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

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Our research centers on molecular recognition 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, protein modeling and population genetics are used to shed light on the large superfamily of G-protein-coupled receptors that underlies odorant recognition. In parallel, we employ molecular recognition formalisms to decipher the very early steps in prebiotic evolution.

Genomic analysis of olfactory receptor genes

The human olfactory subgenome encompasses more than 1000 olfactory receptor (OR) genes in several dozen clusters on all but two chromosomes. Our greatly expanded knowledge of the OR superfamily rests on an in depth analysis of one OR cluster on human chromosome 17, and in parallel on a genome-wide elucidation of the repertoire (Fig. 1). The more local analysis has revealed mechanisms of gene duplication and gene conversion, as well as the intron-exon and promoter structures of a typical OR gene. Employing a novel technology for genome-wide directed OR sequencing, and performing data mining as part of the world-wide human genome project, we were able to completely elucidate the olfactory subgenome. About two thirds of all ORs turned out to be pseudogenes, suggesting a recent remarkable diminution of the functional OR repertoire. A comparison of variation patterns in OR genes and pseudogenes has led to one of the first clear demonstrations of Darwinian positive selection in humans.

Genetic odor blindness

We are investigating the genetic basis for the widespread phenomenon of human odor-specific chemosensory deficits (specific anosmias), as well as for the innate universal loss of the sense of smell (general anosmia). This is done using mutation detection, as well as linkage and association analyses, based on Single Nucleotide Polymorphism (SNP) patterns. Such approaches are also powerful for revealing the relations between individual OR genes and odorant sensitivities.

Proteome analysis of the odorant binding site

The results of the genomic searches are accumulated in our web database (HORDE) equipped with diverse analysis modes, including our OR gene nomenclature system, now officially accepted. A previous proteome analysis, based on a crude structure of the visual photoreceptor rhodopsin, revealed a set of 17 amino acid residues that may constitute the odorant Complementarity Determining Regions (CDRs), in analogy to the hypervariable antigen binding site of immunoglobulins. More recently, we have greatly refined the OR homology model based on the knowledge of all human OR sequences, and on a recently published X-ray crystal structure of rhodopsin. In conjunction with human-mouse comparative genomics tools, a better definition OR of structure and function is expected.

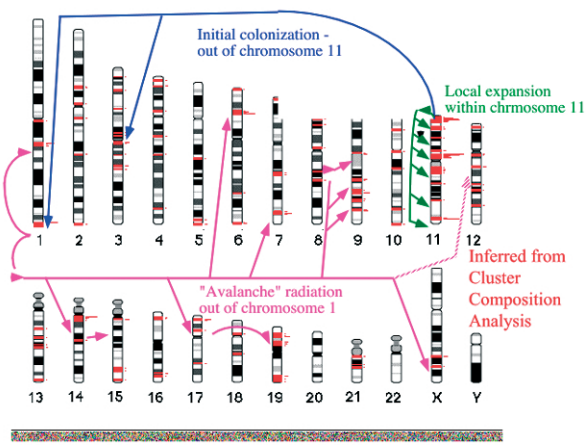

Fig. 1 *The expansion of Olfactory Receptors throughout the human genome. See: http://bioinfo.weizmann.ac.il/HORDE*

A combinatorial lipid world scenario for the origin of life

Based on our Receptor Affinity Distribution (RAD) model for receptor repertoires, we devised a generalized version of this statistical chemistry model to describe the catalytic interactions in random sets of chemicals. This allowed us to develop the Graded Autocatalysis Replication Domain (GARD) model, a platform for kinetic computer simulations of prebiotic evolution. We show that assemblies of lipid-like amphipilic molecules

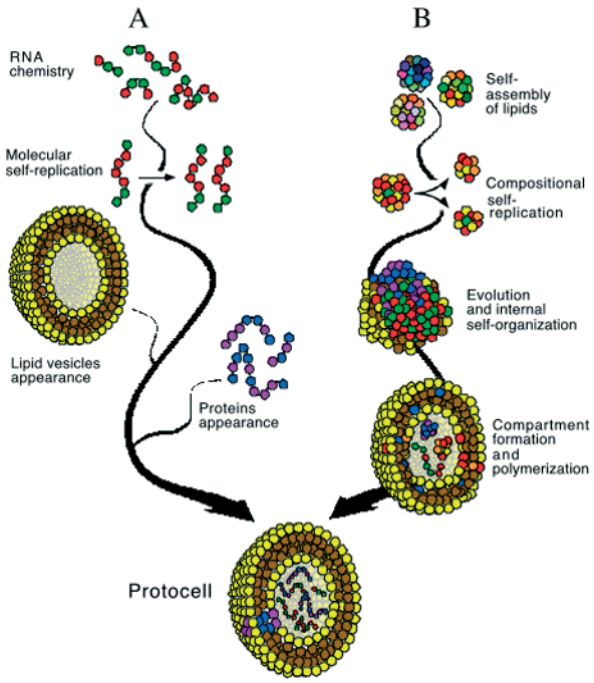

Fig. 2 *Two alternative views for the path leading from "primordial soup" to rudimentary protocellular structure.*

are capable of primordial transfer of compositional genome information (Fig. 2). This embodies a primitive self-replication, which arises via mutually catalytic networks. Such a "Lipid World" may have considerably predated the frequently proposed "RNA world".

Selected Publications

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