Session 12: Evolutionary Biochemistry

Lectures

L12.1

Next-generation genotype-phenotype mapping

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As large-scale sequencing projects uncover new genetic variation, understanding the consequences of this variation becomes increasingly important. In our lab we use synthetic biology, next-generation sequencing, and computational modelling to study the relationships between gene sequence, structure, and function. We recently mapped the fitness landscape of yeast U3 snoRNA by measuring the growth phenotype of 60,000 random mutants of the gene. Surprisingly, most mutations had no effect on growth in isolation, but negatively influenced growth when combined with additional mutations in the same gene. We studied the role of gene-gene interactions by expressing the mutant library in a collection of strains depleted of U3-interacting proteins, and gene-environment interactions by expressing the mutants in a range of temperature conditions. We identified conditionally deleterious mutants that inhibit growth at high temperatures by destabilizing specific stem-loop structures in the RNA, inhibit growth at low temperature by altering conserved noncanonical basepairs, and inhibit growth in protein-depleted strains by altering putative RNA-protein interaction sites. High-throughput genotype-phenotype mapping is an effective approach to study structure-function relationships in biological macromolecules.

L12.2

Searching for factors underlying slower evolution of abundant proteins

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The negative correlation between the rate of molecular evolution and the level of protein expression is strongly evidenced but poorly understood. Several distinct explanations have been proposed to explain why abundant proteins undergo slower evolution. These include selection against erroneous translation leading to protein instability, selection on protein synthesis efficiency and speed, selection on transcript stability and preservation of proper physical interactions of proteins. All these hypotheses are centered on selection and thus neglect other evolutionary forces. We used genomic sequences of multiple *S. pombe* and *S. cerevisiae* isolates and a population genetics approach to search for signatures left not only by the purifying selection but also by a possible mutational bias. There was no convincing evidence of an unequal mutation rate when intronic regions were scrutinized. The coding sequences, on the contrary, diverged at different rates with the highly expressed ones being more conserved. One possible interpretation, strong selection to keep the costs of abundantly expressed genes low, was tested by us experimentally. Contrary to our expectations, overexpression of rare paralogues did not inflict higher costs than overexpression of abundant ones. A negative result obtained with such an artificial system does not falsify the hypotheses invoking a central role of the purifying selection. It nevertheless illustrates how difficult it will be to develop experimental tests of explanations which are still based solely on sequence comparisons. In sum, on the one hand our work strengthens the evidence for operation of selection because it excludes mutational bias. On the other, it underscores the need to develop new approaches enabling solid empirical explanation of the fascinating regularity of molecular evolution.

L12.3

The paradox of dominance: halving the dose of a gene leaves its function unaffected (usually)

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A remarkable example of genetic robustness is the frequently observed and often virtually complete recessivity of mutations inactivating one of the two alleles residing in a diploid locus. This obviously advantageous property of the cellular organisms does not have to be an evolved adaptation but can be an epiphenomenon of metabolic mechanisms. The latter interpretation is currently preferred and actually much admired as it is based on a simple assumption that the overall metabolic reward per additional unit of a single enzyme is much higher when the enzyme is scarce than when it is abundant. In our research we study the impact of heterozygous mutations on major components of organismal fitness. Applying the budding yeast as a model, we have found that losing a single allele is close to be meaningless for a vast majority of loci under standard growth conditions. This pattern is equally true for genes coding for enzymatic and non-enzymatic proteins as well as for essential and non-essential ones. Furthermore, a very good dominance of functional alleles is observed for the phenotype of survival under deep starvation when the cellular metabolism, and presumably the potential to re-balance it, must be very low. Still more surprisingly, a loss of an entire chromosome, and thus halving the dose of hundreds of genes, does not stop the cell from growing which suggests that that the relatively small effects of single heterozygous loci are further alleviated when co-existing in large numbers. Our results do not dismiss the postulated metabolic mechanism but add the condition that it is omnipresent and extremely efficient. One also may get encouraged to rethink the whole problem.