Московский семинар по биоинформатике

Заседание 328

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Mitochondrial mutational spectrum in vertebrates and cancers:

why glioblastoma is similar to an elephant and melanoma — to a mouse?

The mitochondrial mutational spectrum varies between species while stays relatively stable in different human cancer types, thus puzzling the nature of the mitochondrial mutagens. Here using neutral polymorphism data we reconstructed mitochondrial mutational spectra for more than a thousand of vertebrate species and observed two predominant substitution types: G>A and T>C (mtDNA light chain notation). Comparing the mutational spectra of species with different life-history traits we observed that warm- versus cold- blooded species have an excess of G>A, while long- versus short- lived species have an excess of T>C substitutions. We hypothesized that G>As result from the temperature-sensitive DNA damage, while T>Cs result from chemical (alkali) sensitive DNA damage, which is expected to be stronger in slowly-dividing oocytes (i.e. in long-lived animals). To test additionally the potential association between T>C damage and cell division rate, we used a collection of somatic mtDNA mutations observed in 21 human cancer types (TCGA). In line with our hypothesis we observed, that human cancers, originated from slow-replicating tissues, such as glioblastoma, are more T>C rich as compared to fast-replicating tissues such as melanoma. Moreover, based on intratumor variant allele frequencies we observed decrease in T>C substitutions with time, that can be explained by the increase in cell division rate with cancer progression. Finally, comparing more than 3700 species with sequenced complete mitochondrial genome we confirmed that two principal mutagens: temperature (G>A) and generation time (T>C) shape the nucleotide composition of synonymous fourfold degenerate sites in mtDNA of all Vertebrata. Altogether using data from three different scales (within an organism, within species, between species) we clarify the process of mtDNA mutagenesis and demonstrate that different mtDNA substitutions can inform us about life-history traits of vertebrate species as well as cancer progression in humans.

Рабочий язык семинара – русский

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