On the origin of sexual reproduction: a hypothesis

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SUMMARY

Alternation of haploid and diploid is a common feature of the sexual reproduction. Before establishment of such sexual haploidization through meiosis and sexual diploidization through fertilization, I hypothesize the asexual cycle alternating asexual haploidization and asexual diploidization, which deserves to be called primitive sexual reproduction.

Key words: Primitive sexual reproduction, Asexual haploidization, First eukaryote, Genomic enlargement, Safety measure

Essential characteristics of sexual reproduction

Hypotheses on the origin of sexual reproduction have been almost exclusively on the origin of sex or on the advantage of sexuality (Hamilton et al., 1990; Maynard Smith and Szathmáry, 1999; Zimmer, 2009). Here I propose a hypothesis on the origin of sexual reproduction in a completely new context.

General features of sexual reproduction are: (1) sexual differentiation, (2) genetic diversification, (3) rejuvenation (initiation of new generation), (4) meiosis and fertilization, and (5) reconstruction of *soma* from *germ*.

I have long engaged in biology of aging and lifespan in the ciliate protozoan *Paramecium* (Takagi, 1988, 1999) and wondered why some species of *Paramecium* undergo autogamy as a means to alternate generations. Autogamy is a specific form of sexual reproduction including the above-mentioned (3)~(5), but lacks (1) and (2). From the evolutionary viewpoint, autogamy may not be regarded as sexual reproduction because of the lack of (1) and (2), but from the viewpoint of development, autogamy is regarded as sexual reproduction because it satisfies (3)~(5). In fact, autogamy played a historical role of denying the assertion of immortality of *P. aurelia* by revealing the overlooked autogamy, and contributed to establish the concept of clonal life cycle: it begins with sexual reproduction and consists of immaturity, maturity and senescence terminating with clonal death (Sonneborn, 1954). Contrary to autogamy, bacterial conjugation satisfies (1) and (2) but lacks (3)~(5). It is likely, therefore, that (3)~(5) rather than (1) and (2) are the more fundamental features of the genuine sexual reproduction.

Although the features mentioned above are characteristic to the sexual reproduction, (5) is seen also during the asexual reproduction: for ex-

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ample, both *soma* and *germ* are formed in an asexual aggregate of *Dictyostelium* and in colonial phytomonads such as *Eudorina*, *Pandorina* and *Volvox*; the somatic macronucleus is rebuilt from the germinal micronucleus at every cell division in *Loxodes* (Grell, 1973). If fertilization and meiosis are viewed respectively as diploidization (n→2n) and haploidization (2n→n), it is no less a process than the asexual reproduction of a haploid cell. The idea that the process of sexual and asexual reproductions is not necessarily discriminated strictly but somehow related to each other led me to postulate that the primitive form of sexual reproduction might have emerged directly from asexual reproduction.

As shown in Fig. 1, the asexual reproduction of a haploid cell consists of duplication (n→2n) and distribution (2n→n) of the genome, and the simplest form of sexual reproduction comprising one-step meiosis consists of cell fusion (fertilization) (n→2n) and segregation (meiosis) (2n→n). Although n→2n and 2n→n in Fig. 1 are diploidization and haploidization, respectively, but they are only temporary, not real diploidization and haploidization.

In Fig. 2, asexually reproducing cycles consisting of genomic duplication and distribution are shown as du and di for the haploid cell, and Du and Di for the diploid cell. Real diploidization (n→2n) takes place if duplication doubled in the haploid cycle (du-Du), and real haploidization (2n→n) takes place if distribution doubled in the diploid cycle (Di-di). To distinguish the diploidization through the du-Du pathway from the sexual diploidization through fertilization, I here call it asexual diploidization. Similarly, to distinguish the haploidization through the Di-di pathway from the sexual haploidization through meiosis, I here call it asexual haploidization.

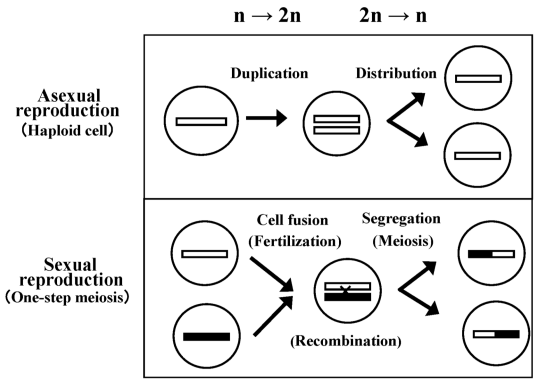

Fig. 1. Diploidization and haploidization are common in both asexual and sexual reproductions. Asexual reproduction of a haploid cell consists of genomic duplication and distribution, and sexual reproduction of a one-step meiosis consists of cell fusion and segregation. Modified from Takagi (2009).

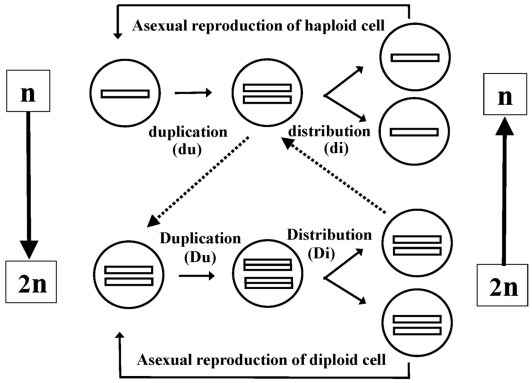

Fig. 2. Diploidization and haploidization in asexual reproductions. Diploidization occurs if duplication is doubled (du-Du) in the haploid cycle, and haploidization occurs if distribution is doubled (Di-di) in the diploid cycle. Modified from Takagi (2009).

How the first eukaryote emerged from the prokaryote?

It still remains unknown how the first eukaryote emerged. Any hypotheses including endosymbiosis cannot answer this question, because they premise the existence of the eukaryote: endocytosis depending on the ability of the host to incorporate the symbiont needs cytoskeletons that only the eukaryote possesses. Even the excellent hydrogen hypothesis (Martin and Müller, 1998) is not exceptional: it explains the origin of the eukaryotic metabolic system, not the origin of the eukaryote itself.

Genomic and cellular enlargement are supposed to be the primary incidence giving the way

to the first eukaryote. Genomic enlargement through whole-genome or partial-genome duplications and horizontal transfers makes many new tasks possible by introducing new proteins. Cellular enlargement occurs concomitantly with the genomic enlargement (Alberts et al., 2002; Storchová et al., 2006), although the mechanism to scale the size is poorly understood. A tenfold increase in cell diameter from 1 to 10 microns on average results in hundredfold increase in cell surface area and thousandfold increase in cell volume. Among the newly introduced proteins, actins and tubulins seem to be earliest because their genetic rudiments are found in prokaryotes as *ftsA* and *ftsZ*, respectively (Pilhofer et al., 2007), and are especially important because they can function as the cytoskeleton. It supports the enlarged cell structure. It makes endocytosis possible. It contributes to establish the internal membrane system, which is useful for compensating the lack of the cell surface, for transporting proteins in an enlarged cell, and for constructing the nuclear membrane to store the enlarged genome safely.

However, the enlarged genome causes a new problem, because it requires elongated time for its duplication. Elongated time for duplication increases the opportunity of harmful mutations. Safety measures for enlarged genome are needed. I propose two safety measures. One is the differentiation of *germ* and *soma*, and the other is the asexual diploidization of the genome (n→2n).

Evolution of sexual reproduction

The du-di module of the asexual reproduction cycle of a haploid cell is capable of repeating infinitely if the genome size is small like bacteria, because the division rate is rapid enough to overcome a harmful mutation; more than a million cells would be produced for 7 hours if a cell divided exponentially every 20 minutes ($2^{21}>10^6$).

The haploid eukaryotic cells with enlarged genome have to undergo asexual diploidization through the Di-di pathway to avoid fatal mutations; the loss of function of a gene by mutation can be masked by the complementary gene. However, the Du-Di module of the diploid cell division could not repeat indefinitely, because the function of the diploidy to mask the harmful recessive mutations would someday become not to work anymore. Since all of the haploidal genes could be expressed, haploidization would result in extinction if it occurred too late, or would result in rejuvenation (restoration to the original state) if it occurred *before* the accumulation of mutations became serious. The timing of the asexual haploidization through the Di-di pathway would play a role of inspecting the usefulness of the accumulated mutations. A new genotype could emerge if some mutations, each being hazardous, were beneficial when worked together. Thus the periodical repeats of the asexual diploidization and the asexual haploidization resemble the sexual reproduction in that they cause rejuvenation and genetic variation to some extent. I name this process "primitive sexual reproduction" (Fig. 3).

The other reasoning to insist that the cycle of the asexual diploidization and the asexual haploidization is suitable to be called "primitive sexual reproduction" is that this cycle can accept the diploidization achieved by cell fusion. This may be the original form of sexual reproduction-I including sexual differentiation and one-step meiosis

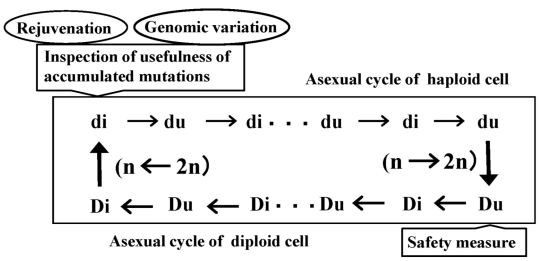

Fig. 3. Primitive sexual reproduction composing alternation of asexual cycles between haploidy and diploidy. Asexual diploidization through the du-Du pathway is a safety measure. Asexual haploidization through the Di-di pathway is a means to inspect the usefulness of accumulated mutations, resulting in rejuvenation and genetic variation to some extent. Modified from Takagi (2009).

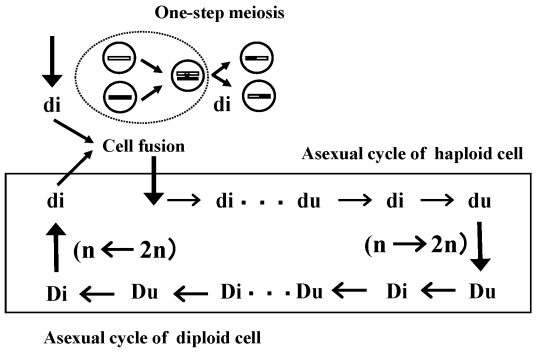

Fig. 4. The asexual alternation cycle between haploid and diploid can accept the sexual diploidization through cell fusion so that the sexual reproduction-I including one step-meiosis is established. Modified from Takagi (2009).

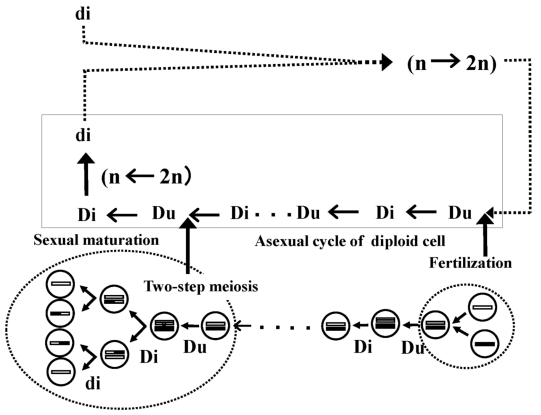

Fig. 5. The primitive sexual reproduction missing the haploid cycle contributes to establish the sexual reproduction-II comprising haploidization through two-step meiosis and diploidization through fertilization. Modified from Takagi (2009).

accompanying recombination (Fig. 4). Also, the primitive sexual reproduction missing the haploid cycle can accept the sexual reproduction-II consisting of diploidization through fertilization and haploidization through two-step meiosis (Fig. 5). The timing of meiosis appears to have been programmed as the timing of sexual maturation.

Because pairing of the homologous chromosomes is involved in meiosis and it facilitates recombinational DNA repair, any form of sexual reproduction including meiosis and fertilization may be advantageous. This appears to be the reason why autogamy has survived without benefits of genetic variation through sexuality.

Consequently the sequence of evolution of the sexual reproduction can be viewed as follows. The asexual reproduction of early eukaryotes that evolved the enlarged genome/cell size cannot be immortal; they become diploid to avoid harmful mutations and periodically become haploid to avoid senescence due to accumulated mutations. The asexual alternation cycle between haploid and diploid resulting from the Di-di and du-Du pathways has the advantage of yielding rejuvenation and genetic variation by checking the usefulness of accumulated mutations. The cycle of the asexual diploidization and the asexual haploidization is, therefore, worth calling primitive sexual reproduction although no sexuality is involved. When sexual differentiation, gametic fusion and recombination become available, the sexual reproduction-I that contains one-step meiosis, and then the sexual reproduction-II that contains two-step meiosis have been connected to the preexisting cycle of the primitive sexual reproduction.

Test for Validity of the hypothesis

Evolution of the ploidy-based life cycle is directed from the exclusive haploidy to the diploidy dominancy via the alternation of haploidy and diploidy (Fig. 6). The alternation of haploidy and diploidy observed in ferns, mosses, brown alga etc. is deemed to be driven by diploidization through fertilization and haploidization through meiosis. However, the hypothesis of the primitive sexual reproduction predicts an alternative cycle of the asexual diploidization through the du-Du pathway (n→2n) and asexual haploidization through the Di-di pathway (2n→n) in these organisms. This is worth examining.

It is a puzzling question why some unicellular eukaryotes such as *Amoeba* and *Euglena* can asexually grow infinitely. Cells with infinite capacity to divide are exemplified in daughter cells of budding yeasts (Liu et al., 2010), embryonic stem cells, cancer cells and so on. But the possibility that *Amoeba* and *Euglena* are undergoing the

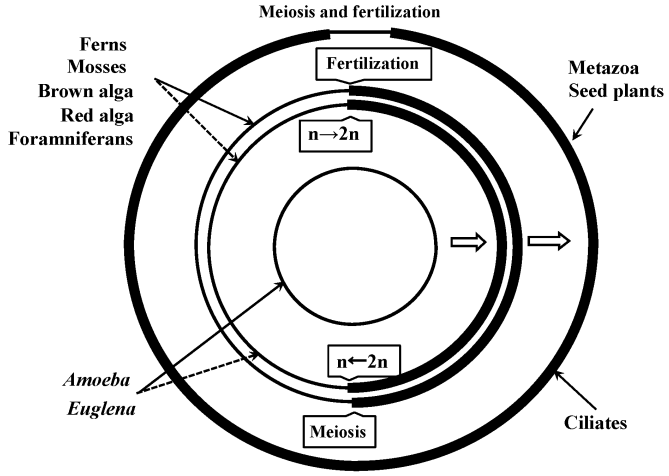

Fig. 6. The ploidy-based life cycles are usually divided into three groups; 1) exclusively n, 2) alternation of n and 2n, and 3) 2n dominancy. Although the alternation of n and 2n is believed to be caused by fertilization and meiosis, I hypothesize the alternation of asexual diploidization (n→2n) and asexual haploidization (2n→n) according to the manner shown in Fig. 2. Dotted lines indicate the possible alternative to be examined. Modified from Takagi (2009).

primitive sexual reproduction with the cycle of asexual diploidization and asexual haploidization appears plausible and amenable to experimental test.

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