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Review

Evolution of vertebrate olfactory receptor repertoires and their function

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Chemosensation is evolutionarily ancient but has split into separate taste and smell channels only much later in vertebrates and insects. Here, we focus on recent advances in understanding vertebrate olfaction. Progress has been made on several fronts, from establishing an ever more complete picture of olfactory receptor repertoires, including their allelic polymorphisms, to a better understanding of their evolutionary dynamics in various branches of the vertebrate phylogenetic tree. The ongoing deorphanization of olfactory receptors begins to allow investigations into evolution of their function. Mechanistic understanding of the highly specific, monogenic expression of olfactory receptors has seen large advances. Finally, internal sensing of metabolites by ectopically expressed olfactory receptors is an active field of research.

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Introduction

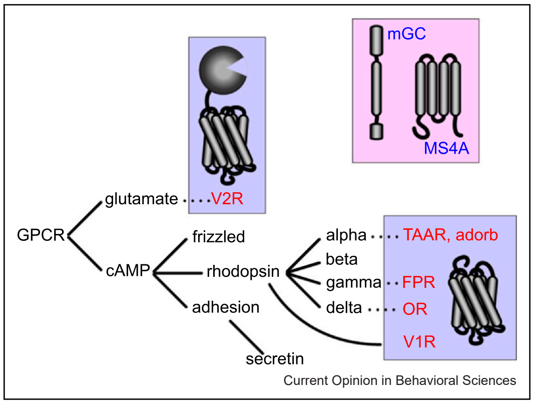
Chemosensation has evolved early in cellular life. Much later, a segregation into an olfactory sense focused on discrimination and a taste sense focused on categorization has occurred in vertebrates and (independently) in insects. The functions of olfaction range from localization of food, predator, and prey over navigation to manifold social purposes, including territorial behavior, social hierarchies, individual recognition, and reproduction [1–3]. In vertebrates, odors are detected by four major and some minor olfactory receptor families (Figure 1). The major families comprise odorant receptors (ORs), trace amine-associated receptors (TAARs and TAAR-like receptors [TARLs]), vomeronasal receptors type 1 (V1Rs, also named ORA in fishes) and type 2 (V2Rs, also named OlfC in fishes). Three of these families were born in the most recent common ancestor (MRCA) of vertebrates [4,5], whereas ORs appeared already in the MRCA of chordates and possibly earlier [6]. In some cases, function as an olfactory receptor is acquired belatedly after the birth of the family: TARLs are present in lamprey, cartilaginous, and bony fish, but they expanded and serve as olfactory receptors only in lamprey [4,7]. Lamprey V2Rs did not expand beyond two genes and do not serve as olfactory receptors [5], in contrast to cartilaginous [7] and bony fish [8] V2Rs.

Current foci in olfactory receptor research comprise, on the one hand, the structure of individual receptors and their interaction with ligands (i) and, on the other hand, the ensemble coding of olfactory information (ii). Another active area of research is the regulation of the expression of olfactory receptors required to generate monogenic expression, that is, limiting the expression in an olfactory sensory neuron to a single receptor gene from a single receptor family (iii). Furthermore, our conception of the evolution of olfactory receptor repertoires — known since a while to be strongly driven by gene birth and death events — becomes ever more comprehensive due to the unabated addition of new genomes to the databases (iv). Very often, an initial characterization of chemoreceptors is included in the corresponding genome publications, see, for example, Refs. [9–11]. Moreover, the same technical advances enabling sequencing of very large data sets have enabled increasing numbers of population genetic studies focusing on or including analysis of olfactory receptor genes (v). An interesting side aspect concerns the evolution of some olfactory receptors to serve as endogenous metabolite sensors, that is, outside of the olfactory system (vi).

Structure and ligand interaction of olfactory receptors

In recent years, cryo-electron microscopy has revolutionized structural studies of G protein–coupled receptors, which had been rather recalcitrant in

Figure 1



Structure and evolutionary relationships of vertebrate olfactory receptors. All major olfactory receptor families (OR, TAAR, V1R, V2R, bluish boxes) are G protein-coupled receptors, whose evolution is schematically shown according to Ref. [80]. V1R constitute an offspring of the rhodopsin group, V2R are the only olfactory family in the glutamate receptor group. formyl peptide receptors (FPRs) are a minor olfactory family in rodents. Minor non-GPCR families (pink box) comprise membrane-bound guanylate cyclase (mGC) and ion channels of the membrane-spanning 4-domains subfamily A (MS4A).

traditional X-ray crystallography. In 2023, the first three such studies for olfactory receptors appeared, analyzing the active state of a human OR [12], both active and inactive conformation for another human OR [13] and a mouse TAAR with several ligands and the appropriate ternary G protein [14].

Recently, for the first time, a TARL has been deorphanized using docking and site-directed mutagenesis [15]. TARLs are the sister clade to TAAR, which are known to be aminergic receptors, and the lamprey TARL indeed turned out to be an amine detector (for polyamines), with a similar binding surface compared to the independently evolved mouse TAAR9 [15]. It will be interesting to see whether the nonolfactory TARL of jawed fish share ligands with the olfactory TARL of jawless fish.

Often, olfactory-guided behaviors ensue from combinatorial activation of several to many olfactory receptors. However, in some cases, activation of an individual receptor is sufficient to elicit particular behaviors, see, for example, Ref. [16]. Itakura et al. [17] identified a V2R receptor activated by male urine, whose knockout dampens intermale aggression. Optogenetic stimulation of a single glomerulus (mimicking activation of the corresponding single OR) was able to recreate a previously learned aversive response (and sensitized the sensory neurons innervating that glomerulus [18]).

A helpful service for the research community is provided by new databases: Chordata Olfactory Receptor Database (CORD) contains nearly a half a million OR sequences annotated by Genome2OR [19] and M2OR contains curated and annotated data for over 50 000 receptor/ligand pairs [20].

Ensemble coding of olfactory information

The entirety of all possible odorants collectively constitutes the odor space. The odor space for a particular species should basically consist of all molecules its olfactory receptors can detect. There have been many attempts to understand the odor space in terms of categorizing odors by physicochemical properties or human perception, for example, Refs. [21,22]. Estimates have ranged between 10 000 [23] and many millions of odorants [24]. A recent publication analyzes this question for airborne odorants and arrives at an impressively large number of over 10^{10} possible odorants [25]. Of course, the actual number of odorants detected by any particular animal species will be much smaller. First, nature does not produce all possible molecules, and second, even the largest olfactory receptor repertoires only contain a few thousand receptors, which often are promiscuous, but not endlessly so.

Natural odors generally are complex mixtures, and an odor activating one receptor may act as competitive antagonist on another receptor [26]. Several studies have shown such antagonism to be a common feature of odorants, for a recent example, see Ref. [27]. Odorants can also function as noncompetitive agonists as shown for the human musk receptor [28].

Teleost fish possess a single olfactory surface, expressing olfactory receptors from all four main families. In contrast, tetrapods have at least two olfactory subsystems: the main olfactory epithelium, whose olfactory sensory neurons innervate the main olfactory bulb, and the vomeronasal epithelium with vomeronasal neurons innervating the accessory olfactory bulb. In mammals, the latter expresses V1Rs and V2Rs, the former expresses ORs and TAARs. Accessory olfactory structures are also present in lamprey and lungfish, but these structures either do not express V1Rs (lamprey [5]) or only rarely express V1Rs (lungfish [29]). Evolutionary transitions in the allocation of olfactory receptors to olfactory epithelia are observed in amphibians and reptiles with (semi) aquatic lifestyles. In amphibians, the V1R family is expressed in the main olfactory epithelium [30], and the V2R family is split between main and accessory olfactory epithelium [31]. Moreover, both amphibians and turtles possess two functionally segregated main olfactory chambers, one dedicated to water-soluble and the other to airborne odorants, which exhibit differential expression of olfactory receptor families [32,33].

Pheromone signals are often but not always transmitted by vomeronasal receptors. Female mammalian tears contain pheromones that dampen male aggression via activation of vomeronasal receptors (mice [34]). However, in humans who lack a vomeronasal system, the same function is elicited by the activation of several ORs [35].

A recent study has looked indirectly at the function of vomeronasal olfactory receptors by conditional knockout of their corresponding G protein in mice olfactory sensory neurons [36]. The authors find that Gαi2 is required for the avoidance of sick conspecifics [36], which suggests V1Rs (known to signal through Gαi2) might be responsible for this behavior.

Regulation of expression of olfactory receptor genes

ORs are the largest gene family in many species and occur in clusters that are distributed over many different chromosomes. About 60 enhancer elements (so-called Greek Islands [37]) interact to form interchromosomal enhancer hubs that regulate OR expression in mice. Pourmady et al. [38] hypothesize that transcribed OR mRNA breaks the symmetry of multiple competing enhancer hubs by recruiting enhancers to its own locus, inhibiting competing OR transcription, and thereby achieving monogenic expression. Ancient balancing selection seems to be responsible for a pronounced polymorphism of enhancers [39].

Another characteristic of olfactory receptor expression is the combination of stochastic receptor gene choice with spatial restriction of individual receptors to so-called expression zones; for a recent example, see Ref. [40]. The underlying mechanism appears to be different in fish [41] and mammals, where two processes, both with spatial preferences, work together to achieve zonal expression [42].

How different are olfactory sensory neurons that settle on expressing different ORs? Horgue et al. [43] showed large differences in transcriptomes of single neurons expressing different OR genes and additionally modification of transcriptomes after exposure to the cognate odors.

The mammalian TAAR gene family is much smaller than the OR family and located on a single cluster. Recently, two groups identified two enhancer elements situated within the TAAR gene cluster that work alone and together to enable TAAR gene expression [44,45].

Evolution of olfactory receptor repertoires

The relative importance of the four receptor families for the sense of smell can vary a lot. An extreme example is found in sharks, where ORs do not play any olfactory role, instead V2Rs constitute the main receptor family [7]. In general olfactory receptor repertoires evolve rapidly, often under positive selection, see, for example, Ref. [46]. Frequent gene gains and losses result in receptor repertoire sizes ranging for ORs from a handful (e.g. sharks) to several thousands (a few mammals) and for V1Rs, V2Rs, and TAARs from a handful to several hundreds [47–49]. It is thought that these processes reflect changing ecological needs of the respective species. Early on, the water-to-land transition was found to result in profound differences between the OR repertoires of fishes and terrestrial vertebrates, the latter gradually losing four subfamilies present in fishes but extensively expanding two other subfamilies [50]. The reverse transition has led to severe shrinkage of the OR repertoire of whales [47].

As more and more genomes become sequenced, ever more detailed comparisons with ecological constraints of the respective species can be performed to test the hypothesis, see Refs. [47,49] for recent large-scale analyses. The size of olfactory receptor repertoires has been correlated positively to nocturnal life and to acquisition of additional environment in a group of amphibious fishes [48], to some habitats (freshwater in fishes [9] and ground level in mammals [49]), to location of food under snow [51], and negatively to domestication [52], group living [47] and altitude (fishes [53], mammals [54], birds [55]).

A very large OR repertoire has been reported for the Southern giant pouched rat, best known for its ability to detect landmines by olfaction [10]. An example of divergent evolution is found in the olfactory receptor repertoires of two marine turtles, where the leatherback (open ocean habitat) has lost one-third of its OR repertoire since the MRCA with green turtles (continental shelf zone), who have expanded their repertoire by an additional quarter [11].

It often has been hypothesized that the importance of olfaction for a species is reflected both in the size of the receptor repertoire and the anatomical complexity and (relative) size of the olfactory structures, suggesting that there should also be a correlation between these parameters. For the olfactory organ, large studies of ray-finned fishes have shown a positive correlation for ORs and V2Rs [49,56], but this correlation does not extend to cartilaginous fish [7], and controversial results have been obtained for ORs in mammals [47,57]. For the olfactory bulb size, a positive correlation with olfactory receptor repertoire size has been reported for nocturnal amphibious fishes [48] and for mammals (ORs and TAARs) [49].

As a caveat, different sequencing technologies may influence apparent olfactory repertoire size [58]. Another potential problem with large-scale phylogenetic analyses is a confounding influence of phylogenetic relationship (repertoires of closely related species are more similar because of phylogenetic inertia, not necessarily because of similar lifestyle). To minimize this problem, several studies have focused on more detailed analysis of smaller phylogenetic clades with divergent lifestyles. Beyond the total size of the olfactory repertoire, several studies have correlated the relative proportions of olfactory subfamilies with ecological parameters.

A study with over 50 rodent species exhibiting very different lifestyles and diet has analyzed OR evolution at the level of 13 OR subfamilies [59]. While they found the fraction of pseudogenes to be impacted by the respective ecological niche, overall, the variations in subfamily size were explained mainly by phylogenetic inertia, with one striking exception: a convergent 10-fold increase of the OR14 family size in two different species families, who independently developed a subterranean lifestyle [59]. Two studies with dozens of different bat species, some animal feeding, some plant visiting, found variable evolutionary rates between species and between OR subfamilies [60,61]. While the earlier study found clear correlation to diet, the latter did not.

Distinguishing between OR subfamilies with volatile ligands and with water-soluble ligands showed expansion of the former and some contraction of the latter in fish species with lungs and terrestrial prey (lobe-finned lungfishes and ray-finned early-diverging Polypteriformes, which still possess lungs), whereas the opposite tendency was observed in strictly aquatic fish (lobe-finned coelacanth and ray-finned early-diverging Acipenseriformes) [62]. However, in the same study, no such correlation was found for teleosts, a group of later-derived ray-finned fish, in which some species also perform air-breathing.

A study comparing five mouse species showed subfamily-specific expansions of V1Rs in the house mouse that likely predate commensal behavior and might have enabled it [63].

New olfactory receptor genes may be gained by local gene duplication or rapidly through polyploidization, although the latter may not always result in increased olfactory receptor repertoire size [64]. Another path to quickly diversify an olfactory receptor repertoire is by introgression, the process of backcrossing of interspecies hybrids into the parental species. In an analysis of several sympatric mouse species, such introgressed DNA segments were found to be enriched for ORs [65].

In few cases, ligands and function of particular olfactory receptors are known enabling studies of the evolution of function. Some receptor genes may acquire olfactory function only late in their evolution (for recent examples, see Refs. [5,66]). Some olfactory receptor genes may be lost during evolution, but their function retained by a similar receptor/ligand pair, see, for example, Ref. [67].

Large polymorphism of olfactory receptors in populations

Many specific anosmias as well as differential sensitivities to particular odorants are known in humans, which are assumed to be caused by allelic differences of the cognate olfactory receptors. Population analyses in humans showed extensive polymorphism for OR genes that often resulted in functional differences between alleles, see, for example, Ref. [68]. Many OR sequence variants were found to be located in structurally and functionally relevant domains of the protein [69]. Several studies show that individual differences in perception of musk odors are linked to different alleles of the main musk receptor, see, for example, Ref. [70].

Another study in humans has examined allelic differences of ORs in connection to ecology. Overall, no differences in selection pressures were seen between agricultural communities and neighboring hunter/gatherers both in Africa and Asia, but among several candidate genes for positive selection, local adaptation of allelic frequency to subsistence style was observed [71]. Interestingly, the alleles in question appeared to be much older than modern humans, suggesting that adaptation to the changed subsistence was due to selection from a preexisting set of alleles.

Evolution of nonolfactory roles of olfactory receptors

OR families are among the largest in the genome, and some of the other olfactory receptor families (V1R, V2R, TAAR) also number hundreds of genes in some species of tetrapods, for example, Ref. [46] and fishes [56]. Olfaction is an essential sense in many species; nevertheless, it could be considered a bit wasteful to dedicate such huge gene families exclusively to detection of odorants. Conversely to nonolfactory receptors gaining an olfactory role by either artificially [72] or naturally [73] coming under olfactory promoter control, one might expect that an olfactory receptor acquiring ectopic expression might serve to detect endogenous metabolites. In fact, expression of some olfactory receptors in nonolfactory tissues has been demonstrated, and more recently, several studies have shown physiological functions of these receptors by knockdown and knockout experiments. For example, activation of ORs expressed in smooth muscle cells furthers bronchodilation (airways [74]) and reduces blood pressure (kidney [75]). Activation of ORs often impairs proliferation, both in healthy [76] and in cancer tissue [77]. Furthermore, chemosensory organs outside the nose may also use ORs for sensing (carotid body [78]).

Nonmammalian OR repertoires have been investigated much less in this respect, and future studies will be required to determine how widespread this nonolfactory role of ORs is. A recent survey of available RNA-seq data for zebrafish, a nonmammalian model organism, combined with *in situ* hybridization and reverse transcription polymerase chain reaction (RT-PCR), has shown widespread ectopic expression of many OR genes both during development and in adult tissues [79]. This is consistent with the notion that the repurposing of ORs for functions outside olfaction could be at least as old as the segregation between lobe-finned and ray-finned lineages, that is, over 400 million years.

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Declaration of Competing Interest

None

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- • of special interest
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