Hypothesis

Resolving the evolutionary paradox of genetic instability: a cost–benefit analysis of DNA repair in changing environments

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Abstract Loss of genetic stability is a critical phenomenon in cancer and antibiotic resistance, and the prevailing dogma is that unstable cells survive because instability provides adaptive mutations. Challenging this view, we have argued that genetic instability arises because DNA repair may be a counterproductive strategy in mutagenic environments. This paradoxical relationship has also been confirmed by explicit experiments, but the underlying evolutionary principles remain controversial. This paper aims to clarify the issue, and presents a model that explains genetic instability from the basic perspective of molecular evolution and information processing.

Key words: DNA repair; Genetic instability; Evolution; Mutagen; Mutation; Information processing

1. Introduction

Genetic instability designates different cellular phenotypes characterized by a relative increase in mutation rate. Such phenotypes evolve spontaneously in neoplastic tumors and microbial populations, and play a critical role in the development of cancer [1,2] and antibiotic resistance [3–5].

Genetic instability has been related to specific genes and biochemical pathways [1,6]. In particular, microsatellite instability is caused by deficiencies in nucleotide mismatch repair [7,8], whereas chromosomal instability has been related to defects in regulation of chromosomal segregation [2,9]. In general, it is evident that genetic instability is caused by permanent or inducible deficiencies in DNA control and repair mechanisms [10], and the molecular details are becoming increasingly clear. Still, the evolutionary dynamics leading to genetic instability remain a controversial issue with fundamental implications for the understanding of biology [4,11,12], and the problem boils down to one question: Why is loss of genetic stability related to a growth advantage in certain environments?

The prevailing dogma is that unstable cells survive because the elevated mutation rate generates adaptive variants [4,12–15], and may be referred to as the mutation for survival hypothesis [16]. The basic problem with this model, however, is that random mutations are statistically far more likely to be unfavorable or lethal than they are to be adaptive. Accordingly, each mutation may be regarded as a risky gamble, and the more bets you make, the more certain it is that you will lose. How then can an elevation of mutation rate confer an evolutionary advantage?

Several authors have tackled this problem by introducing new evolutionary principles. Evolution by second-order selection [17], counterselection [14], associated selection [12], and mutator hitch-hiking [18] are different models which state that genetic instability arises, not because repair deficiency is favorable to the individual cell, but because the elevated mutation rate increases the population's overall chance of survival. In principle therefore, they all explain genetic instability as a consequence of group selection.

The concept of group selection has been extensively debated for more than a century [19], and we will here refrain from further elaborations. We will simply state that the mutation for survival hypothesis is based on controversial premises, and point out several unsolved problems related to genetic instability:

1. Why does genetic instability arise in response to mutagenic environments [20,21]? Under these conditions, it seems highly inconceivable that more mutations should be evolutionarily favorable or otherwise 'needed'. On the contrary, the evolutionary challenge appears to be too many mutations.
2. Why do different mutagenic selection pressures induce specific phenotypes of genetic instability [1,20,21]?
3. Why do cells lose the repair mechanism that presumably has evolved to withstand the specific mutagen they are exposed to [1,22]?
4. Why does loss of some DNA repair mechanisms confer resistance to the cytotoxic effects of mutagens, whereas loss of others confers increased susceptibility [23,24]?
5. Not only mutagenic but also growth-limiting selection pressures favor loss of DNA repair and rise of genetic instability in experimental systems [4,13]. What is the connection?
6. Genetic instability arises in response to environmental stress. Where is the transition point at which DNA repair switches from being a favorable to a counterproductive strategy?
7. Genetic instability is very common in neoplasms, and may

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be an obligatory factor in carcinogenesis [2,6]. In microbial populations, on the other hand, genetic instability is selected for under certain environmental conditions [4,13]. What is the difference?

8. Genetic instability arises by selection of repair-deficient variants or as a consequence of regulatory mechanisms. How are these phenomena related?
9. Finally, the last decades of research have revealed fundamental connections between biological evolution and information physics [25]. Such research has confirmed the old rationale [26] that natural selection necessarily drives a system towards lower, and not higher mutation rates in any given environment [27]. How is this compatible with the observed evolution of genetic instability?

2. Theoretical considerations

Biological evolution basically concerns propagation of information in the form of nucleotide sequences or other physical patterns like those of DNA methylation [1,25,28]. Selection implies conservation of information, and when we say that a cell has been selected, it is actually shorthand for saying that molecular patterns of information have been replicated from one cell to its descendants. It is the genome that is selected. But even that is merely an approximation. Replication is not perfect, and some segments of the genome are necessarily altered. These sequences are by definition not selected. On the contrary, they are mutated. Strictly speaking, it is therefore not the cell that is selected, only its conserved patterns of molecular information.

This level of precision may seem a bit over-explicit. Nevertheless, it is important to recognize that the concept of cellular selection is an approximation. This approximation deteriorates with increasing mutation rate, and in our opinion, it breaks down when it comes to modeling genetic instability. This evolutionary problem therefore demands a strict molecular perspective.

Genetic instability is basically caused by loss or silencing of genes that directly or indirectly promote stringent replication of DNA. These nucleotide sequences, generally referred to as DNA repair genes, are the physically definable objects that underlie evolution of genetic instability. The term DNA repair commonly implies a mechanism more or less directly involved in the recognition and removal of DNA damage. In principle however, it is applicable to any process that somehow contributes to the integrity of the genome. A model of genetic instability should therefore explain why replication fidelity is unfavorable in certain environments, and in general, we have to consider the evolutionary pros and cons of a DNA repair gene.

The evolutionary advantage of a DNA repair gene should be obvious. Not only does it catalyze its own synthesis by template replication, it also encodes proteins that assure high-fidelity replication of its own sequence and the entire genome on which it depends. Consequently, it should be favored by natural selection.

But repair also has a significant downside. Error detection and correction takes time and consumes energy [29], and the price of effective DNA repair is molecularly manifested by its close relationship to cell cycle control [30]. As for all kinds of information processing, DNA replication therefore involves an inevitable predicament between speed and fidelity.

Based on these considerations we, and others, have concluded that DNA repair is not necessarily a favorable strategy [22,31]. There could be environments in which DNA repair costs more than the errors it prevents. In principle, a mutagenic environment could negate the evolutionary advantage of the repair mechanism that withstands it, and this apparent contradiction may be metaphorically resolved by the phrase 'Don't stop for repairs in a war zone' (Fig. 1) [22].

By applying this hypothesis to colorectal carcinogenesis, we revealed a number of previously hidden associations between mutagenic exposure, biochemical pathways and genetic alterations [32]. In particular, we demonstrated that microsatellite and chromosomal instability are associated with methylating and bulky-adduct-forming mutagens, respectively [1]. This relationship was later confirmed by explicit experiments [20].

3. Mathematical assessment

Calculating the costs of DNA repair is a complex matter. Nevertheless, it is fair to assume that there is no direct correlation between the time it takes to repair an error, and the cost the error would have incurred had it not been repaired. For the sake of argument, we will therefore represent the cost of repairing an error by a constant, r. r is the time it takes to repair one particular type of error. Given that replication without errors takes a time c_0, time of replication with repair, c_r, may be expressed as a function of error rate, x:

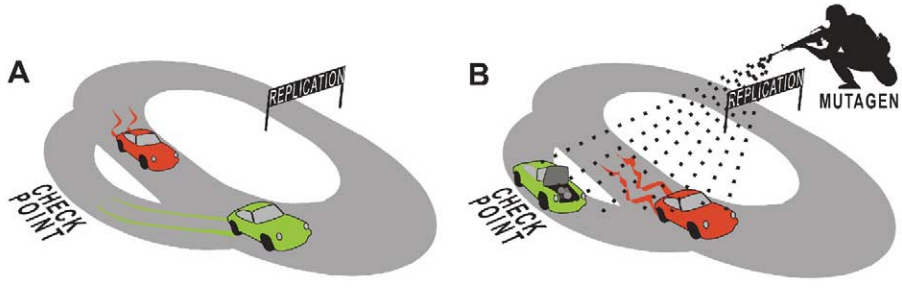

Fig. 1. The cell cycle grand prix, and effects of opposing repair strategies in different environments. Team I (green) always stops for repairs when a problem is indicated, whereas Team II (red) ignores all warning lights. Team I wins under ordinary conditions (A) because it always has a faultless vehicle, whereas Team II accumulates errors. In the harsher environment (B) the vehicles accumulate damage more quickly than can be repaired, and Team I gets trapped in the checkpoint. Team II, on the other hand, jerks along with its faulty vehicle, and still has a fair chance of making the finish line. This simple assessment of repair strategies provides a metaphoric explanation for the paradox that mutagenic environments favor repair deficiency. Reproduced from [22].

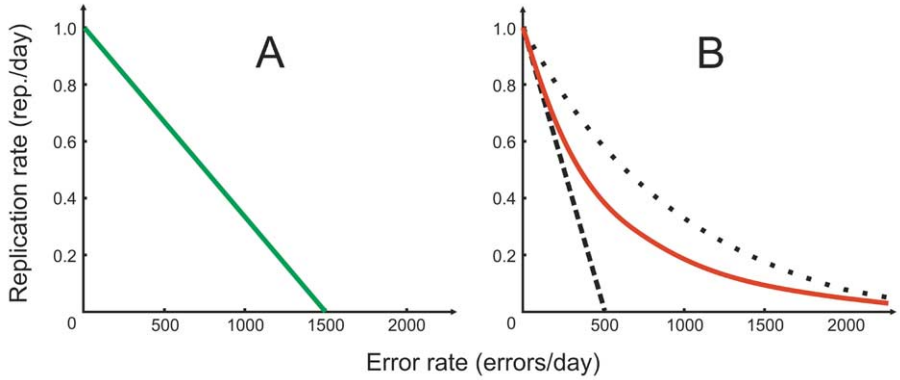

Fig. 2. A graphical representation of replication rate as a function of error rate with and without DNA repair. A: Replication rate with repair $f_r(x)$ falls linearly towards a maximum error rate ($x = 1/r$) at which errors appear faster than they can be removed. B: Replication rate without repair $f_m(x)$ falls sharply at low error rates, but flattens out towards zero as non-lethal errors get less important and replication rate is predominantly determined by the effect of lethal mutations. The curve is modulated between functions based on the initial cost of non-lethal errors (hatched line), and the isolated cost of lethal mutations (dotted line). Values have been selected on theoretical grounds to illustrate the principal relationship.

$$c_r = c_0 + c_0xr + c_0(xr)^2 + c_0(xr)^3 \ldots = c_0\sum_{n=0}^{\infty}(xr)^n$$

Summation takes account of the fact that repair of errors takes a time that allows for more errors. Replication rate with complete repair may then be expressed as a function of error rate:

$$f_r(x) = \frac{1}{c_0\sum_{n=0}^{\infty}(xr)^n}$$

From this assessment it becomes evident that replication with repair has an upper limit ($x = 1/r$). Above this point errors appear faster than they can be removed, and replication is completely blocked by repair-related delay (Fig. 2A). The repair mechanism thus blocks rather than promotes the replication process, and the equation may be understood as a mathematical representation of our metaphor 'Don't stop for repairs in a war zone' [22].

This simple assessment thus explains why DNA repair may be unfavorable in mutagenic environments, and that is indeed the key message of this paper. Still, in order to understand genetic instability, we must also explain why repair deficiency may be a better alternative. In principle, we must assess the effect of errors.

Basically, the effect that each error has on time of replication may be represented by a probability distribution ranging from maximally adaptive to lethal, with an average m (Fig. 3). m represents the cell cycle delay caused by the average error, and replication time without repair, c_m, may be expressed as another function of error rate, x:

$$c_m = c_0 + c_0xm + c_0(xm)^2 + c_0(xm)^3 \ldots = c_0\sum_{n=0}^{\infty}(xm)^n$$

In addition, each error also has a probability p of being lethal, and replication rate without repair may then be expressed as:

$$f_m(x) = \frac{(1-p)^{\left(\sum_{n=0}^{\infty}\right)}}{c_0\sum_{n=0}^{\infty}(xm)^n}$$

By comparing the two functions, it now becomes evident that an increase of mutation rate will have quite different effects on a repair-proficient than on a repair-deficient system. Most obviously, the probabilistic effect of lethal errors makes repair particularly beneficial at low error rates. A single error costs practically nothing to repair, but can still cause complete disaster.

Furthermore, the average effect of a non-lethal mutation is not constant. Fig. 3 illustrates how m is directly dependent on the time of replication. A large c will stretch the probability distribution to the left, and necessarily move m closer to zero. Quite logically, a non-lethal error is more likely to impair replication of an optimized system than a redundant one, and it can do little harm to a system at replication arrest. In fact, for a system at complete arrest, m is negative, and non-lethal mutations can only be neutral or adaptive. That, however, must not be confused with the idea that random mutagenesis is favorable. Each error still has a probability of being lethal, and as m decreases, replication rate approaches:

$$f_m(x) = \frac{(1-p)^{xc_0}}{c_0}$$

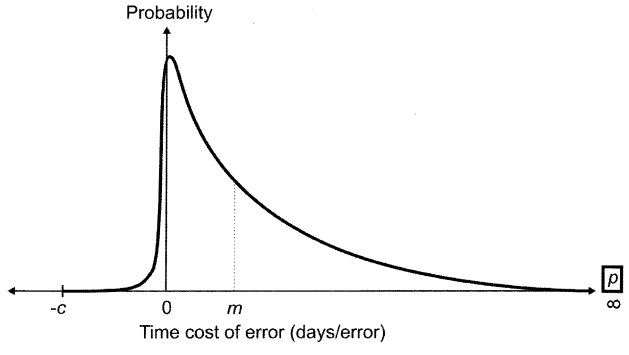

Fig. 3. Theoretical cost of an error in terms of replicational delay. The effect of each non-lethal error has a probability distribution ranging from maximally adaptive ($-c$, replication time = 0) to eternal delay (∞) with an average (m). In addition each error has a probability of being lethal (p). Notice that a reduction in replication time (c) moves the probability distribution to the right, and thus increases the average cost of a non-lethal error. Conversely, high replication time increases the probability for adaptive mutations by stretching the probability distribution to the left.

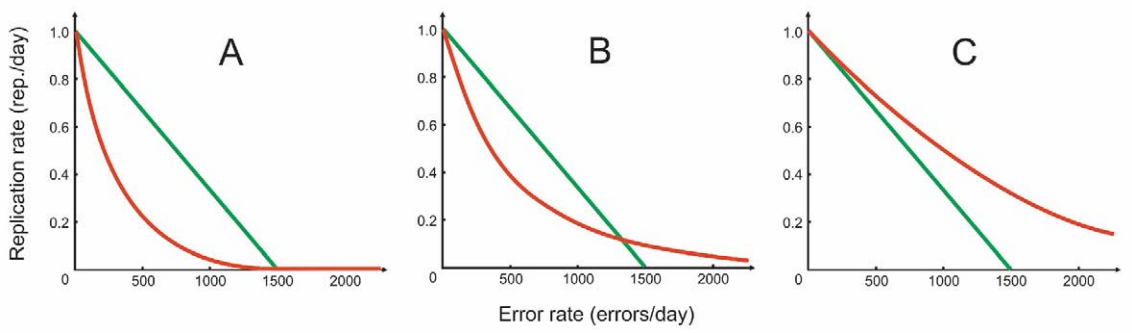

Fig. 4. Replication rate as a function of error rate with (green) and without (red) DNA repair imply three principal configurations. A: Replication rate without repair is lower than replication rate with repair at all viable error rates, and repair represents the best evolutionary strategy. B: Replication rate without repair is lower than replication rate with repair at low, but not at high error rates, thus defining an evolutionary transition point between the two strategies. C: Replication rate without repair is higher than replication rate with repair at all error rates, and the repair mechanism has a negative evolutionary potential.

Modulating from these mathematical considerations, we get a general representation of replication rate without DNA repair as a function of error rate (Fig. 2B). The functions for replication rate with and without repair may then be compared graphically, and reveal three categorically different configurations (Fig. 4).

4. Implications

4.1. Adaptation to mutagenic environments

The three different configurations demonstrate how an elevation of mutation rate may have quite opposite effects on the evolutionary potential of DNA repair. Whereas a cost-efficient repair mechanism will be advantageous at all viable error rates (Fig. 4A), a less efficient mechanism may be favorable at low, but not at high error rates (Fig. 4B). The model thus corresponds directly to the intriguing relationship between *O*(6)-methylguanine-DNA methyltransferase and nucleotide mismatch repair [33].

O(6)-Methylguanine-DNA methyltransferase, which efficiently removes methylating damage from the DNA molecule, confers resistance to the cytotoxic effects of methylating agents [34]. Nucleotide mismatch repair, on the other hand, which functions as an inefficient backup against methylating damage, confers susceptibility [33,35]. Accordingly, the model explains the evolutionary loss of mismatch repair in methylating environments [20,34].

Other repair-related genes, e.g. the *TP53* tumor suppressor gene, may involve a significant growth inhibition even at low error rates [36,37]. Such systems are thus congenitally removed from their replication optimum (Fig. 4C), and loss of function may be seen as an unavoidable consequence of time (aging).

4.2. Adaptation to growth-limiting environments

As demonstrated by Fig. 3, an elongation of replication time will necessarily decrease the average cost of non-lethal errors. Slow growth makes each error statistically cheaper, and repair relatively more expensive. Any growth-inhibiting environment, regardless of mutagenicity, may thus transform the evolutionary potential of a repair mechanism from positive (Fig. 4A) to error rate-dependent (Fig. 4B) and all the way to constitutively negative (Fig. 4C).

This relationship sheds new light on the observation that genetically unstable bacteria have a transient advantage when colonizing a new gut [13]. So far, this effect has been interpreted as a temporary advantage of mutagenesis. In accordance with the mutation for survival hypothesis, the unstable cells have been regarded as more adaptable than the stable variants [4]. We, on the other hand, will argue that the growth-limiting environment increases the relative cost of repair, and instantly favors the repair-deficient variant. But there is no ground for claiming that the unstable genomes are more adaptable. On the contrary, the experiments clearly demonstrate that it is the genetically stable systems that adapt most successfully to the new environment [13].

Reverting to analogies, it may be concluded that fine-tuning the engine is a futile strategy when stuck in the mud, but abandoning the engineer will leave you behind in the long run.

4.3. Transition point for apoptosis and stationary phase mutagenesis

The evolutionary transition point between costs and benefits of repair (Fig. 4B) represents a key aspect of the model. Above this point, the given repair mechanism ceases to be a favorable evolutionary strategy, and thus opens a window of opportunity for repair-deficient variants. A somatic cell that enters this window is in practice beyond the control of the repair mechanism, and represents a potential threat to propagation of the germ-line. The transition point thus defines an evolutionary optimum for switching from repair to apoptosis, and the model provides a conceptual framework for understanding this molecular decision process.

For single-celled systems the transition point represents quite a different challenge. The evolutionary objective is not to prevent but rather to facilitate an efficient transition. Natural selection should therefore favor mechanisms that turn off DNA repair in response to growth-limiting or DNA-damaging environments, and back on again when the stress is relieved. This type of stress response has been observed in different microbial systems. It is commonly referred to as stationary phase mutagenesis, and is generally interpreted in the context of the mutation for survival hypothesis [38]. We, however, will argue that stationary phase mutagenesis should be understood as a direct adaptation to the changing costs of maintaining high-fidelity replication in a dynamic environment.

4.4. Site-specific instability

So far, all our arguments have been based on the assumption that mutagenesis is a stochastic process, which has equal

effects throughout the genome. That, however, is far from being the case. Site-specific mutagenesis is for example well known in immunology. Different genes direct rearrangements and point mutations to highly specific segments of the lymphocyte receptor genes [39], and thus form the basis for adaptive immunity [40]. On the opposite side of the defense line, it is well known that virulence factors are encoded in unstable sequences [41], and accumulating evidence suggests site-specific mutagenesis in microbial systems [42].

In principle, such site-specific mutagenesis is caused by genes that have evolved the ability to alter specific segments of the genome, i.e. genes that alter genes. Quite intriguingly, DNA repair may be seen as the logical opposite. DNA repair genes have evolved the ability to prevent specific alterations in the genome, and loss of function logically affects the corresponding sequences.

Just as mutagenic agents leave specific footprints [43], different types of repair deficiency generate highly recognizable mutagenic patterns. Mismatch repair deficiency frequently affects repetitive nucleotide sequences, and thus causes microsatellite instability [44]. Similarly, defects in the regulation of chromosomal segregation cause chromosomal instability [2,9], which also affects some sites more than others [45]. A comprehensive model of genetic instability must therefore consider the site-specific effects of repair deficiency.

Site-specific instability implies an alteration in the probability distribution of errors, and a low probability of mutations being unfavorable (low m and p) will necessarily favor loss of the repair mechanism. This relationship may thus explain the frequent loss of mismatch repair in tumors and microbes. As the resulting microsatellite instability primarily affects regulatory and non-lethal sequences [46], repair deficiency becomes relatively more favorable. This line of reasoning may also explain why nucleotide excision repair, which removes bulky adducts, is rarely lost in cancers. As each error is likely to cause trouble, this repair mechanism remains a favorable evolutionary strategy despite its high costs [47,48].

5. Conclusion

The dogma that genetic instability arises because random mutations are evolutionarily favorable is deeply rooted in the scientific community, and substantial amounts of evidence have been interpreted in favor of this view [4,12–14]. In this paper, we have presented an alternative model that predicts loss of genetic stability in environments where the evolutionary cost of DNA repair exceeds the cost of errors. The model no doubt represents a gross simplification of biological complexity, but its validity rests on the simple fact that the costs and benefits of DNA repair are asymmetrical functions of error rate. This relationship explains loss of repair and rise of genetic instability in the combined perspective of Darwinian evolution and information processing, and has general implications for the understanding of biology.

A key test of the model would be to experimentally identify the predicted transition point at which DNA repair ceases to be a favorable evolutionary strategy. One interesting approach is to expose e.g. genetically stabilized cancer cells [20] to a dynamic environment alternating between optimal and stressful conditions. This environment should in theory select variants that respond rationally to the transition point by switching repair on and off. We foresee a number of technical difficulties, but hope our model will inspire creative experiments in several fields of research.

In direct opposition to our new ideas it has been claimed that "DNA repair exists to repair DNA" [12]. Therefore, it should be irrational to believe that DNA-damaging environments favor loss of DNA repair. That might seem obvious. In a different perspective, however, the above claim may be seen as reminiscent of the pre-Darwinian idea that biology is designed for a purpose. We claim that DNA repair genes, as all other genes, exist solely for their thermodynamic potential to self-replicate in their given environment. When this environment changes, and the evolutionary potential disappears, so do the genes.

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