Review



# Origin and Adaptive Function of Genetic Recombination in Sexual Reproduction

Carol Bernstein [*,†] and Harris Bernstein [†]

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*Review*

# Origin and Adaptive Function of Genetic Recombination in Sexual Reproduction

**Carol Bernstein *,† and Harris Bernstein †**

Department of Cellular and Molecular Medicine, College of Medicine, University of Arizona, Tucson, Arizona, USA

* Correspondence: bernstein324@yahoo.com Tel: +1-520-241-5260

† Retired.

**Abstract**

Genetic recombination occurs in a wide range of organisms, from simple RNA viruses to mammals and plants with DNA genomes. In sexual reproduction, two parental genomes come together and undergo recombination, producing an offspring genome that has a combination of information from the two parental genomes. Genome recombination occurring during sexual reproduction can involve one of several mechanisms, including copy-choice recombination as well as breakage and exchange. Across widely different organisms, recombination by any mechanism is generally promoted by factors that damage the genetic material. In organisms such as bacteriophage and *Paramecium*, it was experimentally demonstrated that recombinational repair during sexual reproduction can overcome otherwise deleterious or lethal damages. For many decades it has been recognized that there are larger biological costs of sexual reproduction than for asexual reproduction. Much effort has been invested in theories assuming that genetic variation, due to recombination, is the main adaptive benefit of sexual reproduction. Such a benefit was considered to compensate for the large costs of sexual reproduction. However, it has been difficult to find a strong consistent benefit for variation. Repair of lethal damages, involving recombiantional interactions of two different genomes, now appears to be the major selective factor underlying sexual reproduction in organisms both simple and complex.

**Keywords:** DNA damage; DNA repair; sexual reproduction; recombination; breakage and exchange; synthesis dependent strand annealing

## 1. Origin of Sexual Reproduction as Recombination Between Homologous RNA Genomes

Asexual reproduction can be defined as a process by which a single genome can reproduce itself and give rise to progeny with the same genetic sequence as the parent (a clone).

Sexual reproduction can be defined as a process in which two parental genomes participate in producing an offspring genome that has a combination of information from the two parental genomes.

As noted by Haynes and Kunz [1], "DNA is composed of rather ordinary molecular subunits,

and certainly is not endowed with any peculiar kind of physicochemical stability... Its very chemical vulgarity makes it prey to all the horrors and misfortune that might befall any such molecule in a warm aqueous medium... It is also subject to damages from highly reactive free radicals, peroxides, singlet oxygen, reducing agents, etc., as well as low but sometimes significant exposures to ionizing and ultraviolet radiations." This also applies to RNA when it is employed as the genetic material. DNA or RNA genomes are both subject to damage and such damaged genomes would require a mechanism to repair the damage.

The age of the Earth is 4.54 billion years, and it appears that an early life form consisting of RNA molecules that can replicate [2] arose arose roughly a billion years later [3]. These life forms were

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thought to have arisen about 3.8 to 4.2 billion years ago [4,5]. This time period was called the RNA world.

A first requirement for an RNA life form is replication of its genome. For replication in the early RNA World, an RNA genome must have been able to form a ribozyme (an RNA molecule with catalytic activity) that could replicate RNA [6]. Thus, progeny RNA molecules could be produced. But, at the same time, there is a need to repair damages to the RNA genomes. Thus genetic repair must have emerged soon after the first RNA genomes were formed. Genome repair in the RNA World was probably similar to genome repair of single-stranded RNA viruses in the current day. This repair would operate by a copy-choice recombination model. This is where an RNA dependent RNA polymerase (RdRp) (formed by a ribozyme) would replicate along one strand of an RNA polynucleotide genome and then encounter a damage that could not be copied. At this point, the RdRp would switch to a nearby polynucleotide RNA genome to continue replication. If the RdRp were to encounter another damage, the RdRp could switch back to the original polynucleotide RNA genome and continue copying there. As reviewed by Barr and Fearns [7], this type of copy choice repair mechanism appears to occur in a number of extant single-strand viruses and can be extremely efficient. This type of recombination avoids damage rather than directly repairing damage. In early RNA replicators, recombinational repair may have been central to the sexual reproduction process.

## 2. Genetic Recombination in RNA Viruses, an Adaptation for RNA Repair

One of the single strand viruses for which copy choice recombinational repair was reported was the retrovirus designated “spleen necrosis virus” [8]. The authors stated “when the viral RNA genomes are damaged, intermolecular transfer (copy choice strand switching) of minus strand DNA occurs.” Similarly, in polio virus, copy choice recombinational repair was shown to occur at breaks in the RNA genome [9]. Barr and Fearns [7] reviewed the evidence for copy choice recombinational repair in six RNA viruses: bacteriophage MS2, mouse hepatitus virus, bacteriophage Qβ, Sindbis virus, cowpea chlorotic mottle virus and bunyavirus. In all six viruses the copy choice recombinational repair was carried out by the viral RNA dependent RNA polymerase (RdRp) and the recombinational event occurred co-transcriptionally during copying the RNA template. In the RNA viruses described here, there appears to be sexual reproduction accompanied by recombinational repair.

## 3. Genetic Recombination in DNA Viruses, an Adaptation for DNA Repair

Bacteriophage are viruses that infect bacteria. A single bacteriophage can infect a host bacterium and reproduce asexually. A bacteriophage with lethal damage in its DNA genome may still be able to infect a host bacterial cell, but no viable progeny viruses will be produced. However, when two lethally damaged viruses infect the same cell, the DNA genomes of the two viruses may interact in such a way as to produce viable progeny. This phenomenon, referred to as multiplicity reactivation, is effective against a wide array of DNA damages [10]. Figure 1 indicates the great increase in survival of bacteriophage with DNA damages when infection occurs in multiply infected cells compared to infection within singly infected cells.

The model virus in which multiplicity reactivation has been most well studied is bacteriophage T4, although it also has been demonstrated to occur in numerous other bacteriophage as well [10]. On the basis of these studies it was concluded that multiplicity reactivation occurs by a recombinational repair process that involves interaction of at least two viral genomes within the same cell [10,11]. Multiplicity reactivation is a form of sexual reproduction since it involves two homologous genomes from separate bacteriophage that come together in such a manner that recombinational repair occurs between them to form a new genome, and this new genome upon replication can initiate a new lineage. Bacteriophage thus engage in sporadic sexual reproduction which is of benefit when DNA damage is present in an initially infecting phage.

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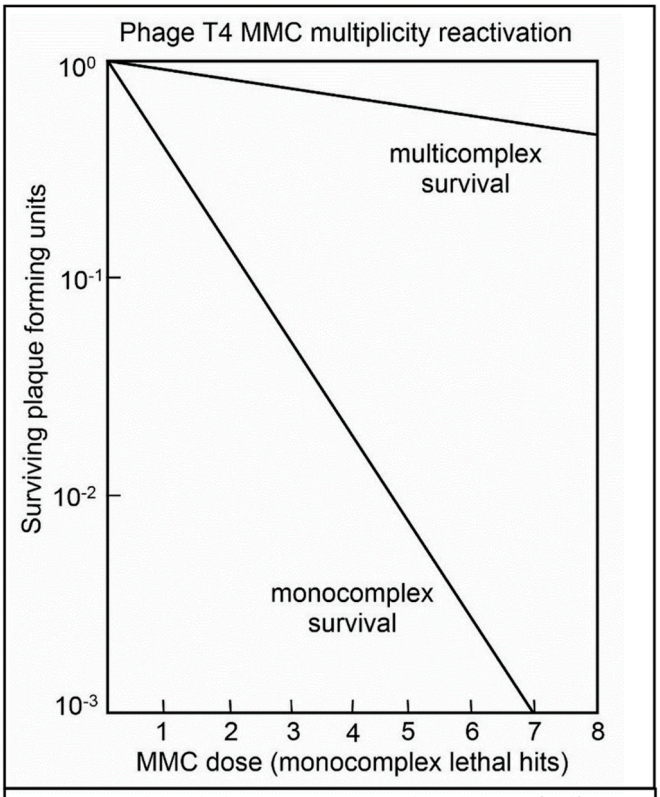


**Figure 1. Multiplicity reactivation.** Bacteriophage T4 were treated with increasing doses of mitomycin C (MMC), a DNA cross-linking agent. Multiplicity reactivation (greatly increased survival) is shown for bacteriophage-plaque forming ability of *E. coli* cells multiply-infected with phage T4 compared to plaque-forming ability of singly-infected cells.
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A multiplicity reactivation experiment was carried out with UV-irradiated phage where survival of each parental type in single infections was at the level of $10^{-3}$ [12]. One parental genome carried 8 conditional lethal mutations and the second parental genome carried 24 conditional lethal mutations, and the infections occurred on a permissive host. With irradiation followed by double-infection multiplicity reactivation, recombination frequencies between mutations increased about 4-fold. Thus most progeny phage were recombinants. However, surprisingly, in 34 single bursts, 29 of them had one or more progeny phage of the genotype of one or the other parent, with no recombination. We could interpret these findings to indicate that most progeny phage are the result of increased recombination, after irradiation, by a breakage and exchange mechanism. But also some recombination, after irradiation, occurs by a copy-choice mechanism, leaving a highly marked parental genome without recombination of markers.

Multiplicity reactivation has been reported to occur in numerous pathogenic viruses including herpes simplex virus, influenza virus, adenovirus, simian virus 40, vaccinia virus, reovirus and polio virus [13]. As one example, when herpes simplex viruses are exposed to doses of a DNA damaging agent that would be lethal in single infections, but are then allowed to undergo multiple infections involving two or more viruses per host cell, multiplicity reactivation can occur. Enhanced survival of these viruses due to multiplicity reactivation has been reported to occur upon exposure to a variety of DNA damaging agents including methyl methanesulfonate and N-Methyl-N′-nitro-N-nitrosoguanidine [14], trimethylpsoralen (that causes inter-strand DNA crosslinks) [15,16] and UV light [17].

Genetically marked herpes simplex viruses were treated with trimethypsoralen plus near UV light to produce DNA damages (monoadducts and DNA cross-links) in the viral DNA [15]. Upon

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infection of human fibroblasts, multiplicity reactivation was observed to occur and recombination between the marked viruses increased [15]. Multiplicity reactivation of herpes simplex virus appears to partially rely on the host cell recombinational repair machinery, since skin fibroblasts defective in components of this machinery (i.e. cells from Bloom's syndrome patients) are deficient in multiplicity reactivation [17]. Multiplicity reactivation in herpes simplex virus infections can be regarded as a form of sexual interaction involving recombination repair between the damaged viral genomes leading to production of recombinant viable progeny viruses. Upon infecting host cells, herpes simplex viruses induce inflammation and oxidative damage [18]. It appears that the herpes simplex virus genome is subject to oxidative DNA damage during infection and that under these conditions multiplicity reactivation enhances viral survival and virulence. Numerous other pathogenic DNA viruses have been reported to undergo multiplicity reactivation in response to DNA damaging conditions. In general, it appears that multiplicity reactivation is a recombinational DNA repair process used by numerous DNA viruses to enhance survival. Multiplicity reactivation in DNA viruses is a type of sporadic sexual reproduction utilizing recombinational repair.

## 4. Genetic Recombination in Bacteria, an Adaptation for DNA Repair

Natural transformation in bacteria is a genetic recombination process that involves the transfer of DNA from a donor to a recipient bacterium and the integration of the donor DNA information into the recipient chromosome. This process has the essential features of sexual reproduction, namely that genomes of separate parental origin interact and undergo recombination to produce a new genome that is then passed on to progeny. Natural transformation depends on the expression of numerous genes [19]. The DNA transfer process requires that the recipient bacterium bind, take up and recombine exogenous DNA from the donor bacterium into its chromosome. To accomplish this the recipient must enter a special physiologic state termed "competence". The development of competence in the bacterium *Bacillus subtilis* employs expression of approximately 40 genes [20]. During transformation, the DNA integrated into the recipient chromosome is (with rare exceptions) from another related bacterium of the same species. The donor DNA thus is ordinarily homologous to the resident chromosome of the recipient. In the case of *Bacillus subtilis*, the length of the donor transferred DNA is greater than one million bases (1,000 kb) and is likely double stranded. Often the transferred DNA is more than a third of the total chromosome length of 4,215 kb [21].

The capability to undergo natural transformation is common among prokaryotes, and at least 67 different prokaryotic species representing seven different phyla have been shown to undergo transformation [22]. The competence of cells to undergo transformation is usually induced by high cell density and/or nutritional limitation, conditions associated with the stationary phase of bacterial growth. In addition, competence often can be induced by conditions that damage DNA. As an example, transformation is induced in *Streptococcus pneumoniae* by the DNA damaging agents mitomycin C (a DNA cross-linking agent) and fluoroquinolone (a topoisomerse inhibitor that causes DNA double-strand breaks)[23]. Experiments involving irradiating *Bacillus subtilis* with UV light yielded results indicating that transforming DNA acts to repair potentially lethal DNA damages caused by UV in the recipient DNA [13,24,25]. The process considered likely responsible for the DNA repair was homologous recombinational repair. Recombination in bacteria is catalyzed by a RecA type recombinase that promotes repair of DNA damages by homologous recombination [26].

Experiments with *Helicobacter pylori* showed that ciprofloxacin, an agent that causes DNA-double-strand breaks by interacting with DNA gyrase, induces expression of competence genes leading to an increased frequency of transformation [27]. An examination of the effect on bacteria of 64 different toxic molecules on the induction of competence to undergo transformation led to the finding that only six, all DNA damaging agents, caused strong induction of competence [28]. Thus, in general, induction of competence in bacteria appears to be an adaptive response to DNA damage that allows interaction of the damaged resident chromosome with an exogenous chromosome (a form of sexual interaction) to facilitate recombinational repair and restoration of an intact DNA genome sequence that can be passed on to progeny.

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## 5. Meiosis and Recombination in Eukaryotes, an Adaptation for DNA Repair

In the contemporary double-stranded DNA world of eukaryotes, including animals, plants, fungi and unicellular protists , sexual reproduction is the most common form of reproduction. Among animals and plants, only a small number of species are considered to be asexual, with one in 100 being asexual for angiosperms and one in 1000 being asexual for animals [29]. Yeasts are eukaryotic fungi which have sporadic sexual reproduction, which primarily occurs under stress or unfavorable conditions, such as nutrient limitation Sexual reproduction in these eukaryotes depends upon and requires the process of meiosis when generating progeny. During meiosis, the genomes that came from two parents become closely paired and undergo recombination. This recombination between non-sister chromatids of homologous chromosomes takes place during the pachytene stage of prophase I [30].

The budding yeast *Saccharomyces cerevisiae* is a major model for meiosis research. This is due to most *S. cerevisiae* genes central to meiosis being conserved among sexually reproducing organisms, including animals, plants and fungi [31]**.** Mitotic recombination is an infrequent event (in the order of $10^{-7}$ to $10^{-4}$ per locus per generation). In contrast, meiotic recombination occurs at very high frequencies (reaching 50% per locus in some cases) [32].

During meiosis in *S. cerevisaie,* approximately two-thirds of recombination events occur by synthesis dependent strand annealing (SDSA) [33*]*. This is a copy-choice type of recombinational repair. SDSA is a DNA repair pathway which repairs a double-strand break without exchange of chromosome arms. The SDSA repair of the double strand break occurs by a localized replicative switch at the double-strand break from an initiating genome to a second genome and then a switch back to the intiating DNA duplex. In Figure 2, SDSA is compared to the other major repair pathway for double-strand breaks, the double-strand break repair pathway (DSBR) which commonly results in exchange of chromosome arms.

The budding yeast *Saccharomyces cerevisiae* reproduces by diploid cells undergoing mitosis when nutrients are abundant, but when starved this yeast undergoes meiosis resulting in formation of haploid spores [34]. These haploid cells may then reproduce asexually by means of mitosis. In natural populations of *S. cerevisiae* both clonal reproduction and selfing (mating with immediate relatives) sexual reproduction (in the form of intratetrad mating) predominate [35]. In nature, mating of haploid cells to produce a diploid cell occurs most frequently between cells of the same clonal population and out-crossing is infrequent [36]. When the ancestry of natural *S. cerevisiae* strains were analyzed it was concluded that out-crossing occurs only approximately once every 50,000 cell divisions [36]. These findings indicate that the potential long term benefits of outcrossing (particularly, the generation of genetic diversity) are unlikely to provide the principal adaptive benefit of sexual reproduction in *S. cerevisiae* [37]. Rather, a short term benefit, such as the repair available through recombinational repair of the germline during meiosis [38,39] is likely the key to the maintenance of sex (mating with a very close relative) in *S. cerevisiae*.

Another yeast switches from asexual reproduction to meiotic sexual reproduction, with recombinational repair, when it encounters an externally damaging situation. *Schizosaccharomyces pombe* is an ascomycete fungus, a usually haploid fission yeast. When *S. pombe* are exposed to hydrogen peroxide, an agent that causes oxidative DNA damage, there is strong induction of sexual reproduction, evident by the induced occurrence of meiotic spores [40].

Thus, with yeasts as a model for all eukaryotes, there is an indication that sexual reproduction, with frequent meiotic recombination, is an adaptation for DNA repair, providing protection of the germline.

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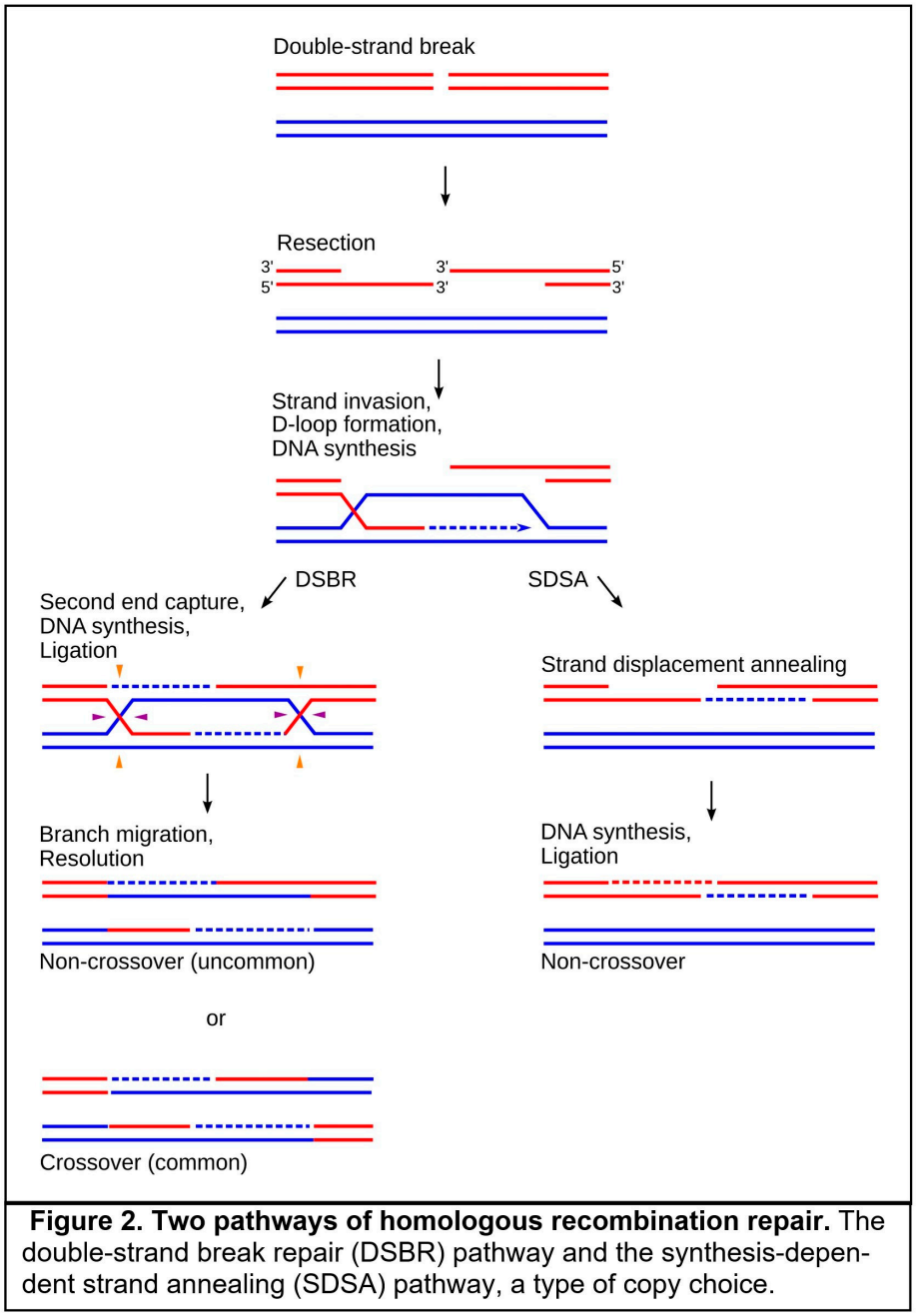


**Figure 2. Two pathways of homologous recombination repair.** The double-strand break repair (DSBR) pathway and the synthesis-dependent strand annealing (SDSA) pathway, a type of copy choice.

## 6. Sexual Reprduction with Meiosis in Protozoa, an Adaptation for DNA Repair

*Paramecium tetraurelia* is a well studied protozoan. *P.* tetraurelia*, when replicating asexually,* has a transcriptionally silent diploid germ-line nucleus and a large transcriptionally active macronucleus. The macronuclear DNA content of *P. tetraurelia* is about 2.42 x $10^{11}$ base pairs, and the haploid micronuclear content is about 2.9 x $10^{8}$ base pairs, giving a macronuclear-to-haploid micronuclear DNA ratio of about 800 [41].

When *Paramecia* undergo sporadic sexual reproduction (conjugation) or self-fertilization (autogamy) they have just a micronucleus. Macronuclear formation involves extensive rearrangements of the germ line genome: fragmentation of micronuclear chromosomes coupled to telomere additions to form the macronuclear chromosome ends and deletion of internal eliminated sequences. This is followed by extensive replication to form the macronucleus [42].

During asexual reproduction in *Paramecium*, the **macronucleus codes for all the functional proteins of the cell.** The macronucleus is responsible for the vegetative functions and gene expression of the *Paramecium*. The micronucleus is diploid and transcriptionally silent during asexual

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reproduction, primarily serving as the germline nucleus for sexual reproduction (conjugation) or autogamy (self-fertilization) when that occurs.

During asexual reproduction (binary fission) in *Paramecium*, the large macronucleus divides by a simple process called **amitosis**, while the smaller micronucleus undergoes true **mitosis**, with the cell then splitting transversely. Amitosis involves simple splitting of the DNA content without spindle formation.

In asexually dividing lines, clonal aging occurs, leading to a gradual loss of vitality. In *Paramecium*, the asexual line of clonally aging cells loses vitality and expires after about 200 cellular fissions if the cells fail to undergo a meiotic process, either autogamy or conjugation.

Functional alterations in the macronucleus, rather than the cytoplasm, of paramecia were shown to be responsible for clonal aging [43]. During clonal aging DNA damage increases dramatically [44–46].

When clonally aged *P. tetraurelia* undergo meiosis by either conjugation or automixis, the descendants are rejuvenated and become capable of undergoing many more mitotic binary fission divisions. During the sexual processes of conjugation or automixis, when the micronucleus undergoes meiosis, the old macronucleus disintegrates. A new macronucleus is then formed by replication of the micronuclear DNA that had recently undergone meiosis. In the new macronucleus, there is apparently little if any DNA damage.

Meiosis, in *P. tetraurelia,* appears to be an adaptation for DNA repair and rejuvenation [47]. The CtlP protein of *P. tetraurelia* is crucial for in the completion of meiosis during sexual reproduction and the recovery of viable progeny [47]. The nuclease protein complex containing CtlP and Mre11 is essential for the repair of double-strand breaks during homologous recombination [47].

Under starvation conditions *P. tetraurelia* can undergo meiosis and self-fertilization, and the benefit of self-fertilization appears to be independent of the generation of any new genetic variation in progeny [48]. These findings suggest that meiosis provides a fitness advantage related to DNA recombinational repair that is independent of any accompanying effect of sex on genetic diversity [48,49].

Thus, in a protzoan, it appears that clonal aging is due largely to progressive accumulation of DNA damage, and that rejuvenation depends on recombinational repair of DNA damage in the germline (the micronucleus) during meiosis.

## 7. Genetic Recombination in Insects, an Adaptation for DNA Repair

Most insect species have obligate sexual reproduction, although aphids and bees and some other insects utilize both sexual and asexual reproduction, having sporadic sexual reproduction. Meiosis is a basic feature of insect sexual reproductive systems, and appears to have an adaptive function similar to that within eukaryotes generally. Studies of the adaptive function of meiosis, particularly at the molecular genetic level in the fruit fly *Drosophila melanogaster*, have contributed to our understanding of the function of meiosis. Meiotic recombination in *D. melanogaster* is induced by the DNA damaging agents ultraviolet light [50] and mitomycin C [51] indicating that genetic recombination is employed in repairing damage in germline DNA.

*D. melanogaster* mutants defective in genes mei41 and mei9 that encode protein products employed in meiosis display decreased meiotic recombination and also have increased sensitivity to the DNA damaging agents x-rays, UV, methyl methansulfonate and nitrogen mustard [52]. These findings link meiotic recombination to DNA repair and suggest that a function of meiotic recombination in *D. melanogaster* is to repair DNA damages in the germ line.

## 8. Genetic Recombination in Outcrossing Plants, an Adaptation for DNA Repair

Plants may reproduce by either an outcrossing sexual meiotic process, or a parthenogenetic meiotic process, or by a vegetative reproductive process that does not involve meiosis. Outcrossing sexual reproduction ordinarily involves the production of haploid gametes by meiosis followed by

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fertilization. Fertilization is the union of gametes from separate lineages to produce a new progeny diploid lineage. In plants, meiosis provides an effective DNA repair capability for dealing with DNA damages, including oxidative DNA damages in germline reproductive tissue [53]. During meiosis in the plant germline, double-strand breaks are produced in the DNA genome, and these breaks can be repaired by a process involving recombination. This recombination process employs the gene products RAD51 and DMC1 that are homologous to recombinases employed generally by eukaryotes [54]. Central features of eukaryotic meiosis are pairing of homologous chromosomes, double-strand break formation and homologous recombinational repair [55]. These processes appear to be adaptations for repairing DNA damage in the germline [55].

In flowering plants there appear to be two fundamental aspects of outcrossing sexual reproduction. The first is meiosis, that is maintained by the advantage of repair of germline DNA. The second is cross-fertilization (outcrossing) that is maintained by the advantages of genetic complementation, (the masking of deleterious recessive alleles) [49].

The multicellular, facultatively sexual green alga *Volvox carteri* is able to undergo sexual reproduction upon induction by oxidative stress [56]. The *V. carteri* genes needed for sexual reproduction can be activated by cellular reactive oxygen species that are associated with oxidative stress [57]. The induction of sex in *V. carteri* can be inhibited by exposure to antioxidants [58]. On the basis of these findings it was proposed that in the early evolution of *V. carteri*, sexual reproduction emerged as an adaptive response to oxidative stress and the DNA damage caused by reactive oxygen species [57]. DNA damage induced by oxidative stress may be repaired during the process of meiosis associated with the germination of the zygospore and the start of a new generation [58].

## 9. Meiosis and "Asexual" Modes of Reproduction in Plants

Almost all "asexual" modes of reproduction in plants maintain meiosis either in a modified form or as an alternative pathway [59]. Repair of oxidative damage in nuclear DNA was proposed to be a major driving force in the evolution of meiosis [59]. A review of the evolutionary origin and processes in normal meiosis and the alternate forms of meiosis involving uniparental reproduction (apopmixis, apomictic parthenogenesis, automixis and selfing) suggested that homologue pairing, double-strand break formation and homologous recombinational repair at prophase I are the least dispensable elements of meiosis, and these elements are likely optimized for repair of oxidative DNA damage rather than genetic recombination [55].

## 10. Repair of Mammalian Oocyte DNA by Recombination During Meiosis

Female mammals and female birds are born with all the oocytes needed for future ovulations [60]. During adult development, their oocytes are arrested in the prophase I stage of meiosis in which they have two sister chromatids of each chromosome, that is equivalent to four copies of each chromosome (4C stage of meiosis) [60]. This arrest at the 4C stage allows recombinational repair of DNA damage between sister- as well as non-sister homologous sequences.

The oocytes of mammals are often very long-lived and thus are subject to the accumulation of DNA damage and epigenetic alteration over a large portion of female lifetime [61]. During the maturation of oocytes, damaged DNA is repaired by the processes of non-homologous end joining or homologous recombination [61]. Homologous recombination involves the exchange of undamaged genetic sequence information from a chromosome to correct the damaged portion of its homologous partner chromosome. The DNA synthesis machinery present during oocyte maturation is dynamically recruited to sites of DNA damage and polymerase delta is crucial for oocyte DNA synthesis in the repair of DNA damage [61]. DNA double-strand breaks in oocytes, in particular, can be repaired by a process involving RAD51 mediated homologous recombination [62].

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## 11. Repair of Mammalian Spermatocyte DNA During Meiosis

Spermatocytes are able to overcome double-strand breaks and other types of DNA damage in the prophase stage of meiosis. DNA damages are often caused by oxidative free radicals produced as products of normal metabolism. In spermatocytogenesis, special DNA repair processes are utilized during meiosis that remove DNA damages and assist in the maintenance of the integrity of the genome that is passed on to progeny [63]. These repair processes include homologous recombinational repair and non-homologous end joining [63].

In mice, homologous recombinational repair of double-strand breaks occurs during sequential stages of spermatogenesis but is most prominent in spermatocytes [64]. In spermatocytes, homologous recombinational repair events occur primarily during the pachytene stage of meiosis. During this stage, the gene conversion type of homologous recombinational repair predominates. However in other stages of spermatogenesis the reciprocal exchange type of homologous recombination is more prevalent [64]. During spermatogenesis in the mouse, the frequencies of mutation of cells at the different stages, including pachytene spermatocytes are approximately 5-10-fold lower than the mutation frequencies in somatic cells [65]. The elevated repair ability of spermatocytes likely has a central role in the maintenance of these lower mutation rates, and therefore in the preservation of the genetic integrity of the male germ line.

## 12. Advantage of Outcrossing

The main focus of this presentation has been that sexual reproduction arose early in evolution and has been maintained as a mechanism for dealing with genome damage. However, it is also important to note that in many species outcrossing sexual reproduction provides an additional advantage related to the masking of the expression of deleterious recessive alleles in the diploid phase of the life cycle. This masking effect is referred to as genetic complementation. The masking also can be referred to by the terms hybrid vigor, heterosis and heterozygote advantage. In those species where outcrossing has been the principal mode of reproduction, circumstances that limit outcrossing while allowing inbreeding may have deleterious consequences. This phenomenon, referred to as inbreeding depression, is considered to be due largely to the expression of deleterious recessive mutations [66]. Inbreeding depression has been demonstrated in numerous species and many species have evolved mechanisms to avoid inbreeding as indicated by the following examples.

Experiments in the mouse involving *in vitro* fertilization indicated the occurrence of sperm selection at the gametic level [67]. It was observed that when the sperm of sibling and non-sibling males were mixed, there was a fertilization bias towards the sperm of the non-sibling males. These findings were interpreted as egg-driven sperm selection against related sperm.

In competition experiments male fruit flies (*Drosophila meanogaster*) of four different degrees of genetic relatedness were mated with female fruit flies [68]. Sperm competitive ability was observed to be negatively correlated with genetic relatedness.

A small highly inbred population of gray wolves (*Canis lupus*) resides in Isle Royale National Park, Michigan USA. This population has been undergoing population decline and is nearing extinction due to the homozygous expression of strongly deleterious recessive mutations leading to decreased genetic viability [69,70].

Inbreeding avoidance is highly variable among animals [71]. Inbreeding avoidance by means of mate selection appears to only evolve under circumstances where there is both a risk of inbreeding depression as well as frequent encounters between sexual partners that are genetically related to each other [71].

## 13. Meiosis Associated with Parthenogenesis in the Animal Kingdom

Although outcrossing sexual reproduction is the principal means of reproduction in most eukaryotic species, reproduction involving meiosis without outcrossing also occurs as indicated by the following examples.

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Rotifers are microscopic animals of the class Bdelloidea that are known for their long-term persistence in the apparent absence of outcrossing sexual reproduction [72]. The longevity of the asexual Bdelloid rotifer clade is greater than 60 million years [73]. Homologous recombination appears to occur either during mitotic DNA double-strand break repair or when resolving programmed DNA breaks during a modified meiosis [73] In the bdelloid species *Adineta vaga*, a noncanonical meiosis appears to be the mechanism of germline DNA repair [72].

Facultative parthenogenesis is widespread in the animal kingdom [74]. As an example, king cobra snakes are able to undergo facultative parthenogenesis [74]. Parthenogenesis in this case occurs by a modification of meiosis termed terminal fusion automixis, a process in which the meiotic products formed at the anaphase stage of meiosis fuse together [74].

The Burmese python, when maintained in captivity, was demonstrated to be able to reproduce asexually [75]. Offspring are clones of their mother and the reproductive process is a form of parthenogenesis involving a variation of meiosis [75].

Female unisexual mole salamanders of the genus Ambystoma are common in the North American Great Lakes region [76]. These salamanders are the oldest known vertebrate unisexual lineage, as they emerged about 5 million years ago [77]. They engage in kleptogenesis. Females steal sperm from co-existing males of a bisexual species. The acquired sperm serve to stimulate meiosis [78].

These examples illustrate that although sexual reproduction, involving both the meiotic production of gametes and outcrossing, is the main mode of reproduction in the animal kingdom, reproduction by a parthenogenetic meiotic process also can occur. Under certain circumstances, particularly when there are substantial costs in finding mating opportunities, a parthenogenetic strategy involving meiosis may be the most effective means of reproduction. In these cases, meiosis retains the benefit of recombinational repair of DNA damages in the germ line and may occur without introducing new genetic variation.

## 14. Small Adaptive Advantage of Genetic Variation Due to Recombination During Sexual Reproduction

As reviewed by Sarah P. Otto [79], sexual reproduction is more costly to an organism than asexual reproduction. There is an initial two-fold cost since a sexual parent may transmit only 50% of its genes to the next generation, compared with 100% for an asexual parent. In addition, recombination in sexual reproduction may break apart favorable combinations of genes built by past selection. Further, mitotic asexual reproduction may take much less time than that needed for complicated meiosis during sexual reproduction. She asks, “Given the costs of sex and the widespread potential for asexual reproduction, why do so many species reproduce sexually?” Many biologists have proposed that sex and recombination evolved because they give rise to the variation needed by selection. This was first proposed by August Weisman in 1889. Otto [79] describes the many attempts to mathematically find a benefit in the variation produced by recombination during sexual reproduction that exceeds the costs of sex, and the difficulties with each model, so far.

**Discussion**

The fundamental function of sexual reproduction appears to be conservation of the integrity of the informational content of the genome that is passed from parents to progeny [53,80].

Genetic recombination, a central feature of meiosis in eukaryotes, is likely maintained by the adaptive advantage of recombinational repair of genomic DNA damage in the germ line [49]. The association of outcrossing with meiosis is likely maintained because outcrossing promotes the masking of expression of deleterious recessive mutations (genetic complementation) in progeny [49].

Genetic variation is often produced as a byproduct of these processes, and such variation may provide long-term advantages in those sexual lineages that favor outcrossing [49]. However, it has also been argued that producing more variable offspring is not necessarily favorable [81]. In addition, outcrossing may be absent as in obligate parthenogens with meiotic capability, or limited as in species where the costs of finding a mate exceed the benefits of masking deleterious mutations, such as in

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species where individual organisms are highly dispersed. The production of genetic variation may sometimes be a beneficial outcome of sexual reproduction. However, the information reviewed here indicates that the main driving force in the origin and evolution of sexual reproduction has been recombinational repair or avoidance of genome damage.

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