Generation of Genetic Variation: A Proposed Mechanism

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ABSTRACT: A conceptual analysis of the literature supports the proposal that "less-repaired changes" in DNA generate genetic variation that natural selection acts upon.

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Eukaryotic cells have repair mechanisms that repair mutations to DNA caused by ionizing radiation and other mutagens. However, these mechanisms are not constant. While the rate of repair is uniformly distributed within highly repeated, moderately repeated, and single copy DNA, depending on the mutagen and species, the amount of repair is variable, with less repair to highly repeated DNA than to bulk DNA (reviewed in Friedberg, 1985). Regarding this phenomenon, Friedberg concluded "...the repair of different kinds of DNA can be differentially affected by some as yet unidentified property or properties of heterochromatic DNA." Moreover, recent research on repair mechanisms suggested preferential repair of mammalian DNA according to activity and/or function (Bohr et al., 1985; Bohr et al., 1986; Mellon et al., 1986; Mellon et al., 1987). The correlated differential repair of altered subsets of DNA provides a reasonable explanation regarding the non-random mutation rates of some genes: differential repair would appear as non-random mutation when analyzed electrophoretically.

Combining the phenomenon of differential repair to sub-sets of DNA with 1) Lande's (1976, 1981) suggestion that normal mutation rates (at polygenes) could maintain sufficient genetic variation on which selection (sexual) could act, and 2) Ohta's (1987a, 1987b, 1988) models of complex genetic systems arising via mutations in genes duplications, I propose the unidentified property (or properties) that mediate the differential repair in DNA is a mechanism that repairs DNA according to the function of the changed area. Thus, a low amount of repair in highly or moderately repeated DNA sequences (termed a "less-repaired change" to avoid associations conveyed by the term "mutation") would provide some of the genetic variation that natural selection acts on in natural populations, and a high amount of repair to single copy/essential genes would conserve uniformity in the structure of those proteins necessary for critical functions in a given species. I am not proposing that all single copy genes are always fully repaired or that repeated genes are always less repaired. Rather, the proposed mechanism would variably repair those genes that code for traits more likely to be affected by natural selection (i.e. hair length and color, skin color, pattern, salinity tolerance, and other morphological and physiological adaptations to local conditions). No teleological meaning is implied in this proposal; a stochastic change or changes in a pre-biotic structure or the DNA of a primitive cell could have resulted in this mechanism. Assuming the

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above, then logically the evolution of this mechanism closely followed, and was second in importance in biological evolution, only to the initiation of life itself.

All less-repaired changes would be neutral; natural selection would act on them in a time-space continuum. This mechanism provides an explanation of how the genetic diversity predicted by the selectively neutral mutation theory (e.g. Kimura and Ohta, 1971) would be generated. It also provides support for inbreeding theory (e.g. Bateson, 1983; Shields, 1982) in that it explains how populations genetically adapted to local conditions would retain genetic variation.

Two recent studies made similar observations regarding how unrepaired changes/mutations in DNA would be adaptive (as opposed to those models that assume mutations are rare and usually deleterious). Friedberg (1985) suggested that unrepaired chromosomal damage could be selectively adaptive by allowing the generation of nucleotide sequence divergence, and used the hypervariable region within the most variable region that codes for immunoglobin production in the mouse germ line as an example. Slutsky et al. (1985) reported that under a low dose of ionizing radiation, the mutation rate of yeast Candida albicans colonies increased 200-fold, an increase they felt was due to an inherent, plastic response within each cell, and would be selectively adaptive in that it could provide the genetic variation necessary to colonize new habitats. (Although Slutsky et al. [1985] did not propose a specific mechanism as I do here, they appeared to be suggesting the same idea.)

Because less-repaired changes in DNA would result in nucleotide sequence divergence, some amino acids may exhibit discrete variations; variations that could be undetectable using the current technology in biochemical analysis (e.g. see Iizuka's [1988] discussion of electrophoretically cryptic alleles). Also, small variations in electrophoretic data may be due to inconsistencies in the test apparatus (see Reeder, 1987). However, such variations could also be due to minute differences in the charge of a protein when a less-repaired change occurred in DNA and was amplified in the protein's structure. (See Mercer [1981] for a description of how events at the sub-atomic level in DNA may be expressed in an adult organism as well as in populations.) Thus, the subjectivity involved in applying values to minute differences in the "same" protein could mask the presence of many subsets of some proteins. This possibility serves to illustrate the potential limitations associated with instrument-mediated observations of micro-phenomena. (See Ihde [1977] and Mercer [1981] for further discussion.)

There is no biochemical principle that precludes the existence of this proposed mechanism, since molecular selection (as defined in Van Valen, 1983) in DNA is well-described (e.g. reviews in Cavalier-Smith, 1985; Borst and Greaves, 1987; Reik et al., 1987; Sapienza et al., 1987; Seidman et al., 1987; Woodruff et al., 1987). Also, this proposal does not conflict with neo-Darwinian or punctuated evolution theory.

If experimentation shows this proposed mechanism is extant in biological systems, it will elucidate how biological systems have generated increased novelty and complexity over time within the boundaries of physical laws, and will bring biology and physics closer to what Mercer (1981) termed a "unified theory" between both

systems.

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