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On the Origin of Sexual Reproduction — In Relation to Lifespan —

Yoshiomi Takagi

What is lifespan? — I define the lifespan as the period during which self-identity is maintained. It is identical to the period from sexual reproduction to individual death, or from fertilization to clonal death. Self-identity is guaranteed by the semi-conservative replication of DNA occurring at the cell division or asexual reproduction.

Prokaryotes have no lifespan, because they can maintain their life through continuous cell divisions. Since self-identity maintained by asexual reproduction is broken by sexual reproduction, eukaryotes that undergo sexual reproduction should have lifespan.

Why do eukaryotes undergo sexual reproduction? — The general answer may be that genetic diversification through sexual reproduction boosts adaptability to expand the niche. This story is, however, not true for such organisms as *Paramecium tetraurelia* that undergoes autogamy, a primitive type of sexual reproduction.

Autogamy involves a part of the cytological characteristics of sexual reproduction, i.e., occurrence of meiosis and fertilization, and reformation of soma (macronucleus) from germ (micronucleus). But, autogamy occurs in a single cell irrelevant to sexuality, and it generally produces no genetic diversity. These give reason for some biologists claiming that autogamy should not be regarded as sexual reproduction. However, autogamy that resets the biological time to zero to mark the starting point of the new lifespan is a genuine sexual reproduction according to the definition.

Why was the sexual reproduction of autogamy-type needed for early eukaryotes? — Any hypotheses including symbiosis are incapable of explaining the emergence of the first eukaryote, because symbiosis accompanies the host's endocytotic engulfment of the symbiont, and the endocytosis empowered by cytoskeletons is a characteristic of the eukaryote.

As the primary incidence giving the way to the first eukaryote, I propose a big increase in the genome/cell size through gene duplications. The life strategy for prokaryotes, "make copies as more and faster as possible" is based on their

small genome/cell size; genes of the smaller number are compactly arranged to allow a rapid replication. This strategy gives a survival opportunity for a cell with a rare mutation appearing with a probability of 10^{-6}, because more than a million copies are produced only in 7 hours if the cell divides every 20 minutes. Different jobs are done by different cells. But different jobs can be done by the same cell given the bigger genome size. Major characteristics specific for the eukaryote such as cytoskeletons, intracellular membrane network system and chromosomes housed in the nucleus are all adaptive products for the cell with an increased genome/cell size; cytoskeletons for supporting the bigger construct, membrane network for the lack of the cell surface as well as for the transportation of proteins in a giant sapace, and chromosomes in the nucleus for safety.

How the primitive form of sexual reproduction was: A hypothesis

(1) *Meaning of diploidization and haploidization*

For early eukaryotes with huge haploid genomes, diploidization was a measure of safety to cover harmful recessive mutations with the complement, and haploidization was, in addition to retrieve the undamaged genome, a means to evaluate accumulated mutations because a harmful mutation could work in an advantageous way if combined with other mutations.

(2) *Diploidization and haploidization are common for both sexual and asexual reproductions*

The process of asexual division in the haploid cell is consisted of genomic duplication (Du) and its distribution (Di). This Du-Di module is no less a process than diploidization and haploidization. Diploidization is possible also through the fusion of the haploid cell. But the simpler genomic duplication appears to take the precedence of the haploid cell fusion that requires mechanisms such as cell recognition, cell fusion and dissolution of incompatibility.

(3) *Alternation of asexual cycles between haploid and diploid as primitive sexual reproduction*

If Du is inserted in the division cycle of a haploid cell in such the way of Du-Du-Di-, the division cycle changes from haploid to diploid. If Di is inserted in the division cycle of a diploid cell in such the way of Du-Di-Di-, the division cycle changes from diploid to haploid. The alternation of asexual cycles between haploid and diploid makes sense for early eukaryotes that have an increased genome/cell-size. When the diploid phase is switched to the haploid phase at a proper time, cells are rejuvenated because accumulated mutations are cancelled.

This switch also would bring diversity to some extent because useful mutations could be introduced. Needless to say, diploidization connotes fertilization, and haplodization connotes meiosis.

I also stress that this alternation cycle can easily accept the advanced form of sexual reproduction beginning with the haploid cell fusion. Because the genomic duplication (Du) is equivalent to the genomic cell fusion (Fu) as for diploidization, one of the Du-Di modules of the haploid cell cycle is easily replaced with a Fu-Di motif: it is nothing but the one-step meiosis. If a transition from diploid to haploid occurs in such the way of Fu-Du-Di-Di- instead of Du-Di-Di-, it is nothing but the two-step meiosis.

Taken altogether, the alternation of asexual cycles between diploid and haploid is considered the primitive form of sexual reproduction.

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Cancer as a mini-evolutionary process

Yoh Iwasa

Department of Biology, Kyushu University

Cancers result from the accumulation of inherited and somatic mutations in oncogenes and tumor suppressor genes. Those mutations increase the net reproductive rate of cells. Many aspects of carcinogenesis can be handled as evolutionary processes.

[1] Chromosomal instability (CIN) is a feature of most human cancers. From the mathematical analysis of situations where inactivation of one or two tumor suppressor genes is required for tumorigenesis, we conclude that CIN is likely to emerge first and then enhance the risk of cancer.

[2] Most epithelial tissues have common architecture -- a tissue is organized into numerous small compartments, and within each compartment includes a few stem cells and numerous differentiated cells. This design can slow down delay the onset of cancer.

[3] The ABL tyrosine kinase inhibitor imatinib in chronic myeloid leukemia (CML) serves as a model for molecularly targeted therapy of cancer. We show that a four-compartment model can explain the kinetics of the molecular response to imatinib in a 169-patient data set. We also calculate the probability of developing imatinib resistance mutations.