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DNA Repair

Minireview

A path for coevolution of recombinational DNA repair, transposition, and the common nucleotides

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Homologous genetic recombination is required for recombinational DNA repair, is involved in the successful segregation of chromosomes at cell division, and contributes to the generation of genetic diversity in all organisms. Whereas recombination is a key enabling mechanism in the continuing evolution of life on earth, it is widely believed to have originated in bacteria or their progenitors as a DNA repair process (Dougherty, 1955; Maynard Smith, 1978; Bernstein et al., 1985, 1988; Crow, 1988; Ghiselin, 1988; Maynard Smith, 1988; Potter and Dressler, 1988; Cox, 1991, 1993; Clark and Sandler, 1994; Michod, 1995; Kuzminov, 1996). A scenario is presented here for the stepwise development of very early recombinational DNA repair systems, the presumed antecedents of the homologous genetic recombination systems found today in all organisms. The scheme is built in part on functional constraints imposed on nucleic acid structure by a requirement for recombinational repair. These constraints may have helped to establish the GAT(U)C constellation of nucleotides as the standard components of nucleic acids. The same constraints may have facilitated the evolution of transposons.

The ideas draw heavily on recent advances in several diverse research areas. Evolutionary biology provides a picture of a likely environment within which life evolved (Miller, 1987; Orgel, 1994; Lazcano and Miller, 1996), as well as detailed theories on the function of recombination and sex in both prokaryotes and eukaryotes (Maynard Smith, 1978; Bernstein et al., 1985, 1988; Crow, 1988; Ghiselin, 1988; Maynard Smith, 1988; Michod, 1995). The biochemistry of recombination (especially the prokaryotic RecA protein) has reinforced a long-established link between recombination and repair (Cox, 1993; Kuzminov, 1996; Roca and Cox, 1997). The study of unusual nucleic acid structures in recombination has focused attention on a parallel triplex nucleic acid form as potentially a key recombinagenic intermediate (Stasiak, 1992; Shchyolkina et al., 1994; Zhurkin et al., 1994; Baliga et al., 1995; Cox, 1995; Frank-Kamenetskii and Mirkin, 1995; Podyminogin et al., 1995, 1996; Rao et al., 1995; Roca and Cox, 1997). Recent advances in the study of nucleic acids containing non-standard base pairs have raised questions about why the cellular coding system is based almost entirely on the 4 common

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nucleotides found in extant nucleic acids (Switzer et al., 1993; Tor and Dervan, 1993; Horlacher et al., 1995).

Recombinational DNA repair is a specialized process directed at DNA damage only when it occurs in certain contexts. Much DNA repair is made possible because DNA is double-stranded. If one strand contains a lesion, a segment of the strand containing the lesion can be removed. The second strand can then be used as a template for replacement of the damaged strand segment. No recombination is required. However, there are important situations where a second DNA strand is not available to direct repair. In some cases, crosslinks or double-strand breaks produce damage in both strands. Alternatively, a DNA lesion can be located in a single-stranded region of the DNA. In these situations, the information for faithful DNA repair must come from a different homologous DNA molecule via recombination. If a DNA polymerase encounters a DNA lesion in the template prior to its repair, replication halts and the lesion is left in a region of single-stranded DNA. Some current models for repairing lesions in this situation are presented in Fig. 1 (see also Kuzminov (1996)). In these and other models for recombinational DNA repair, the pairing of two DNA molecules involves one single-stranded DNA and one duplex DNA (Cox, 1995; Roca and Cox, 1997).

The first replicating nucleic acids evolved over 3.5 billion years ago in an environment with little molecular oxygen (Lazcano and Miller, 1996). The absence of an ozone layer around the primitive earth would have subjected any exposed early replicators to high fluxes of damaging ultraviolet radiation. In addition, early replication was probably relatively slow, increasing the probability of both induced and spontaneous damage of many types (Lindahl, 1993; Lazcano and Miller, 1996) occurring before replication could be completed.

Whereas the evolution of nucleic acid repair systems in response to these circumstances seems preordained, it is more difficult to envision the series of molecular steps that led to any form of enzymatic repair. In the case of recombinational repair, a logical starting point can be found in the nucleotides themselves. The common nucleotides (GATC or GAUC) are not unique in their capacity to form base pairs with a Watson–Crick (WC) geometry. In 1962, Rich pointed out that isocytosine (iC) will pair with isoguanosine (iG) to form a base pair consistent with

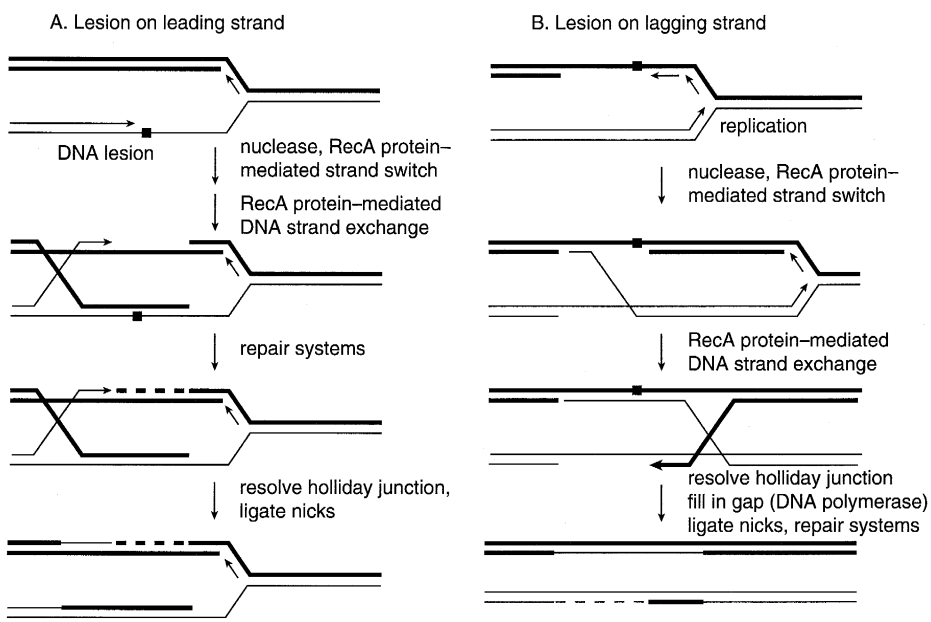

Fig. 1. Pathways for the postreplication repair of DNA. Pathways for repair of a lesion in the leading or lagging strands are shown. ■ represents a DNA lesion. Dashed lines represents new DNA synthesis.

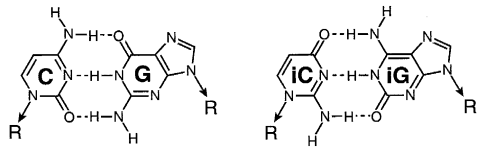

Fig. 2. The isocytosine (iC) and isoguanosine (iG) base pair, compared to the cytosine–guanosine base pair.

the Watson–Crick DNA structure (Fig. 2), and suggested that it might have been a component of early nucleic acids (Rich, 1962). More recent studies have shown that there are at least 12 bases capable of forming 6 different and WC-compatible base pairs (including CG and AT(U)) by mutually independent hydrogen bonding patterns (Horlacher et al., 1995). In some cases, the non-standard nucleotides are inserted opposite their complements by DNA or RNA polymerases and form double-stranded nucleic acids of appreciable stability (Switzer et al., 1993; Tor and Dervan, 1993; Horlacher et al., 1995). However, in most of the alternative pairs, the pyrimidine analog must be joined to ribose via a carbon–carbon bond, and these analogs are hard to envision as products of prebiotic chemistry (Benner et al., 1987; Horlacher et al., 1995). The key exception is the iC–iG pair, which is predicted to form polymers with a thermal stability comparable to those formed with standard G–C pairs (Leach and Kollman, 1992). There are plausible biosynthetic pathways for the generation of iC and iG, and one can ask why nucleic acids did not evolve to exploit the iC–iG pair for coding. Isocytosine undergoes deamination faster than cytosine, and isoguanosine has a minor tautomeric form which mispairs with T or U (Switzer et al., 1993). Either or both of these factors may have disfavored the iC–iG pair in evolution. I would like to offer another factor which may have helped to establish the GAT(U)C nucleotides in evolving nucleic acids: their recombination potential.

DNA damage would have presented the first replicating nucleic acid with a seemingly insoluble evolutionary problem. Without a pathway to repair, the early replicator would have to be sufficiently inaccurate to bypass lesions such as pyrimidine dimers. However, evolution would logically favor improvements in the fidelity of the system so that successful sequences were reproduced faithfully. Increases in fidelity would prevent lesion bypass. In effect, early templates could be replicated efficiently or accurately, but not both.

The effects of heavy damage on early replicators could be overcome by the establishment of a postreplication repair pathway. The simplest effective repair process one can envisage is quite similar to that proposed for present-day recombinational repair by Paul Howard-Flanders and colleagues (West et al., 1981) (see Fig. 1), but would depend on a much simpler array of catalytic functions. It is outlined in Fig. 3. The type of nucleic acid involved is not specified, although the pathway is compatible with a biological universe based on RNA or an RNA progenitor. A stalled replicator would leave a region of single-stranded nucleic acid in the template strand. Homologous double-stranded nucleic acid from elsewhere in the pond or protocell (or on the other side of a replication fork in the case of a system capable of semidiscontinuous replication) would pair with the single-stranded region, forming a triplex nucleic acid structure. Early hydrolytic catalysts could remove a segment of the strand complementary to the region requiring repair, and the segment could be inserted into the discontinuous strand by transesterification if the segment overlapped the gap at both ends. The hydrolysis and formation (by transesterification) of phosphodiester bonds are known activities of extant ribozymes, and may have been among the earliest enzymatic activities. The resulting bypass of the lesion would permit the newly synthesized strand of nucleic acid to complete its synthesis and thereby pass its information on to subsequent generations. The nucleic acid segment donated for repair could be replaced by the replicator.

The important features of the scheme of Fig. 3 are a nucleic acid triplex in which like strands are parallel and nucleotide pairings are constrained by specific hydrogen-bonding patterns, as well as the transesterification steps. A 3-stranded DNA intermediate of this kind has been proposed for DNA strand exchange reactions in recombination catalyzed by the bacterial RecA protein, although the idea remains controversial. Evidence both for and against the existence of a recombination triplex as an intermediate in RecA-mediated DNA strand exchange reactions has been presented (Adzuma, 1992; Stasiak, 1992; Shchyolkina et al., 1994; Zhurkin et al., 1994; Baliga

et al., 1995; Cox, 1995; Frank-Kamenetskii and Mirkin, 1995; Podyminogin et al., 1995, 1996; Rao et al., 1995; Roca and Cox, 1997). This review focuses not on this controversy (summarized in detail elsewhere (Frank-Kamenetskii and Mirkin, 1995; Roca and Cox, 1997)), but on the evolutionary implications of the triplex structure to the extent it exists.

A parallel nucleic acid triplex with even a modest degree of stability could have had an important role in the evolution of nucleic acid structure and function. Triplex base-pairing patterns suggested by some of the studies cited above are summarized in Fig. 4. In each case, two of the bases are paired via Watson–Crick hydrogen bonds, while the third (R) strand is in the major groove with hydrogen bonds to both the W and C strands. In each case, the hydrogen bonding patterns are unique, providing a code to guide the pairing of homologous sequences. The base triplets are nearly isomorphic, resulting in a triplex with a uniform backbone structure and significant predicted stability (Zhurkin et al., 1994). The resulting structure is sometimes referred to as R

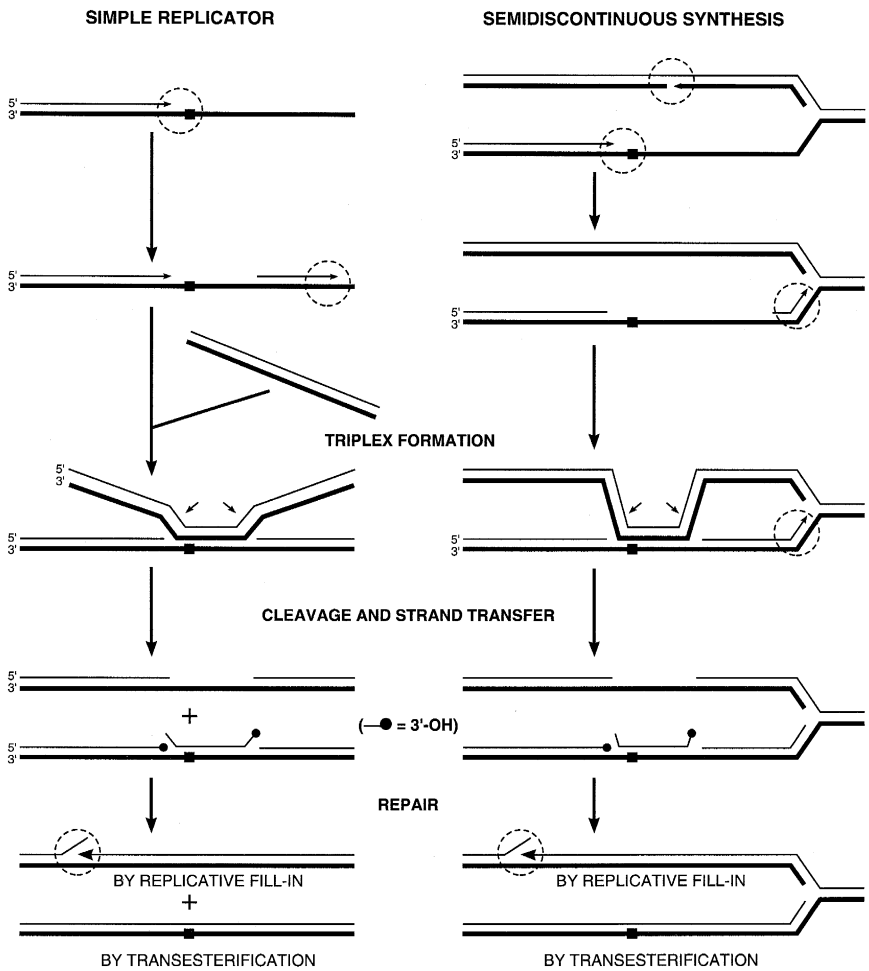

Fig. 3. Hypothetical pathway for primitive postreplication repair. The pathway at the left assumes a simple replicator utilizing a single-stranded nucleic acid as a template. Replicator accuracy leads to cessation of replication at a pyrimidine dimer (■), leaving a single-strand gap. A homologous duplex nucleic acid forms a triplex structure in the gap, leading to a strand switch. A segment of the complementary strand in the duplex is cleaved out by hydrolytic activities, and spliced into the gapped strand by transesterification. The segment is replaced in the donor duplex by the replicator. The repaired daughter strand can then transfer its information to subsequent generations. The pathway at the right is identical except that the donor strand is derived from the other side of a replication fork.

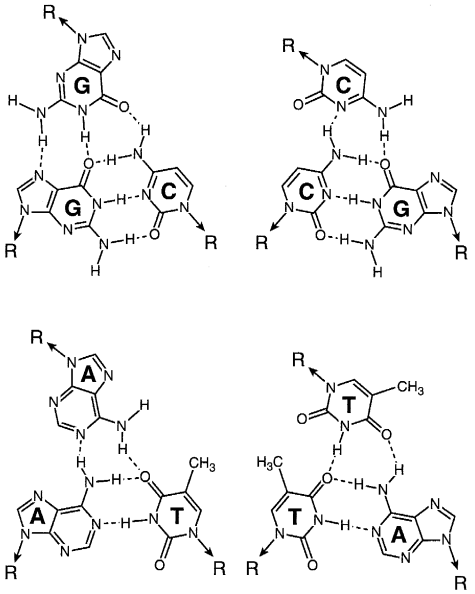

Fig. 4. Proposed hydrogen-bonding patterns in an R-form triplex. The structures shown follow those of Zhurkin et al. (1994). See also Rao et al. (1995). Hydrogen binds are denoted by dashed lines.

DNA (Zhurkin et al., 1994; Rao et al., 1995), and has been a topic of speculation in the recombination field for over 30 years (Lacks, 1966). Most work to date suggesting the existence of R DNA has focused on DNA structures formed by the action of RecA protein. Spontaneous formation of a structure presumed to be R DNA was detected in only one rather limited study (Shchyolkina et al., 1994), although the results suggested a relatively low T_m. The relative paucity of evidence for the spontaneous formation of an R-form triplex is a weakness of the scheme outlined in Fig. 3. The possibility of an equivalent structure in RNA, or in nucleic acid variants, such as PNA (Frank-Kamenetskii and Mirkin, 1995; Nielsen, 1995), has not been carefully explored. To proceed, we must assume that a structure approximating this triplex has at least a marginal stability within the context of early nucleic acids and the environment they evolved in. Alternatively, the type of pairing shown in Fig. 4 must play some role in facilitating a strand exchange between DNA molecules of similar sequence, perhaps providing a low energy path for an otherwise uncatalyzed strand switch or providing some stabilizing effect on the hybrid nucleic acid product of a strand switch.

If at least a transient formation of an R-form triplex was a prerequisite for or facilitated recombination, the biological requirement for postreplication repair could in turn have helped to fix the GAT(U)C nucleotide constellation as the standard in early nucleic acids. All of the bases have hydrogen bonding potential in addition to that used in WC pairing, and the arrangement of that additional potential in the major groove permits (in principle) the formation of specific base triplets with homologous strands of nucleic acid (Fig. 4). The structure of the iC–iG pair, in contrast, does not permit the formation of specific base triplets (Fig. 5). Any nucleic acid containing significant numbers of iC–iG pairs might thereby be excluded from repair via the pathway of Fig. 3. This limitation may have contributed to the evolutionary exclusion of many of the potential alternative base pairs from nucleic acids.

A stepwise elaboration of the pathway of Fig. 3 can be envisioned, based on the presumed instability of the triplex intermediate. At early times, triplex stability and/or catalytic function could have been dependent on solution components such as metal ions. Specialized ribozymes may have evolved to stabilize the triplex, perhaps augmented by molecules such as polyamines. As the RNA world was supplanted by proteins and DNA, the continued need for repair could have led to the evolution of a protein to stabilize the triplex, a forerunner of the RecA protein. Much evidence summarized elsewhere shows

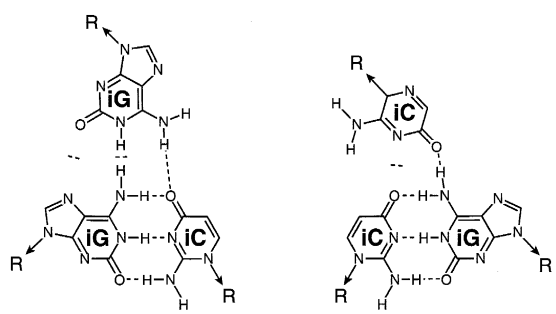

Fig. 5. Incompatibility of iC and iG with an R-form triplex. The non-complementary positioning of hydrogen bond donors and acceptors (indicated by --) precludes the formation of specific or stable triplets.

that the RecA protein efficiently binds and coordinates only three DNA strands (Cox, 1995). As the primitive rec protein evolved to promote a complete strand switch within the 3-stranded complex (Menetski et al., 1990; Adzuma, 1992; Baliga et al., 1995; Podyminogin et al., 1995), and to utilize ATP to drive the process to completion (Cox, 1994), postreplication repair would become more certain whenever it was needed. Additional enzymes would evolve to prepare substrates for RecA and process the branched DNA intermediates created by RecA (Kowalczykowski et al., 1994; West, 1994). The evolution of bacterial sex (transformation, transduction, conjugation) would have taken advantage of the existing recombinational repair pathways. The introduction of DNA from outside the cell, albeit rare, could have contributed to DNA repair (Selander and Levin, 1980; Levin, 1988). At the same time, the resulting slow distribution of new gene combinations could have provided a substantial stimulation of the overall evolutionary process (Levin, 1988; Smith, 1991, 1993).

The second feature of the pathway in Fig. 3 is transesterification. Just as nucleic acid repair and the possibilities for nucleic acid pairing could have led to the evolution of the recombinational repair of RNA or its progenitors, the development of catalyzed transesterification reactions involving large segments of nucleic acid could have led to the evolution of transposons. Transesterification is a key feature of transposition recombination (Mizuuchi, 1992). With the appearance of the first inefficient early replicators, transposition (simply hopping into another molecule that could be replicated) would represent a potentially important alternative to replication itself as a pathway for successful reproduction. Replicators and transposons could have existed in a primitive symbiotic relationship, each providing potential avenues for accelerating the evolution of the other.

Many vestiges of a repair origin can be seen in the recombination systems found in modern bacteria (Cox, 1993). The core of the genetic argument that the requirements for repair still provide the primary selection pressure for the universal maintenance of recA centers on the phenotype of recA mutant cells, in particular their sensitivity to DNA-damaging agents. A dramatic example can be seen in recent work on the bacterium *Deinococcus radiodurans*, which can survive a dose of radiation several thousand times that required to kill other organisms. This extraordinary radiation resistance depends completely on an intact recA gene (Daly et al., 1994; Minton, 1994; Minton and Daly, 1995).

The evolutionary scenario described above suggests that the relationship of nucleic acid structure to its function should not be couched in terms of replication and transcription only. All aspects of nucleic acid metabolism are intimately linked. A need for repair of genetic material may have imposed important constraints in the evolution of nucleic acid structure. Evaluation of the proposed pathways for early recombinational repair will require a much more complete investigation of the putative R-form triplex structures in nucleic acids. A study of the capacity of DNA containing iC + iG to participate in RecA protein-mediated DNA strand exchange could also be illuminating. At a detailed molecular level, a DNA strand switch between homologous DNA molecules is a complex problem of chemical motion and weak interactions. The role in this process, if any, for the secondary hydrogen bonding potential of DNA base pairs in the major groove remains to be elucidated.

Acknowledgements

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