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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 focuses on molecular recognition within biological repertoires. We ask how protein receptor families 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 statistical molecular complementarity formalisms to decipher the very early steps in prebiotic self-organization.

Genome analysis of olfactory receptors (ORs)

Employing novel technologies for genome-wide OR sequencing and data mining, and as part of the world-wide human genome project, we have completely elucidated the human olfactory subgenome – the entire collection of OR genes and pseudogenes. The results of these genomic searches are accumulated in a unique database (HORDE) equipped with diverse analysis modes, including our instituted nomenclature system, now officially accepted worldwide. HORDE now includes 854 ORs in 17 families (Fig. 1). The OR genes are organized in 136 genomic clusters on all but two human chromosomes. The same methodologies were applied to the genome of the dog, a species with an unusually sensitive nose. Surprisingly, its overall olfactory repertoire size is only 50% larger than that of man. However, the canine OR repertoire contains only 14% pseudogenes, as compared to 55% in humans.

Olfactory receptor genes

Analysis of OR genes in several primate species has revealed that humans and apes have undergone a recent and massive OR gene loss. We have shown that this correlates with the acquisition of full (trichromatic) color vision. Perhaps kin recognition and food selection, dominated by olfaction in lower mammals, have evolved into largely visual tasks. Our research further showed that the relatively recent process of OR gene pseudogeniziation has created a highly unusual phenomenon of segregating pseudogenes (SPG). These are OR-coding genomic loci that have intact functional ORs in some human individuals and inactive ORs in others. Importantly, these SPGs are the most likely mechanism to underlie the long known phenomenon of odor blindness (specific anosmia) - functional variability in human olfaction akin to color blindness. Individualized SPG combinations generate an olfactory "barcode", whereby every human nose is genetically different. Ongoing research with hundreds of volunteers, and using high-throughput DNA variation analysis, attempts to associate the

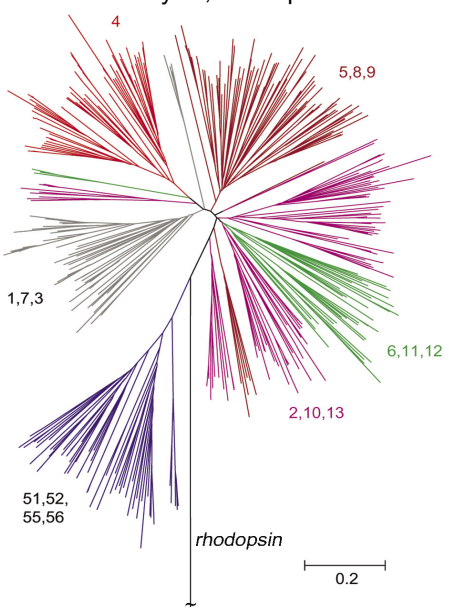

Fig. 1 *A phylogenetic analysis of the human olfactory receptor repertoire. The families are divided into two classes; Class I (families 51-56) and Class II (families 1-13). See http: //bioinfo.weizmann.ac.il/HORDE.*

genetic deficits with behavioral phenotypes.

Structural and functional features of olfactory receptor proteins

A proteome analysis, based on a human-mouse comparative study, revealed set of 22 amino acid residues that may constitute the odorant Complementarity Determining Regions (CDRs), in analogy to the hypervariable antigen binding site of immunoglobulins. These amino acid positions are found to be clustered around a pocket defined within a structural model of ORs that we have developed. The latter constitutes a refined rhodopsin-based homology models that incorporates sequence conservation/variability signals, molecular dynamics considerations and a detailed analysis of kinks within the transmembrane helices.

A lipid world scenario of the origin of life

The 'lipid world' scenario for origin of life suggests that life emerged from primordial assemblies of lipid-like amphiphilic molecules. Based on our Receptor Affinity Distribution model, we devised an artificial chemistry formalism, the Graded Autocatalysis Replication Domain (GARD) model, to describe the catalytic interactions in large molecular repertoires. GARD depicts the kinetics of molecular assemblies that are kept far from equilibrium by occasional fission. Computer simulations demonstrated the capacity of primordial transfer of "compositional genome" information (Fig. 2). This implies a primitive self-replication mechanism, simpler than the ones suggested by scenarios that invoke nucleic acid sequence templating. Extensions of GARD portray enantiomeric selection, primordial population organization and development of sequence complexity. Recently, we have launched the computational origin of life endeavor (CORE), an effort to study life's emergence utilizing the idle computer power harvesting by ool@home.

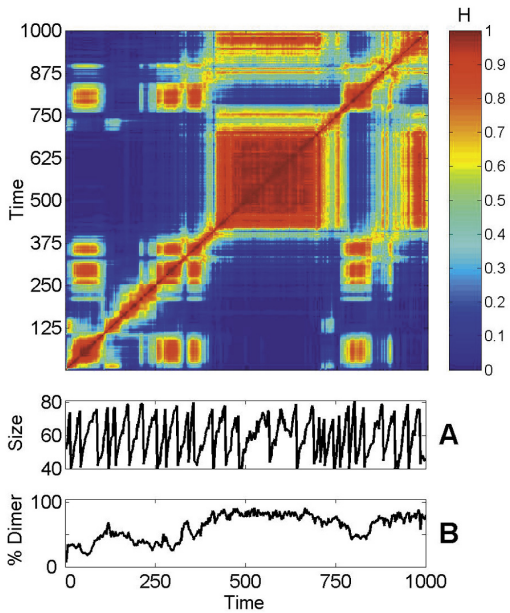

Fig. 2 *Time auto-correlation matrix from a Polymer-GARD simulation. Red squares (high mutual similarity H) are "composomes" with high efficiency of inheritance across splits (panel A). Dimers takeover is seen in panel B. See:* ***http//ool.weizmann.ac.il***

Selected Publications

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