Global Journal of Science Frontier Research
Biological Sciences
Volume 12 Issue 8 Version 1.0 Year 2012
Type : Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4626 & Print ISSN: 0975-5896

On the Origin of Sex

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Abstract - The problem of sex origin of eukaryotes in the process of evolution still has not settled. Existing theories and hypothesizes mainly concern the maintenance and biological reasonability of sexual mode of replication. Their theoretic foundation is based on Darwin's and Mendel's ideas that sex was originated due to natural selection and genes. Another model is proposed – sex of eukaryotes was originated as a result of long-term evolution of non-coding DNAs in a genome at one of the branches of prokaryotes. Non-coding DNAs accumulation and evolution in prokaryotes' ring chromosomes eventually led to emergence of mitotic chromosomes and mitotic way of cell division. Sex and sexual replication became possible since that time when modified variant of mitosis – meiosis – have originated. Separate stages of the proposed model may be exposed to experimental check.

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GJSFR-C Classification : *FOR Code: 060403, 940113*

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I. Introduction

The evolution and maintenance of sexual replication is one of the central questions in modern evolutionary biology (Bell 1982; Williams 1975; Maynard-Smith 1978; Michod 1995; Hurst and Peck 1996). The evolution of sex contains two related, yet distinct, themes: its origin and its maintenance. Reasons for origins of sex are not necessarily the same as for the maintenance of sex (Birdsell and Wills 2003). Since the hypotheses for the origins of sex are difficult to test experimentally, most current work has been focused on the maintenance of sexual reproduction.

There are many contested theories for what made organisms evolve in a pattern which is less efficient for population growth, but no sure-fire answers (Maynard Smith and Szathmáry 1999). Several explanations have been suggested to explain how sexual reproduction is maintained in a vast array of different living organisms (Bell 2001; 2006; Bernstein et al. 1989; Hamilton et al. 1990; Michod 1995; Agrawal and Chasnov 2001; Cavalier-Smith 2002; Otto 2003; Dolgin and Otto 2003; Hörandl 2009). Yet, as these theories valiantly attempt to explain why sex exists now, they do not explain the origin of sex (Harrub and Thompson 2003). We have no intention to make comprehensive analysis of works devoted to maintenance of sexual reproduction.

Most theories of the origin of sex include either facultative or obligate sexual cycles (Crow 1994; Dacks and Roger 1999). Simply stated, organisms that have facultative sexual cycles can reproduce sexually or asexually, whereas organisms that reproduce in an obligate sexual cycle are forced to reproduce sexually or not at all. Dacks and Roger (1999), for instance, suppose that facultative sex was most likely the sexual cycle which developed first, at the origin of sex and the arrival of obligate sex may have something to do with the evolution of increasingly complex multi-cellular organisms. Nevertheless, this article dodges the question of why mammals don't reproduce through a facultative sexual cycle.

The predominant theory for the origin of sex has always been the benefits of DNA repair. However using DNA repair as the strongest argument for sex is problematic as it gives asexual diploids an equal footing with sexual organisms in that regard. DNA repair in and of itself does not provide a satisfactory explanation for the necessity of sex, only a strong argument for diploidy (Harrub and Thompson 2003).

According to Rothschild (1999) the origin of sex is that UV radiation stirred evolution in such a way as to make sex advantageous. UV radiation is a mutagen, and exposure thereto causes genes to mutate in ways that may or may not be good for the organism. Sex splits the homologous pairs of chromosomes and allows them to recombine in haploidy before they are passed on, so that daughter cells receive different combinations of beneficial and harmful mutations.

Another theory is that sex originated as a way to protect cells from infection by plasmids and other parasitic bodies (Sterrer 2002). According to this theory, cells that come to contain parasites through phagocytosis or another method of ingestion will co-evolve with the parasites, allowing the primary cell protection against further infection and the secondary body assurance of reproduction. Sex must emerge to keep this relationship stable, preventing the parasite from taking over the host by breaking up the symbiont genomes and asserting host control over replication.

It is one thing to develop a theory or hypothesis to explain something that already exists, but it is entirely another to develop a theory or hypothesis to explain why that something (in this case, sex) does exist. In his book, The Masterpiece of Nature: The Evolution of Genetics and Sexuality, G. Bell (1982) described: 'Sex is the queen of problems in evolutionary biology. Perhaps no other natural phenomenon has aroused so much interest; certainly none has sowed as much confusion. The insights of Darwin and Mendel, which have illuminated so many mysteries, have so far failed to

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shed more than a dim and wavering light on the central mystery of sexuality, emphasizing its obscurity by its very isolation'.

Indeed it is hard to believe that having impressive breakthrough in modern genetics and molecular biology the reasons and mechanisms of sex origin are still unknown. This probably has to do with the fact that in the basis of all hypothesizes and theories on sex biology lies idea on all-powered role of natural selection and genes in eukaryotic organisms' evolution. Although they help to explain reasonably and justify such widespread propagation of sexual reproduction in the world of eukaryotes; nevertheless, these approaches had little help in the development of theories and hypothesizes explaining sex origin. More over they were not able to show ways of their experimental check. As Ridley (2010) begrudgingly admitted: 'Sex is not used simply for want of an alternative. Nothing, in an evolutionary sense, forces organisms to reproduce sexually'.

II. Theoretic Modeling

Our approach is relies on the non-coding DNAs (ncDNAs) evolution. Hypothesis is based on suppositions that: a) sex was originated at one of the branches of prokaryotes, in genome of which ncDNAs were accumulated and then evolved; b) the beginning of sex emergence is related to linear chromosomes emergence from a "bare" ring chromosome which due to ncDNAs presence in its composition has acquired nucleosomal structure (mitotic chromosome); c) on the basis of various types of ncDNAs centromeres, telomeres and kinetochores originated; they help chromatids of replicated mitotic chromosomes keep together or on the contrary split on two daughter cells in the process of cells division (mitosis); d) sexual replication became possible due to emergence of modified mitosis – meiosis (Ibraimov 2003; 2004; 2008; 2009; 2010).

It is commonly known that eukaryotic organisms have meiotic sex. Since meiosis is modified mitosis it is obvious that sex origin directly connected with mitotic chromosomes emergence. Unfortunately we were not succeeded in finding in literature any hypothesis explaining origin of mitotic chromosomes (Ibraimov 2009). Perhaps this is due to the fact that it is impossible to explain the origin of mitotic chromosomes by simple increase of genes number in prokaryotes chromosomes and by their further multiplication. Note that centromeres, telomeres and kinetochores consist of high repetitive DNA sequences and do not have structural genes which testify that they were originated from ncDNAs. As for the amount of coding DNAs in human's chromosomes they constitute less than 2% of total DNA of his genome.

Earlier, we presented data that probably sex and sexual reproduction of eukaryotic organisms are the result of the long evolution of ncDNAs, which step by step led to the origin of mitotic chromosome, mitosis, meiosis, sex determination and differentiation mechanisms (Ibraimov 2008; 2009; 2010). As we suppose, so complicated evolutionary changes were the consequence of an amazing ability of ncDNAs to provide the very different forms of DNA organization: from nucleosomes to mitotic chromosome body. Apparently, the basis of the ncDNAs' potential for different forms of self-organization is formed by their common capability of mutual nonspecific attraction – "stickiness", – which is connected to the presence of short repeated sequences of nucleotides in them.

Though, the modes of DNA packaging into interphase cells do not influence on the contents of the genetic information of a nuclear genome, nevertheless, they are essential factors in a vital activity of not only single cells (Ibraimov 2003), but of the whole organism (Ibraimov 2004; 2007; 2011). Hereby, we do not assert that ncDNAs are capable of specific reactions. Their nonspecific molecular composition does not allow this. We just want to say that nonspecific reactions can serve as the basis for the creation of specific forms of response to different environmental changes, and this circumstance can be related to the sex origin of eukaryotic organisms.

Formation of nucleosomes is the first step in DNA packaging into a minor metaphase structure. We believe that it is connected with the availability in eukaryotic genomes intervening sequences of ncDNAs, which has the ability to attach to histones (by DNA-protein recognition mechanisms). Lack of nucleosomes in prokaryotes in spite of the availability in the cells the histone-like proteins is possibly attributed to this important reason. In other words for formation of nucleosomes, chromomeres, centromeres, telomeres, kinetochores and chromosome bands it is necessary that in the DNAs should be nucleotide sequences with anchorage dependence features, due to which they will be inside the nucleus (in more detail see Ibraimov 2003, 2004; 2009; 2011).

Since meiosis represents a special type of mitosis, and mitosis is not possible without mitotic chromosome, then the solving of the sex origin problem is probably to be started with the mitotic chromosome origin examination. The following model of the origin of mitotic chromosomes and mitosis seems highly probable (Fig. 1).

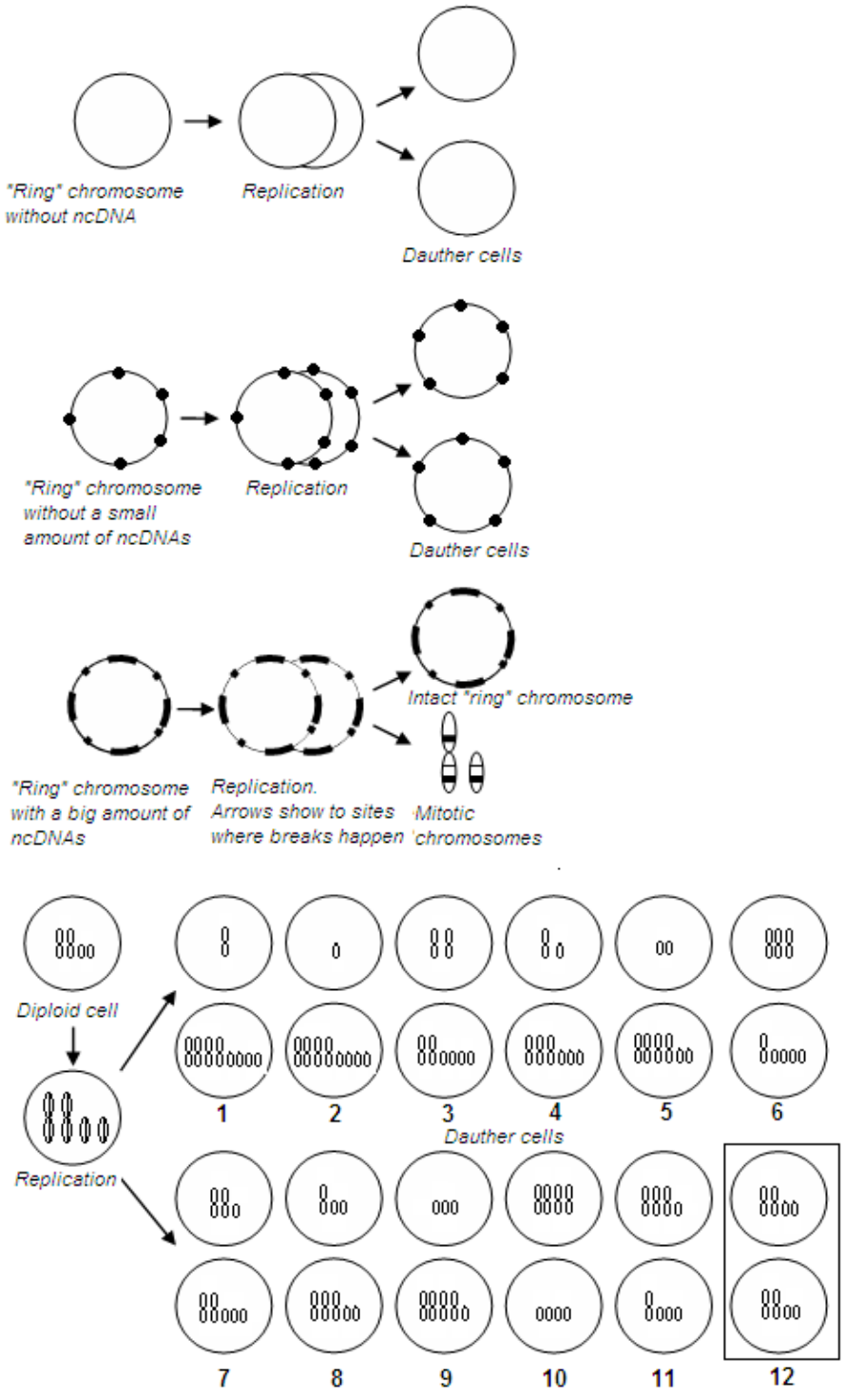

Figure 1 : Origin of mitotic chromosomes and mitosis.

At a certain stage of "bare" ring chromosome evolution of some lines of prokaryotes the sites with ncDNAs started to emerge (Ibraimov 2003, 2004). This has led to: a) the increase of the length of such chromosomes; b) the delay of separation of already replicated DNAs because of the mutual attraction of chromosome sections with ncDNAs. To divide such ring chromosomes, at the least they need to be shortened to

the maximum. This can happen only owing to ncDNAs according to the principle, which has a place at mitotic prophase stage. When the thickness of such cylinder reaches the certain limit, "sister ring chromosomes" will start to repulse from each other and finally will divide in two.

In the cases when this division mode becomes difficult, ring chromosomes break. Perhaps, more favorable outcomes expected those ring chromosomes where breaks happened in the sections with the considerable amount of ncDNAs. In due course, these ends could be transformed into centromeres, telomeres and kinetochores (Lima-de-Faria 1983). Thus, could be originated the eukaryote genetic linkage groups in the form of meta-, acro- or telocentric chromosomes. There appeared possibilities for the endless combination of genes in the population of eukaryote organisms through meiosis, having opened yet unknown prospects for their further development.

Major problems happen at attempt to explain transformation of mitosis into meiosis. As it is known, meiotic division having much in common with mitosis, nevertheless has a number of peculiar properties: at mitosis centromeres divide and sister chromosomes, connected to them, move towards the opposite poles. At meiotic division paired centromeres do not divide, but each one moves separately from others, carrying one chromosome from each pair to the opposite poles.

It ought to be admitted that we know almost nothing about the mechanism of chromosome pairing in meiosis, due to which homologues appear to be so tightly brought together that there can start synapsis with the formation of synaptonemal complex. We assume that during temperature reduction the slow down of heterochromatin (one of the types of ncDNAs) compactization takes place, and as a consequence formation of metaphase chromosome body detains, thus giving time to prophase homologous chromosomes to "know" each other (Ibraimov 2009).

As we assume, ncDNAs in chromosome bands play the important role in both mutual attraction and repulsion of chromosomes. In mitosis, for instance, sister chromatids separate without the help of mitotic spindles having the dividing cells treated with colchicine ("C-mitosis"). Apparently, the separation of sister chromatids in "C-mitosis" is also caused by a complete fusion of chromomeres and chromosome bands along the chromosome into one homogeneous body at the end of metaphase. When chromatids turn into short "thick" cylindrical bodies, the contact area between sister chromatids becomes so small that they are not in the position to remain tied together in the "boiling" cytoplasm. Here, the attractive forces between chromatids, even if remained, depend mainly on the quantity and the quality of repeated DNAs.

Hence, at the stage of the cell division, ncDNAs derivatives participate: 1) in shortening and dense packaging of the chromatin fibres for formation of the body of the metaphase chromosomes; 2) in keeping the sister chromatids up to the end of anaphase together; 3) in repulsion of sister chromatids from each other at the stage of anaphase; and 4) it gives chromosomes the necessary strength and flexibility so that they can pass the mitotic cycle.

Could certain stages of sex origin be experimentally checked? Fortunately, the certain stages of the supposed sex origin account can be checked experimentally. In principle the proposed model of mitotic chromosome origin can be considered to have been already checked. Hereof testify the experiments on generation of artificial chromosomes for use in gene therapy. For example, it is demonstrated that the short arm of human acrocentric chromosomes, which contains tandemly repeated ribosomal DNA genes and different satDNA sequences, is an optimal chromosomal region for inducing *de novo* chromosome formation (Hadlaczky 2001).

Evidently, with sophistication of cell cultivation, cloning and *in vitro* fertilization methods there has come the time for experiments on carrying out meiotic division of somatic cells – *in vitro* meiosis (IVM). The main point of IVM is to expose somatic cells to meiotic division in order to receive haploid cells ("gametes") for *in vitro* fertilization (IVF). As we believe there already exist methodical and theoretical prerequisites for realization of IVM:

a) Availability of culture of Sertoli cells;
b) Techniques of germ cell transplantation;
c) The demonstration that spermatogenesis can be successfully carried out in a testis of different species;
d) Fertilization has been achieved even when sperm motility and morphology is poor. Sperm recovered from the epididymis or from the testis can also be used in introcytoplasmatic sperm injection. For men whose ejaculates contain even a few sperm, in which a single sperm is injected into the cytoplasm of the egg, has proved unexpectedly successful, giving pregnancy rate equaling that normal IFV;
e) There have been no published reports of primordial germ cells entering meiosis *in vitro*, when maintained as isolated cells. However, if mouse germ cells do indeed have a cell-autonomous tendency to enter meiosis irrespective of the urogenital ridge, then theoretically somatic cells can also enter meiosis in an environment of a tissue or an organ culture system;
f) It has managed to show that the diploid spermatogonia progressing *in vitro* to haploid spermatidis involves coculture with an immortalized

Sertoli cell line (in more detail see Rassoulzadegan et al. 1993; McLaren 1998; McLaren and Southee 1997).

Hence, we believe that inasmuch as all somatic cells are pluripotent, then at least some of them (e.g. less specialized cells, like fibroblasts) can experience the meiotic division, if the respective *in vitro* conditions to be created. Schematically, for realization of such experiments it is required to:

a) Prepare a culture of fibroblast cells from a donor as a source material for receiving haploid cells – "gametes";
b) Have a culture of Sertoli cells as supporting tissue to nourish and regulate the development of somatic cells from diploid to haploid stages;
c) Prolong the mitotic prophase stage as much as it is required to make prophase homologous chromosomes conjugate as they do during the ordinary spermatogenesis. For that, carry out IVM at a temperature 2-3 °C lower than the core temperature of a corresponding type of mammals;
d) Separate donor cells with haploid sets of chromosomes;
e) Use nuclei of such "gametes" for further IVF or intracytoplasmic injection.

III. Discussion

Our hypothesis on possible mechanisms of sex origin is close to well-known works of Margulis and Sagan (1984; 1986) as we also believe that organization of the genome in chromosomes and the evolution of mitosis are important. These authors developed a comprehensive hypothesis for the evolution of sexual reproduction in the context of the endosymbiotic origin of eukaryotic cells. Organization of the nuclear genome in chromosomes is coupled with the evolution of mitosis. Starvation and cannibalism are seen as the main triggers for merging of cells and the evolution of outcrossing. Meiosis evolved out of mitosis through tardy kinetochores, consequently segregating chromosomes rather than chromatids. Meiosis was maintained as a mechanism to sort better the genetic diversity that has resulted from the merging of genomes. These two evolutionists have admitted that meiosis is critical for sexual reproduction. However our point of view on cell nucleus and mitotic chromosome origin substantially differ from the hypothesis on endosymbiotic origin of eukaryotic cells (see Ibraimov 2003; 2004).

As it seen from Fig.1 at the process of disjunction only two pairs of mitotic chromosomes into two daughter cells out of twelve possible combinations only one is compatible with life. For three pairs of mitotic chromosomes only one out of 44 possible combinations is viable, etc. If the situation was similar to what we think than it is not hard to imagine why in the process of evolution sex and sexual reproduction originated so late. Margulis and Sagan (1997), for instance, suppose that meiotic sex evolved '520 million years ago'. At that major problems perhaps were connected with the emergence of mitotic way of division than with emergence of mitotic chromosomes.

We certainly do not say that we were able to unravel the mystery of the origin of sex. Another hypothesizes will occur and they may be exposed to experimental check. We only would like to say that it is too early to despair and give up by quoting such lines of biologists: 'But we would suggest that there is no naturalistic explanation at all for the origin or maintenance of sex. The highly complex and intricate manner in which the human body reproduces offspring is not a matter of mere chance or a "lucky role of the dice." Rather, it is the product of an intelligent Creator' (Harrub and Thompson 2003).

IV. Acknowledgements

I apologize to everybody who has published on this topic but could not be cited because of the limits of space in a journal paper.

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A. Prokaryotic cell with "bare" ring chromosome without ncDNAs disjunction into two parts after replication.
B. Small amount of ncDNAs in ring chromosomes might not affect on their disjunction into two daughter cells.
C. In some cases replicated ring chromosomes might have difficulties with disjunction into daughter cells due to "sticking" of parts with a big amount of ncDNAs. For successful disjunction of such ring a chromosomes breaking on separate pieces is demanded. As is known parts of chromosomes with ncDNA are inclined to ruptures and complicated structural transformations that probably, eventually transformed into centromeres, telomeres and kinetochores (Lima-de-Faria 1983).
D. In the absence of due mechanism of mitotic division, replicated chromosomes to divert into daughter cells in different number and combinations. Cells, for instance, containing only two pairs of mitotic chromosomes are able to produce daughter cells with twelve different combinations of chromosomes where only one of which is viable.