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

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A shared theme in our research is molecular recognition within biological repertoires. Two main topics are the olfactory receptor repertoire and prebiotic networks of mutual catalysis in repertoires of small molecules. In the olfactory system, we focus on genetic variations that shape our olfactory individuality. Olfactory receptors (ORs) are G-protein coupled receptors, which constitute the largest gene superfamily in the human genome. We use the tools of human genomics, bioinformatics, and population genetics to shed light on this huge repertoire. In the realm of prebiotic evolution, we employ chemical kinetics-based computer simulations to decipher the very early steps in prebiotic self-organization.

Genome analysis of olfactory receptor genes

Employing computational methodologies for genome-wide analyses of olfactory receptor (OR) genes, we have completely elucidated the entire olfactory sub-genome - the collection of OR genes and pseudogenes in human and other mammals such as dog, opossum and platypus. The results are accumulated in a unique database (HORDE) equipped with diverse analysis modes, including a nomenclature system, now officially accepted worldwide.

The immense magnitude of the mammalian olfactory gene superfamily attests to the importance of chemoreception for such species. In mouse, dog and opossum, organisms which highly rely on their sense of smell, the gene family contains 1200-1600 genes with 20% pseudogenes. In human and platypus, which are less dependent on olfaction, the gene family is smaller (700-850) and more than 50% are pseudogenes.

The OR gene superfamily was classified by us into 18 families (Fig 1), and more than 400 subfamilies. This indicates that most of the mammalian OR families and subfamilies are inherited from their common ancestor. However, species-specific expansions can be observed in each species, perhaps important to their unique chemosensory capacities. An example is the considerable expansion of family 14 in platypus.

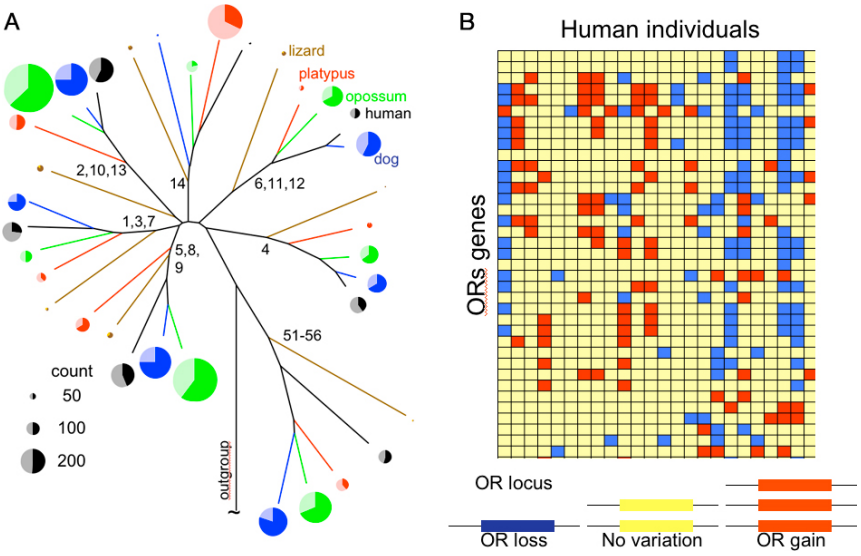

Fig. 1 *a. A representative phylogenetic tree of the OR repertoire in mammals (human, dog, opossum, platypus) and a reptile. The tree shows the relative size and pseudogene content of different OR family groupings (enumerated beside internal branches). Pie-charts illustrate the proportions of intact genes (heavily shaded) versus disrupted pseudogenes (lightly shaded). See http://bioportal.weizmann.ac.il/HORDE.*
b. Copy Number Variation creates a specific genotype in each individual. About 130 ORs are variable among different individuals in their copy number, and the most 50 variable ORs are shown in the figure. The data were measured by a high resolution CGH experiment in 15 individuals. Each column is an individual and each row is a specific olfactory receptor. Red indicates gain of copy number, blue- loss of copy number and yellow- no change.

Genetics of human olfactory variability

Humans exhibit high variability of sensitivities towards specific odorants, including the phenomena of specific anosmia (diminished sensitivity) and specific hyperosmia (enhanced sensitivity), attributed in significant part to genetic variation. We strive to identify the genes underlying such variation. Previously we identified an unusual phenomenon of segregating pseudogenes (SPG), i.e. genes showing both functional and inactivated alleles in the population. Importantly, OR SPGs are natural knockouts, perfect candidates to underlie the olfactory variation phenotypes. Indeed, we have now successfully uncovered a significant association between the genotype at one segregating pseudogene locus (OR11H7P) and a sensitivity phenotype for the odorant isovaleric acid. Copy Number Variation (CNV) is another type of polymorphism, potentially responsible for variability in olfactory function. We employed a high-resolution Comparative Genomic Hybridization (CGH) microarray for all human ORs. Using DNA from 15 individuals, we identified 139 OR loci with apparent variability in copy number. Most importantly, we identified two regions with null allele (deletion). One of these homozygous deletions involves a ~100kb interval on chromosome 11 which contains 4 intact ORs and 2 OR pseudogenes. Such deletions should display a strong deleterious phenotype now under study.

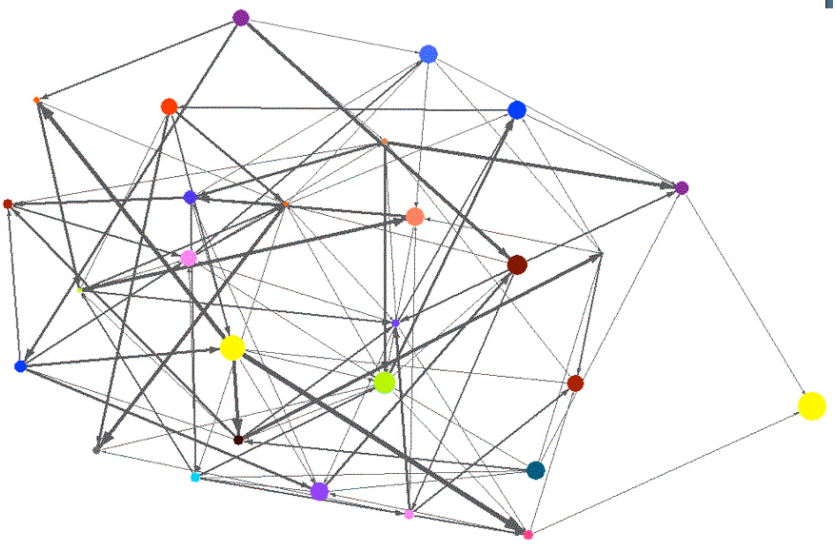

Fig. 2 *The GARD model can be depicted as a catalytic network. In this network the nodes are chemical compounds with their size proportional to their concentration in the semi-stationary "composome" state, and the arrows are the strength of the catalytic interaction. See: http//ool.weizmann.ac.il*

A lipid world scenario of the origin of life

In the 'lipid world' scenario for origin of life we have suggested that life emerged from primordial assemblies of lipid-like amphiphilic molecules. We devised an artificial chemistry formalism, the Graded Autocatalysis Replication Domain (GARD) model. This describes by computer simulations the chemical dynamics in large molecular repertoires of prebiotic molecules. GARD depicts the biased accretion kinetics of molecular assemblies that are kept far from equilibrium by occasional fission. Our simulations demonstrate the capacity of primordial transfer of "compositional genome" information. This implies a primitive self-replication mechanism, simpler than the ones suggested by scenarios that invoke nucleic acid sequence templating (RNA world). Extensions of GARD portray development of polymers, and the formation of metabolism-like networks. We recently initiated a new project which aims to invesigate using the GARD network the phenomenon of synthetic lethality, in which two non-lethal mutations yield a lethal phenotype when combined. Synthetic lethality in real cells is a valuable tool to uncover genetic buffering. Our aim is to shed light on the quantitative aspects of this phenomenon, and to further our understanding of synthetic lethality in present-day cellular networks.

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Acknowledgements

D. Lancet holds the Ralph and Lois Chair in Human Genetics.

This research is supported by NIH grant 5 R01 DC000298-17, the Tauber fund, Inc and the EU grant 043312.

INTERNAL support

Part of the research is supported by the Crown Human Genome Center.