human orthologue of mouse *Olfr-78*, interacts with the adenosine  $A_{2A}$  receptor, which is widely expressed in mammalian organs and tissues (Lillo et al., 2023b).

The mRNA for OR2L13 is one of the most expressed class II olfactory receptor transcripts in the human brain, predominantly detected in the frontal, parietal, and occipital cortices (Gaudel et al., 2021). In a recent study, decreased OR2L13 gene methylation has been correlated with an increased probability of Parkinson’s disease (Du et al., 2024). Other olfactory receptors detected in neurons in various regions of the human brain include OR2H2, OR2A4, and OR6K3 (Ferrer et al., 2016). However, their specific functions remain unknown. The substantia nigra, a key region in the pathophysiology of Parkinson’s disease, expresses olfactory receptors. Notably, post-mortem analysis of substantia nigra samples of Parkinson’s disease patients reveals a significant decrease in transcripts for OR2L13, OR2T33, OR2J3, OR52L1, OR10G8, OR11H1, OR2D2, and OR4F4, suggesting a potential link between olfactory receptors and the disease’s pathology (Grisson et al., 2014). Regarding Alzheimer’s disease, in 5xFAD mice, a murine model of the pathology, a significant downregulation of *Olfr110/111* and *Olfr544* in the brain has been detected (Gaudel et al., 2019). Conversely, increased expression of OR2T33 and OR4F4 has been observed in human brain cortical samples suffering from dementia with Lewy bodies (Garcia-Esparcia et al., 2017). Overall, the literature highlights the relevance of olfactory receptors in ectopic expression in glial cells and neurons and their altered expression in pathophysiological processes (Franco et al., 2024).

The largest organ in the human body, the skin, is a barrier to harmful external agents (Peate, 2021). There are olfactory receptors expressed in the skin that are not related to any chemosensory action. Overexpression of OR10G7 has been observed in keratinocytes of atopic dermatitis patients (Tham et al., 2019) and, accordingly, olfactory receptors in the skin may become therapeutic targets of dermatitis and psoriasis (see below). OR2AT4 expressed in human hair follicles is considered a target to combat hair loss. Odorants that activate this receptor inhibit apoptosis and increase the production of growth factors, whereas a chemical reported as an antagonist inhibits hair growth (Chéret et al., 2018).

The variety of olfactory receptor expression in mammalian testis has long been well known, with between 20 and 60 of these receptors being detected, depending on the species analyzed (Parmentier et al., 1992). These include hOR17-4 and mOR23, which are implicated in sperm–oocyte chemotaxis (Fukuda et al., 2004), and OR4S1, OR4C13, and OR11I, which appear to have a key role in sperm maturation and motility (Milardi et al., 2018). In addition, the finding of a prostate-specific-G-protein-coupled receptor 2 as equal to OR51E1 highlights a key role of ectopically expressed olfactory receptors in mating and sex-related functions (Wang et al., 2006; Pronin and Slepak, 2021). Regarding function, activation of OR51E1 but also OR51E2 by aliphatic acids inhibits the proliferation of a human prostate cancer cell line; furthermore, the overexpression of these receptors produces cell death, thus opening the possibility that they could become therapeutic targets for certain types of prostate cancer (Pronin and Slepak, 2021).

In mammals, there is a close interrelationship between olfaction and taste. One of the components of the mechanism of taste–odor perception interactions is the set of olfactory receptors expressed in taste cells. In particular, OR51E1, OR5P3, OR5A1, and OR2W1 olfactory receptors have been detected in taste cells and their signaling appears to be relevant for gustatory detection (Malik et al., 2019).

In the heart, the OR51E1 might have a role in the regulation of cardiac function; in fact, downregulation of OR51E1 has been reported in the failing heart (Ashraf et al., 2023). Moreover, OR51E1 activation plays a regulatory role by triggering a negative inotropic action via cardiac trabeculae (Jovancevic et al., 2017).

Olfr15 and Olfr821 are expressed in mouse pancreatic islets, and their involvement in food molecule recognition triggers insulin

secretion and contributes to glucose homeostasis (Munakata et al., 2018). Olfr544 is another receptor expressed in pancreatic islets. In mice, Olfr544 receptor-mediated  $\text{Ca}^{2+}$  mobilization from the endoplasmic reticulum promotes glucagon secretion from pancreas  $\alpha$ -cells (Kang et al., 2015).

Olfactory OR1D2 and OR2AG1 receptors were detected in several areas of the lungs including bronchial epithelium and smooth muscle and submucosa cells. While OR1D2 activation leads to increased smooth muscle cell contraction, OR2AG1-mediated signaling leads to the opposite action, inhibiting muscle contraction (Kalbe et al., 2016a).

Transcripts of OR51E1 and OR11H7 receptors have been detected by RT-qPCR in human kidney cells and the ability of these receptors to regulate cytosolic  $\text{Ca}^{2+}$  levels has been shown (Kalbe et al., 2016b). In mice, changes in the expression of several olfactory receptors in the kidney have been detected and associated with the progression of renal fibrosis (Motahharynia et al., 2022). The loss of Olfr1393, which regulates renal glucose reabsorption in rodents, improves glucose homeostasis in a rodent model of type I diabetes (Shepard et al., 2016; Schiazza et al., 2021). To our knowledge the human ortholog of Olfr1393 is not yet known; it is then urgent to identify it to check whether it is expressed in the human kidney and whether it could be a target to combat diabetic nephropathy.

Overall, olfactory receptors play diverse roles in various tissues and organs. Examples of ectopic expression are provided in **Figure 1**. Relevant is the evidence showing that dysregulation of these receptors has implications for various diseases. More research is needed to fully understand the physiological and pathological functions of ectopically expressed olfactory receptors.

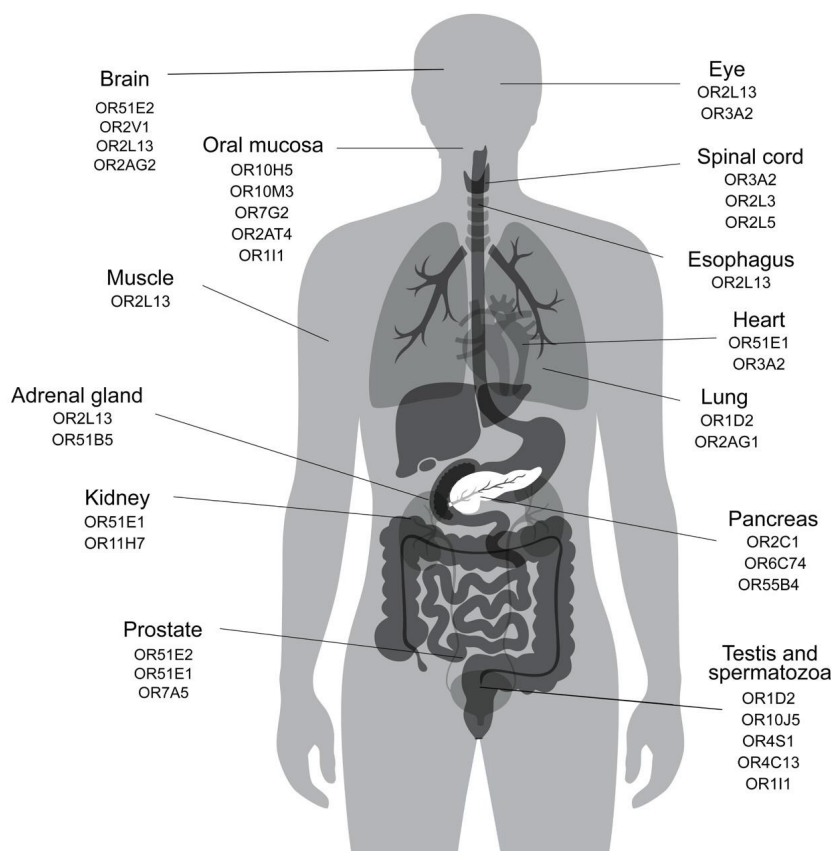


**Figure 1 | Olfactory receptors expressed out of the olfactory system.**

Several olfactory receptors are ectopically expressed. The image of the human body was downloaded from istockphoto (<https://www.istockphoto.com/es>) using a temporal license that allows the copyright-free use of the downloaded image. Receptors were selected from data in the literature and data deposited in the human protein atlas (<https://www.proteinatlas.org/>) database. An exhaustive listing of olfactory receptors expressed in the different organs/tissues of the human body is out of the scope of the review.

In the CNS, olfactory receptors are expressed in both neurons and glial cells. In activated mice primary microglia transcripts of olf58 and olf78 olfactory receptors are detected; their human orthologs are 51E2 and 2V1 (Lillo et al., 2023a). Olfr920 is an olfactory receptor discovered in primary astroglia that responds to small-chain fatty acids (Cho et al., 2019). More olfactory receptors will likely be identified in CNS glial cells along with differential expression upon cell activation.

Taking a given brain area, the substantia nigra, the seminal and pioneering study by Grison et al. (2014), produced by the FANTOM consortium, uses convergent approaches to detect the most abundant olfactory receptors expressed in mesencephalic dopaminergic neurons. In the human tissue and using transcriptomics, and immunohistochemistry or immunoblotting, OR2L13 is the most highly expressed, whereas OR51E2, which is widely expressed in other locations, is expressed at lower levels. Other brain regions likely express a diverse repertoire of olfactory receptors that await to be properly characterized in terms of expression and function.

### Specific ligands for ectopically expressed olfactory receptors

Characterization of olfactory receptors is difficult due to lack of tools. Activation of olfactory receptors to assess functionality is often achieved by testing solutions of odorants or of mixtures of odorants. "Odorify" is a prediction engine available to try to find ligands for olfactory receptors (<https://odorify.ahujalab.iitd.edu.in/olfy/>; accessed on March 28, 2024) (Gupta et al., 2021). Ectopically expressed olfactory receptors may not be designed to "smell" and may therefore primarily detect endogenous compounds. Several studies report olfactory receptor activation by a variety of endogenous compounds and by molecules produced by mucosal colonizing microbiota.

OR51E2 is probably the receptor that has been studied the most to identify molecules that activate it. The results are intriguing as a wide variety of chemical structures reportedly activate OR51E2. Relatively high potencies are reported for compounds as diverse as carboxylic acids (hydroxypyruvic, palmitic, N-acetyl glutamic, glyceric, 2-ketoglutaric), peptides (bradykinin), alcohols (L-histidinol, pelargonidin) and steroids (epitestosterone, androstenedione), glycine, urea or 8-hydroxyguanine (Abaffy et al., 2018). An earlier study used  $\beta$ -ionone, a ketone, to activate the receptor (Neuhaus et al., 2009; Xie et al., 2019). Nonanoic acid has been used to activate the receptor in intestinal enteroendocrine cells (Han et al., 2018). The ortholog in the mouse, Olfr78, is activated by propionate and acetate (not butyrate) to regulate in enteroendocrine cells the secretion of anorexic gut hormone peptide YY (Nishida et al., 2021). The receptor is also expressed in the renal juxtaglomerular apparatus where it responds to short-chain fatty acids to regulate the renin-angiotensin system. The hypothesis that these acids may come from fermentation in microbiota is supported by a correlation between the reduction of gut biomass by antibiotics and elevated blood pressure in Olfr78 knockout mice (Pluznick et al., 2013). Isovaleric acid regulates the expression of OR11H7, OR51E1, as well as of  $G_{olf}$  in the HK-2 human proximal tubule cell line and is proposed as a ligand of these receptors because it leads to the activation of cAMP-dependent signaling (Kalbe et al., 2016b).

OR41E2 may be activated by a metabolite of testosterone, suggesting that it may respond to endogenously produced steroid hormones (Abaffy et al., 2018). Olfr1393 expressed in the proximal tubules of the kidney regulates glucose transport. Knockout mice decrease the expression of a renal glucose transporter, resulting in marked glucose wastage through the

urine. Large-scale screening has established a ligand profile of receptor ligands including atypical structures containing 7- or 8-carbon cycles. While cycloheptanol and cycloheptanone are receptor ligands, the non-functionalized cycle, cyclooctane is not (Shepard et al., 2016). Therefore, this receptor accepts the same core structure in both ketone and alcohol forms.

Using biologically relevant odorants and a heterologous expression system to express some human olfactory receptors, Gonzalez-Kristeller et al. (2015) proposed fructose and a variety of ketones and methyl and ethyl esters, as structures of reference for the activation of human olfactory receptors. They also showed that two compounds, one aldehyde (vanillin) and a ketone ( $\alpha$ -damascone), may activate up to 5 out of the 9 human olfactory receptors tested (Gonzalez-Kristeller et al., 2015).

Screening of odorants in 14 olfactory neurons using alcohols (from pentanol to nonanol) and carboxylic acids (from butanoic to nonanoic and from bromobutanoic to nonanedioic) deciphered strong responses to all except butanoic and pentanoic. 17 out of the 19 odorants tested were recognized by the 14 neurons. Authors highlighted that a single odorant was able to be recognized by different neurons, i.e. by different receptors (Malnic et al., 1999). In 2001, among the dozen compounds tested in two mouse olfactory receptors expressed in heterologous cells, heliotropine (a ketone), 2-methoxy-4-ethylphenol, and eugenol derivatives were identified as able to activate them (Kajiya et al., 2001). Often ketones and/or alcohols are reported as activators of olfactory receptors. Lyrar, a compound with an aldehyde function on one edge and an alcohol on the other induces OR23-mediated chemotaxis in mouse spermatozoa (Fukuda et al., 2004). Two aldehydes, bourgeoinal and undecanoal, behave, respectively, as agonist and antagonist of hOR17-4, involved in sperm chemotaxis (Spehr et al., 2003).

An exhaustive study running in parallel screenings for mouse and human olfactory receptors confirms previously proposed agonists and the discovery of new ones. Olfr558 may be activated by a variety of carboxylic acids whereas Olfr90 is activated by 2-methyl-4-propyl-1,3-oxathiane and various alcohols. The impressive amount of data shows (i) structural diversity among agonists, (ii) that a given molecule may activate different receptors, and (iii) the similar ligand profile of the human orthologs of Olfr558 and Olfr90. Additionally, it is noticed that some of the newly detected (putative) agonists are not produced by humans but by fungi (Halperin Kuhns et al., 2019). A review in 2019 provides data confirming that olfactory receptors may respond to a variety of chemical structures (Di Pizio et al., 2019).

Isononyl alcohol activates OR51B5 in the lymphocytes of patients with acute myelogenous leukemia (Manteniotis et al., 2016). Isononyl alcohol, which is used as a fragrance in soaps/gels, seems to have benefits in atopic dermatitis and psoriasis (Geng et al., 2023). Although OR51B5, is expressed in skin cells, it is not known however whether the therapeutic potential of this alcohol is mediated by this receptor (Tsai et al., 2017; Son et al., 2021). Olfactory receptors expressed in lung macrophages may be activated by octanal and amyl acetate (Li et al., 2013), compounds that are not endogenously produced by mammals, and diaminopimelic acid, which cannot be produced by mammals but by Gram-positive and Gram-negative bacteria.

Odorant receptors in fishes and insects respond to a variety of carboxylic acids (Huff and Pitts, 2020; Ben Khemis et al., 2024). Furthermore, the first resolved structure of an olfactory receptor was achieved with bound propionate; the carboxylic acid is located in an occluded pocket that is probably part of

the orthosteric center (Billesbølle et al., 2023). Therefore, one possible role of ectopically expressed olfactory receptors is to sense extracellular carboxylic acids derived from metabolism. Examples of the action of short-chain fatty acids can be traced back to the eighties. One example is the effect of butyric, acetic, and propionic acids on vascular tone in colonic specimens taken from cancer patients; authors suggested that their results could explain the trophic action of these acids on the colonic mucosa (Mortensen et al., 1990). Smooth muscle cells isolated from the lungs of asthmatic and non-asthmatic individuals respond to acetate and propionate probably through OR51E2 (Aisenberg et al., 2016).

It has been shown that nonanoic acid modulates chemotaxis and T lymphocyte infiltration into tissues (Clark et al., 2016). One hypothesis about the function of ectopically expressed olfactory receptors is that they detect odors or odor-derived metabolites that reach tissues through the bloodstream. A mixture of aromas may activate class-I olfactory receptors and induce the chemotaxis of human neutrophils in a pertussis-toxin-sensitive manner, i.e. involving cAMP as a second messenger (Geithe et al., 2015). Alternatively, receptors ectopically expressed may respond to endogenous compounds, i.e. to molecules produced by cells of the body and/or by microorganisms in mucosae.

Overall, it is unknown whether this diversity of structures able to interact and, eventually, activate, one or various olfactory receptors, arises from receptor promiscuity or is due to a lack of identification of “cognate” agonist(s). A wide variety of odors may need to be detected by olfactory receptors in sensory areas; however, one could speculate that ectopically expressed olfactory receptors are designed to respond to fewer chemicals, either produced endogenously or by microorganisms in the mucosa. In terms of the CNS, the lack of microorganisms restricts ectopically expressed olfactory receptor ligands to those produced endogenously and those produced elsewhere in the periphery but capable of crossing the blood–brain barrier. The recent resolution of OR51E2 structure (Billesbølle et al., 2023) raises hopes for understanding how olfactory receptors can respond to structurally different chemicals and for detecting, through *in silico* screening, cognate ligands of olfactory receptors in ectopic expression.

Finally, the possibility that ectopically expressed olfactory receptors respond to mechanical stimuli should be considered. Patch clamp techniques on olfactory neurons have been shown to respond to both odorant and mechanical stimuli. These responses appear to be mediated by olfactory receptors because the elimination of proteins involved in odor perception or the alteration of the coupling of these receptors to the signaling machinery alters mechanical responses; furthermore, responses to mechanical stimuli vary from one OSN to another (Grosmaître et al., 2007; Connelly et al., 2015; Diez et al., 2024). Mechanical triggers can occur in several ways in every tissue/organ; examples are changes in the shape of cell membranes inherent to chemotaxis, movements of cilia in the intestine/lung/etc., mucosa cells, and movements of the plasma membrane after neuronal differentiation, glial activation, or in cells that contract and dilate.

## Role of Olfactory Receptors in Neuroregeneration

Neurogenesis is the biological process through which new neurons are formed in the nervous system. It involves the proliferation, migration, and differentiation of neural stem cells or progenitor cells into mature neurons. These newly generated neurons then integrate into existing neural circuits, contributing to the structural and functional plasticity of the

brain. Neurogenesis is crucial for various physiological processes, including learning and memory, sensory processing, and mood regulation (Ribeiro and Xapelli, 2021).

Neurogenesis was initially believed to be limited to embryonic and early postnatal stages in vertebrates. However, several studies illustrated that neurogenesis extends beyond embryonic development and persists in specific regions at a significant rate into adulthood. There are three main areas of neurogenesis in the nervous system, the subgranular zone, contributing new granule cells to the dentate gyrus of the hippocampus, the subventricular zone, providing new interneurons to the olfactory bulb (Gage, 2000), and the olfactory epithelia, generating new excitatory sensory neurons that project their axons to the olfactory bulb (Ming and Song, 2011).

Olfactory epithelia neurogenesis is a well-described phenomenon, and probably the one with more neurogenesis activity among these three areas. During the animal’s lifetime, the stem cells resident in the olfactory epithelia produce sensory neurons (Leung et al., 2007). It has been proposed that this neurogenesis is due to the turnover of the population of immature sensory neurons, rather than due to the replacement of mature sensory neurons (Mackay-Sim and Kittel, 1991). One principal explanation of this enhanced neurogenesis of the olfactory epithelium is its direct contact with the environment and its susceptibility to lesions or injuries. When the primary olfactory system is damaged, neurogenesis is activated (Graziadei and Graziadei, 1979). Under that situation, new primary olfactory neurons grow axons towards the olfactory bulb establishing new functional connections (Sipione et al., 2023).

Primary olfactory neurons are in the mucosa in the nasal cavity. Primary olfactory neurons extend axons to the olfactory bulb, located at the front part of the brain within the skull. The epithelium is composed of different cell types, including primary olfactory neurons, basal cells, glial-like sustentacular cells, and flat cells forming the ducts of the Bowman’s glands, which are found in the lamina propria (Choi and Goldstein, 2018).

Olfactory ensheathing glia (OEGs) are a type of cell that provides support to olfactory neurons. OEGs do provide structural and functional support to olfactory neurons and their axons (Nazareth et al., 2020). The primary olfactory system exhibits extraordinary regenerative capabilities after damage, and OEGs play a critical role by providing a conducive environment for the growth of newly formed axons. This regenerative capacity has led to research exploring the potential therapeutic use of OEG in promoting nerve regeneration in other parts of the nervous system, particularly in the context of spinal cord injuries (due to the lack of the ability to restore connections among axons) and neurodegenerative disorders (Yao et al., 2018). Due to these special characteristics, OEGs may be used for CNS regeneration. The exact mechanism by which OEGs carry out their regenerative properties is not yet fully understood. However, it is thought that the role of OEG role in neuroregeneration requires an ability to help axonal growth and the expression of adhesion molecules such as PSA-NCAM and L1 (Moreno-Flores et al., 2002).

Damage to axonal tracts within the spinal cord leads to enduring functional connection loss. The spinal nerve tracts are unable to regenerate due to an insufficient neuronal growth capacity and due to the axon regrowth impediment caused by the formation of a fibroglial scar, a dense connective tissue formed in the CNS in response to injury or damage, primarily composed of glial cells, astrocytes, and fibrous tissue. While the fibroglial scar plays a protective role by preventing the uncontrolled spread of

inflammation, it also presents a challenge for neural regeneration. The scar tissue can act as a physical and chemical barrier that inhibits the regrowth of axons and the repair of neural circuits (Ramer et al., 2005).

Numerous investigations have explored the capability of OEG to enhance axonal regeneration in the injured CNS (Gómez et al., 2018). Most of these studies have delved into the impact of transplanting OEG in various spinal cord injury models. Five positive outcomes associated with OEG have been documented, all of which could contribute to an enhanced functional recovery. These outcomes encompass (i) stimulation of axonal outgrowth, (ii) axonal and tissue sparing, (iii) the ability of OEG to migrate from the lesion site into the host scar tissue, (iv) promotion of angiogenesis, and (v) remyelination of spinal cord axons (Franssen et al., 2007).

The olfactory ensheathing cells (OECs) can regenerate Schwann cell-like myelin sheaths that may surround demyelinated axons (Franklin, 2003). Thus, studies of myelin formation *in vitro* present OECs as promising to treat demyelinating diseases such as multiple sclerosis, searching for appropriate signals and targets that could induce OEC activation, producing both myelin proteins and functional, compact myelin (Azimi Alamouti et al., 2015).

Due to the plasticity and the ability of OECs to improve outcomes in various diseases, the implantation of cells into surviving tissue to enhance reorganization and regenerative processes has become an attractive strategy for spinal cord injuries and neurodegenerative diseases (Björklund and Lindvall, 2000). Regarding Parkinson's disease, the co-grafting of neural stem cell-derived dopamine neurons with OEC, not only significantly increases survival, neurite outgrowth, and dopamine release, but also protects against 6-hydroxydopamine neurotoxicity in co-culture conditions (Shukla et al., 2009). These results suggest that OECs increase the survival and function of transplanted neural stem cell in 6-hydroxydopamine lesioned rats. Regarding the therapeutic potential of olfactory stem cells, Murrel et al. (2008) delved into the utilization of autologous olfactory stem cells sourced from the olfactory mucosa as a promising therapy for Parkinson's disease, proving that stem cells of the olfactory system, obtained from mucosa, could be induced to differentiate into cells resembling dopaminergic neurons, both *in vitro* and *in vivo* after being transplanted into the injured striatum.

Extending the potential applications of cell-based therapies beyond spinal cord injuries and neurodegenerative diseases, recent research has explored the therapeutic potential of olfactory stem cells in restoring neurological function. For instance, in a study examining the efficacy of transplanting human ecto-mesenchymal olfactory stem cells into mice with hippocampal lesions, it was observed that these cells migrated towards the damaged areas, differentiating into neurons, and stimulating endogenous neurogenesis. As a result, synaptic transmission was restored, long-term potentiation improved, and memory and learning were recovered in treated mice compared to untreated controls (Nivet et al., 2011).

The collective data presented in this review underscore the remarkable regenerative capacity of the olfactory system and highlight the neuroplasticity of the olfactory epithelium. The olfactory epithelium, rich in neural stem cells, continuously produces sensory neurons throughout an animal's lifetime, contributing to neuroplasticity proving that olfactory stem cells could serve as a viable source of replacement cells for the nervous system, thus holding significant promise for cell-based therapies in neurological disorders.

The exploration of olfactory receptors in the dentate gyrus is an emerging field that extends our understanding of these receptors beyond their traditional confines of the olfactory system. The dentate gyrus, a key part of the hippocampal formation, is integral to cognitive functions such as memory encoding and spatial navigation (Botterill et al., 2021). The presence and functionality of olfactory receptors in this brain region may uncover novel aspects of neuronal signaling and neurophysiological mechanisms.

### Potential roles of olfactory receptors in the dentate gyrus

One of the most critical roles of the dentate gyrus is to facilitate adult neurogenesis, the process by which new neurons are generated throughout life. Olfactory receptors could influence this process. Studies in other tissues have shown that these receptors mediate the regulation of intracellular signaling pathways that are relevant for the proliferation, differentiation, and survival of neural progenitor cells in the dentate gyrus (Whitman and Greer, 2009).

Olfactory receptors might modulate neuronal activity and synaptic plasticity within the dentate gyrus. This could be achieved through the regulation of neurotransmitter release, modulation of ion channel activity, or via signaling cascades that alter synaptic strength (Avshalumov and Mandyam, 2021). Such mechanisms are crucial for learning and memory, suggesting that olfactory receptors might play a part in optimizing these cognitive functions.

Investigating whether manipulation of olfactory receptor activity in the dentate gyrus affects behavioral outcomes related to hippocampal functions (e.g., memory, learning, and anxiety) could provide insights into their physiological roles. Such studies would help bridge the gap between molecular activity and complex cognitive behaviors.

The dentate gyrus serves as a critical input filter and integration center within the hippocampus, processing information before it is transmitted to other hippocampal subregions. Olfactory receptors might influence how information is processed and integrated into the dentate gyrus by modulating local interneuron activity and affecting the overall excitatory and inhibitory balance in this area.

Identifying specific olfactory receptors expressed in the dentate gyrus is needed to further understand the role of ectopically expressed olfactory receptors in the regeneration of non-chemosensory areas of the CNS. Whereas there is already information from RNA sequencing, *in situ* hybridization, and immunohistochemistry must be used to confirm the presence and map the distribution of these receptors.

Discovering which specific ligands activate dentate gyrus olfactory receptors, and which downstream signaling pathways are engaged, requires comprehensive functional assays. Despite olfactory receptors being assumed to be coupled to  $G_{olf}$  and mediating increases in intercellular cAMP levels, there is evidence of regulation of calcium homeostasis (Jones and Reed, 1989). Regulation of cytoplasmic calcium is key for neuronal functionality and for neurogenesis and, in this regard, there is evidence that olfactory receptors may modulate calcium fluxes and calcium release from the endoplasmic reticulum. Accordingly, it would be very informative to perform calcium imaging to observe intracellular calcium fluxes indicative of receptor activation or to employ optogenetic tools to manipulate olfactory receptor-expressing cells and observe resultant changes in neural circuitry and behavior.

The investigation into olfactory receptors in the dentate gyrus is not just about understanding a novel aspect of sensory receptors but about appreciating the versatility and ubiquity of GPCR function in the brain. The findings from such research could open new therapeutic avenues for treating neurological disorders, enhancing cognitive functions, and understanding the molecular intricacies of hippocampal operation. This area, rich with potential, calls for innovative research approaches and interdisciplinary collaboration to unravel the complexities of olfactory receptors outside their primary sensory domain.

### Role of olfactory receptor heteromers in neuronal regeneration

The potential of the mammalian olfactory system to regenerate in adults is remarkable. Cell renewal in the olfactory epithelium occurs constantly but, in addition, any damage is quickly compensated based on neuron-competent progenitor cells, which are always available and, if necessary, based on multipotent globose basal cell progenitors (Schwob, 2002). These progenitor stem-like cells have the potential to differentiate into olfactory sensory neurons but also into other cells of the olfactory epithelium (Schwob et al., 2017). This multipotency is critical for the long-term maintenance and repair of the olfactory epithelium. In response to damage or injury, globose basal cells can proliferate and differentiate to replace lost or damaged cells, thereby playing a vital role in tissue repair and regeneration (Muniswami et al., 2017). It is therefore suspected that olfactory receptors actively participate in chemosensory neuroregeneration.

Neuronal regeneration requires both the appearance of new neurons with specific phenotypes and the correct positioning of axons. The process of regeneration in cells of the olfactory system, both naturally and in response to injury, is complex (Yu and Wu, 2017). One important issue is that the sorting and convergence of axons of olfactory sensory neurons depend mainly on axon-axon interactions; indeed, this specific sorting of axons can occur in the absence of the olfactory bulb (St. John et al., 2003). About a decade ago the first evidence of the requirement of olfactory receptors for axon sorting was provided (Richard et al., 2013). Adhesion in a murine cell model was afforded when one of the cells expressed the MOR256-17 olfactory receptor and the other the M71 olfactory receptor. Adhesion was also demonstrated when MOR256 was substituted by the  $\beta_2$ -adrenergic receptor, which is expressed in olfactory epithelia (Richard et al., 2013). As one would expect, olfactory receptors participate in olfactory system regeneration. Furthermore, with the role of the  $\beta_2$ -adrenergic receptor in the regeneration of olfactory neurons being notable, future work should address whether other GPCRs can also actively participate in neuronal regeneration.

A seminal paper in 2006 identified genes needed for axon fasciculation in the olfactory bulb, they were coding for Kirrel2 and Kirrel3, homophilic adhesive proteins, and the repulsive ephrin-A5 molecule. Important was the discovery that gene transcription was activity-dependent, i.e. it required the activation of olfactory receptors. It was further shown that the gain of function of the aforementioned genes generated duplicated glomeruli (Serizawa et al., 2006). Glomeruli play a crucial role in the initial stages of olfactory signal processing by integrating, refining, and transmitting sensory information from the nose to the brain, enabling the perception of odors. Therefore, these results support the notion that odorants are key for the expression of axon guidance molecules in “nascent” neurons.

Another relevant piece of information is provided by OR51E2 expressed in prostate cancer cells, where its activation leads

to neuroendocrine trans-differentiation and the trigger is 19-hydroxyandrostenedione, a product of testosterone metabolism (Abaffy et al., 2018).

Fatty acids are necessary in a variety of physiological functions and their participation in neuronal regeneration is no exception. Apart from being neuroprotective propionate is a short-chain fatty acid that participates in the regeneration of peripheral nerves (Grüter et al., 2023). Further actions of free fatty acids in neural cell lines and primary neurons include signaling to cAMP response element-binding protein and the mitogen-activated protein kinase signaling pathways (Zamarbide et al., 2014). Interestingly, the inactivation of a free fatty acid receptor leads to reverting the cognitive impairments of a mouse model of Alzheimer's disease (Zamarbide et al., 2014, 2022). Although those effects have been attributed to the activation or suppression/inhibition of a free fatty acid receptor, the involvement of olfactory receptors cannot be ruled out. Another short-chain fatty acid, butyrate, facilitates oligodendrocyte differentiation and promotes remyelination in cerebellar slices from the cuprizone rodent model of multiple sclerosis. It is suggested that butyrate may come from gut microbiota (Chen et al., 2019). Although the mechanism was not deciphered, the involvement of any of the various olfactory receptors responsive to butyrate cannot be ruled out. It is also tempting to speculate that the benefits of butyrate, in terms of cognitive improvement and neuroblast differentiation in the hippocampus of animals with sirtuin 2-induced memory impairment (Yoo et al., 2015), are not only due to its inhibition of histone deacetylases but to its direct actions on ectopically expressed olfactory receptors.

The Olfr-78 receptor is expressed in mice primary microglia activated using lipopolysaccharide and interferon- $\gamma$  (Lillo et al., 2023a, b); its human orthologue, 51E2 may interact with the adenosine  $A_{2A}$  receptor, which is also expressed in activated microglia in patients with Alzheimer's disease (Angulo et al., 2003). The adenosine  $A_{2A}$  receptor, a GPCR heavily expressed in the striatum, is involved in neurodegeneration and, consequently, is a therapeutic target of neuroprotection. It can interact with a variety of GPCRs in both neurons and glia, and the interactions lead to particular properties, that is, to functionalities that individually expressed receptors could not achieve (Armentero et al., 2011; Franco et al., 2020; Rivas-Santisteban et al., 2023). One of the relevant features of some GPCRs is the need for interaction with other GPCRs for proper surface expression. Probably the first example was provided by  $\gamma$ -amino butyric (GABA) receptors since GABA $_{B1}$  and GABA $_{B2}$  receptors must interact to give rise to a functional GABA $_B$  receptor located at the plasma membrane (White et al., 1998). Difficulties in localizing olfactory receptors on the surface of heterologous cells may be due in part to the need to interact with other receptors to facilitate their route to the plasma membrane. Surprisingly, about 20 years ago it was reported that interaction with  $\beta_2$ -adrenergic receptors was necessary for cell surface expression of the mouse olfactory receptor M71 (Prinster et al., 2005; Hague et al., 2006). As in this case, it is expected that there are other scenarios in which olfactory receptors require interaction with other receptors to achieve expression on the cell membrane. Activation of the adrenergic receptor enhances neurogenesis in the amyloid precursor protein/presenilin 1 mice model of Alzheimer's disease (Chai et al., 2016). In another model of this disease, receptor blockade using selective antagonists inhibits dendrite ramification of hippocampal neurons in a model of Alzheimer's disease (Wu et al., 2017). More evidence linking the receptor to neural regeneration comes from the effect of salmeterol and clenbuterol in, respectively, nerve regeneration (Frerichs

et al., 2002) and adult hippocampal neurogenesis (Bortolotto et al., 2019). Qualitatively similar results were obtained in the dentate gyrus using agonists in a model of Down syndrome (Emili et al., 2020). The few data on the role of GPCR heteromers in neuronal regeneration suggest that some may play a relevant role. While waiting to analyze whether the  $\beta_2$ -adrenergic/M71 receptor heteromer is expressed in the dentate gyrus and plays a role in neurogenesis, it has been reported that an orexin/ $\beta_2$ -adrenergic receptor heteromer participates in the modulation of hippocampal plasticity (Noorani et al., 2021).

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