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PERSPECTIVE

From Plants to Man: The GPCR "Tree of Life"

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ABSTRACT

This *Perspective* focuses on the article by Fredriksson and Schioth in the April 2005 issue of *Molecular Pharmacology*. Their article describes the expansion and evolution of G protein-coupled receptors during the nematode-to-chordate split.

From the comparison of nucleotide sequences, molecular phylogeneticists can construct a "tree of life", suggesting a hierarchical and evolutionary classification of a protein. According to the founders of modern phylogenetics, Emile Zuckerkandl and Linus Pauling, molecular sequences define "the essence of the organism". Sequences do this not only by revealing a pattern in the chaos but also by embodying and engendering (Zuckerkandl and Pauling, 1965). A prime example of this essence is the GPCR superfamily, embodied by the seven transmembrane spanning domains that engender ligand specificity and functional integrity. To further illustrate this principle, Fredriksson and Schioth (2005) in this issue of *Molecular Pharmacology* describe the "tree of life" for GPCRs and how the major families have expanded and evolved from the nematode and chordate split.

An illustration and review of a typical "tree of life" modified from the Fredriksson and Schioth (2005) article is shown in Fig. 1. Fredriksson and Schioth (2005) show that all of the major GPCR families in the human genome (Glutamate, Rhodopsin, Adhesion, Frizzled, and Secretin) arose before the evolutionary split of the nematodes from the chordate lineage. Recent phylogenetic analyses indicate that vertebrate gene families did undergo large genome duplication in the early chordate [650–350 million years ago (Mya)], and 13% of all human genes are still recognizable as duplicates from that era (McLysaght et al., 2002). In another study, it was suggested that there were two waves of gene expansion, in addition to an ancient component (900–750 Mya). The first wave (430–80 Mya; the time of the mouse-human split) is characterized by tandem or segmental duplications, whereas the second wave (750–430Mya; the time of the vertebrate-amphioxus split) was paralogous where chromosomal positions of the genes remained intact and whole chromosomes were duplicated (Gu et al., 2002). Both of these models are in support of a largely debated "big-bang theory" of large-scale gene duplication. It is evident from Fig. 1. that GPCRs also followed the "big-bang theory" of gene duplication. There are few GPCRs in the plant and fungi genomes, but large numbers of GPCRs exist in the nematode and chordate lineages. Fredriksson and Schioth (2005) go on to show the distribution of the classes of GPCRs, and it is evident that the rhodopsin family had the most evolutionary success.

GPCRs are thought to be of an ancient origin because they are present in insects (Hill et al., 2002) and plants (Josefsson, 1999). The insect class is very interesting, comprising rhodopsin-like GPCRs as well as members from each of the main classes of GPCRs. A dominant feature of the molecular evolution of the malaria vector mosquito, *Anopheles gambiae,* and the fruit fly, *Drosophila melanogaster*, GPCRs is the expansion of subfamilies unique to each Arthropoda lineage. For example, there is a large subfamily of 27 *A. gambiae* GPCRs with no close *D. melanogaster* relatives and a large subfamily of 18 *D. melanogaster* GPCRs with no close *A. gambiae* relatives (Hill et al., 2002).

Likewise, Fredriksson and Schioth (2005) point out that only a few groups demonstrate this lineage-specific expansion of GPCRs. For example, there are chemosensory receptors in the nematodes that are not found in any other species but compose about 87% of the GPCRs in *C. elegans*. In addition, the gustatory GPCRs are found in only two species of

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ABBREVIATIONS: GPCR, G protein-coupled receptor; VH, heavy chain variable.

insects, where they compose about 20% and 28% of the genome in *D. melanogaster* and *A. gambiae*, respectively. Members of the gustatory GPCR family are expressed in subsets of neurons in proboscis, pharynx, and the leg (Dunipace et al., 2001; Scott et al., 2001). These observations imply that fruit flies and mosquitoes have high taste discrimination compared with other insects, which is self-evident on a hot day or with ripe fruit. Most gustatory GPCRs share as little as 8% amino acid identity, making them highly divergent. Scott et al. (2001) introduced the notion that the two families of odorant and gustatory receptors are evolutionarily related in an insect chemoreceptor superfamily. The odorant genes seem to be a highly expanded class within the larger gustatory family. Lineage-specific expansions most likely result through both differential duplication and loss of specific ancestral copies.

Other GPCRs that have undergone large and rapid expansions are the olfactory receptors (in the rhodopsin family) in both humans and mouse, the chemosensory receptors in *Caenorhabditis elegans*, and the pheromone receptors in the mouse, which belong to the glutamate family. Fredriksson and Schioth (2005) reveal that these groups share a common feature in that they bind small ligands. This may promote a more "dynamic" gene repertoire by having fewer or weaker constraints in duplication events, which promotes better survival, thus allowing for the unusual expansion of these groups. This may be a plausible explanation. The expansion of the immunoglobulin and the major histocompatibility complex genes in response to selective pressures is well known. The human heavy chain variable (VH) region III gene subgroup underwent a significant gene expansion compared with the mouse subgroup. Amino acid sequence data indicate that human VH III genes correspond to only a small subset of mouse VH III genes (Rechavi et al., 1982). Therefore, a smaller subset of amino acids could have better survival or dynamics over the much larger repertoire, aiding in its expansion. Furthermore, the small-liganded rhodopsin family is by far the largest proportion of the chordate and arthropoda GPCR genomes [Fig. 3 in Fredriksson and Schioth (2005)]. Although this GPCR class is not expanded, it is well survived.

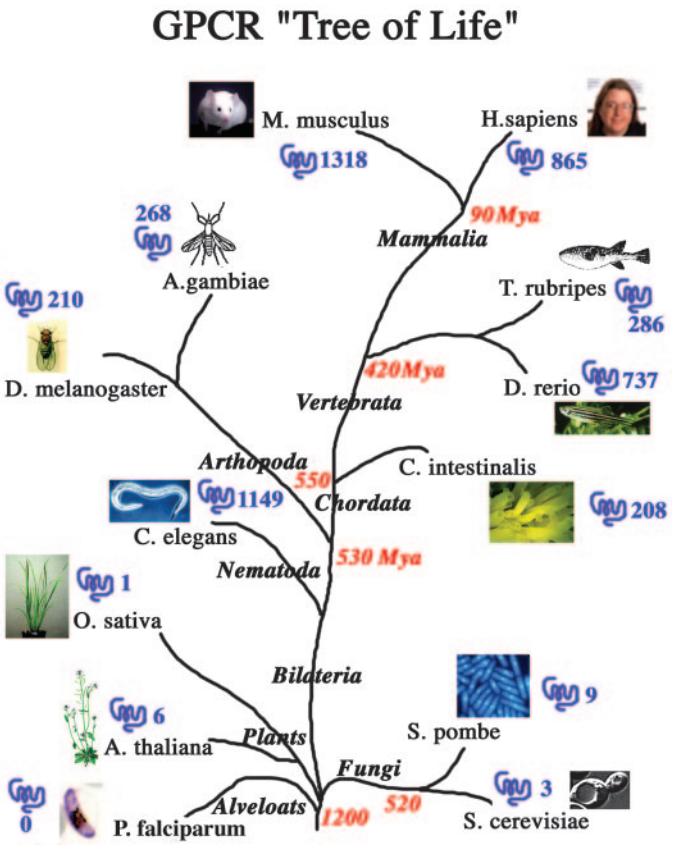

Fig. 1. Phylogenetic GPCR tree of the different species. An image from that species is illustrated for review. The numbers (in red) at the nodes indicate the time in million of years [(millions of years ago (Mya)] since the split at that node occurred [based upon the figure in Fredriksson and Schioth (2005)]. Blue GPCRs and numbers represent the number of GPCRs in the different main classes predicted in the various genomes [data taken from Table 2 in Fredriksson and Schioth (2005)].

Finally, Fredriksson and Schioth (2005) tantalizingly suggest that the ancient mother-of-all-GPCRs could be a member of the Adhesion/Secretin family. This is based upon finding a GPCR in *Arabidopsis thaliana* that shows resemblance to the Adhesion/Secretin model that all other GPCRs in plants and fungi show little homology to bilateria. However, the sequence in *A. thaliana* is a stripped-down version of an Adhesion GPCR because it does not have a long N terminus (Bjarnadottir et al., 2004), again suggesting that the simplest GPCR has the best advantage and survival.

We all like to know where we came from. Our impulse is to classify and organize. Phylogenetic analyses can capture information that may be useful to the pharmacology community, such as orphan receptor classification and characterization. It also investigates potential links between endocrine, neurological, or immune development and their regulation by the different classes of GPCRs. Knowing where we came from can help us go forward.

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Correction to "From Plants to Man: The GPCR 'Tree of Life'"

In the above *Perspective* article [Perez DM (2005) **67:**1383–1384], the abstract states that "This *Perspective* focuses on the article by Fredriksson and Schioth in the April 2005 issue of *Molecular Pharmacology*." The article by Fredriksson and Schioth, however, appears in the May issue.

The online version has been corrected in departure from the print version.

We regret this error and apologize for any confusion or inconvenience it may have caused.