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Molecular recognition and evolution in biological repertoires: from olfaction to the origin of life

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Summary

Our research centers on molecular recognition phenomena within biological repertoires. We ask how protein receptor repertoires evolve and function, using the olfactory system as a model. The tools of human genomics and bioinformatics are used to shed light on the large repertoire of G-protein coupled receptors that underlie odorant recognition. In parallel, we employ similar molecular insight to try to decipher the very early steps in the evolution of life on earth.

Genome analysis of olfactory receptor genes

The human olfactory subgenome represents several hundred genes coding for olfactory receptors (ORs) several dozen clusters on practically all chromosomes. Based on our complete DNA sequence analysis of the chromosome 17 cluster, we have identified seventeen genes and pseudogenes, which have undergone events of gene duplication and gene conversion. Comparative analysis of the duplicated genes has revealed the intron-exon structure of OR genes, including a putative control regions, which could be meaningful for OR clonal exclusion.

Evolution of a multigene family

One of the central aspects of our research is deciphering evolutionary mechanisms. Thus, the generation of pseudogenes, instances of “gene death”, has been studied in the olfactory receptor multigene family

by comparative sequencing of the same ORs in several primate species, suggesting a rather recent diminution of the functional OR repertoire. This could underlie the widespread phenomenon of human odor-specific olfactory deficits (specific anosmias). We are now investigating by genomic linkage analysis (using microsatellite polymorphic markers) the potential relationship of individual OR genes to odorant sensitivities.

Single Nucleotide Polymorphisms (SNP) analysis

The Single Nucleotide Polymorphism (SNP) patterns of OR have been studied, as a tool for fine linkage mapping and for elucidating evolutionary mechanisms. OR genes were found to carry a rather high number of SNPs, as compared to other G-protein-coupled receptors. This may be the result of overdominant selection, which tends to increase heterozygosity, so as to generate new receptor specificities. In addition, an unusual dichotomy has emerged between genes and pseudogenes, whereby the latter had a much higher incidence of ancient alleles. We interpret this in terms of a general evolutionary mechanism involving higher recombination rates in pseudogenes and in introns, as compared to functional exons. This could constitute a basic phenomenon in genome dynamics, related to evolutionary exon shuffling.

Proteome analysis of the odorant binding site

In another project, we are sequencing hundreds of human OR genes using human genome methodologies.

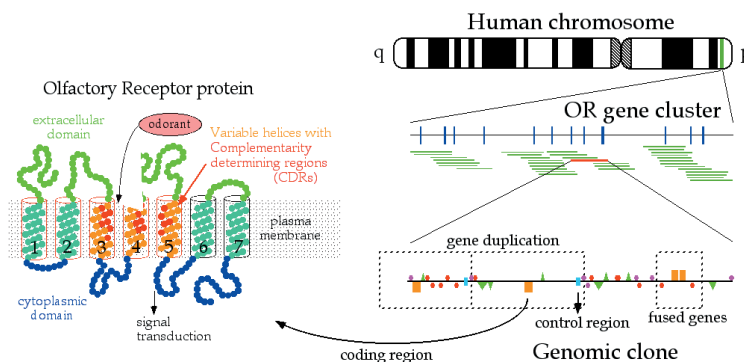


Fig. 1. Interpreting human genome information on olfactory receptors by computational analyses.

The results are displayed in a web database (HORDE) equipped with diverse analysis modes, including our OR gene nomenclature system, now officially accepted. The accumulation of such OR sequences, along with the recent availability of detailed models of other G-protein coupled receptors, allowed us to analyse the OR amino acid variability patterns in a structural context. A Fourier analysis showed an alpha-helical periodicity in the variability profile. Rhodopsin-based homology modeling, together with a novel algorithm for inferring the orientation of transmembrane helices (kPROT), demonstrated that the inferred variable helical faces (mainly in TM3, 4 and 5) largely point to the interior of the receptor barrel. We proposed that a set of 17 inward-facing hypervariable residues constitute the odorant Complementarity Determining Regions (CDRs), in analogy to the antigen binding site of immunoglobulins.

Statistical chemistry scenario for the origin of life

We have suggested previously that olfactory receptors form a random repertoire evolved for recognizing odorants on a probabilistic basis. In order to describe the recognition properties of such a repertoire, we have developed the Receptor Affinity Distribution model that allows to assign a probability to any degree of affinity between a receptor and a ligand. We are now applying a generalized version of this statistical chemistry model to describe the statistical properties of catalytic interactions in a random set of chemicals. Based on the same principles we developed the Graded Autocatalysis Replication Domain (GARD) model, a platform for kinetic computer simulations for prebiotic evolution. We show that primordial self-replication could have arisen as a consequence of mutual catalysis within assemblies of randomly disposed simple amphiphilic molecules (a "Lipid World"). This may have considerably predated the proposed "RNA world", that requires highly specific monomers, and the energy-dependent generation of polymers.

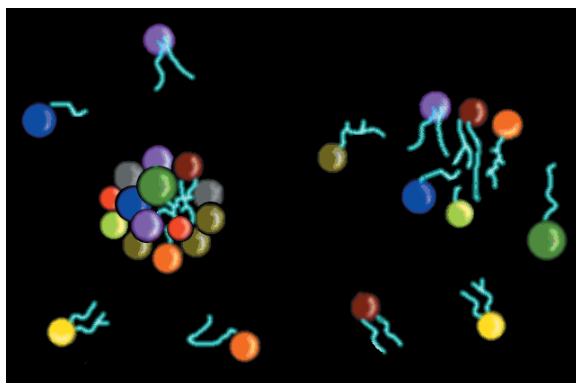


Fig. 2. A schematic depiction of a "lipid World" Origin of Life scenario.

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