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Historical perspective on the DNA damage response

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ABSTRACT

The DNA damage response (DDR) has been broadly defined as a complex network of cellular pathways that cooperate to sense and repair lesions in DNA. Multiple types of DNA damage, some natural DNA sequences, nucleotide pool deficiencies and collisions with transcription complexes can cause replication arrest to elicit the DDR. However, in practice, the term DDR as applied to eukaryotic/mammalian cells often refers more specifically to pathways involving the activation of the ATM (ataxia-telangiectasia mutated) and ATR (ATM-Rad3-related) kinases in response to double-strand breaks or arrested replication forks, respectively. Nevertheless, there are distinct responses to particular types of DNA damage that do not involve ATM or ATR. In addition, some of the aberrations that cause replication arrest and elicit the DDR cannot be categorized as direct DNA damage. These include nucleotide pool deficiencies, nucleotide sequences that can adopt non-canonical DNA structures, and collisions between replication forks and transcription complexes. The response to these aberrations can be called the genomic stress response (GSR), a term that is meant to encompass the sensing of all types of DNA aberrations together with the mechanisms involved in coping with them. In addition to fully functional cells, the consequences of processing genomic aberrations may include mutagenesis, genomic rearrangements and lethality.

1. Introduction

The proliferation of living cells requires that the genomic DNA must be replicated. A proliferating cell must duplicate its entire complement of DNA with astonishing precision in the face of a barrage of deleterious endogenous and environmental genotoxic agents, as well as the intrinsic chemical instability of the DNA molecule itself [1]. Naturally occurring non-canonical DNA structures can also pose a challenge to replication [2,3]. Transcription complexes, translocating along the same DNA track, may collide with replication forks [4]. Some types of encumbrances are more critical than others; one double-strand break or an interstrand crosslink can, in principle, be sufficient to preclude the generation of viable daughter cells [5]. It is not surprising that a complex set of responses has evolved within the past four billion years to deal with all types of damage and other obstructions that might prevent completion of the DNA replication cycle and the allocation of essentially identical genomes to progeny. Somewhat less important to cell proliferation are the consequences of most mutations, even though a subset of those will also impact the essential processes of replication and completion of the cell cycle.

The primary approach to minimize mutagenesis and to ensure completion of genomic replication is to repair the offending DNA lesions. Several of the DNA repair pathways (e.g., base excision repair (BER) and those initiated by ATM-Rad3-related (ATR) are so important that life cannot be sustained without them (cf. [6])). Furthermore, there are a number of hereditary diseases with predisposition to cancer and/or aging that are linked to deficiencies in DNA repair. These are detailed in numerous reviews and several texts in this rapidly developing field (cf. [7–11]). The various DNA repair pathways sometimes compete with each other for processing the same lesion, and each step in a multistep repair pathway creates an intermediate that constitutes another lesion (e.g., strand break or single-strand gap), which may be susceptible to intervention by enzymes from another pathway. The overall response to DNA damage may be viewed as a set of successive stages, with a decision point at each stage until the DNA integrity has been restored [12]. Sometimes the first protein to access the lesion may be a transcription factor or another protein that is not directly involved in DNA repair. The outcome for the cell, and the organism of which it is a part, may depend upon which protein first encounters the lesion [13]. Also, the response to the damage may require a threshold level of damage so that very low levels of lesions might

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be overlooked, whereas substantial amounts of damage or particular types of lesions (e.g., double strand breaks) may induce a robust response. Thus, the overall DNA damage response consists of many separate and sometimes competing components, and the outcome for the cell may not necessarily be ascribed to a particular pathway without full knowledge of the growth phase and cellular environment; for example, it is particularly important to know whether the cell is undergoing DNA replication, or is in a quiescent or terminally differentiated state. The comprehensive response could be termed the genomic stress response (GSR) to accommodate those situations in which there is no initial damage, even though one or more of the processing steps may generate damage in the course of the response. The cellular outcome, in terms of mutagenesis or lethality, is clearly a downstream event that is dependent upon many factors following the initial recognition of an aberration.

2. Early history of DNA damage responses

Photoreactivation was probably the first example of an elucidated DNA damage response (see recent review [14]). In the early 1960s photoreactivation was shown to require a photolyase, which binds UV-induced cyclobutane pyrimidine dimers (CPDs) and upon activation by visible light, reverses them without breaking phosphodiester bonds in the DNA backbone. Photoreactivation is arguably the first DNA repair mechanism to have evolved, since it was likely essential for the survival of early life forms under the intense UV flux from sunlight, before there was a protective ozone layer in the stratosphere. Of course, the shorter UV wavelengths would have continued to generate CPDs while photolyase was attenuating them, so the resulting steady-state level of these lesions must have been an ongoing threat. Although CPDs were not identified until 1960 [15], evidence for mechanisms to deal with UV-induced damage in the dark arose from the phenomenon of liquid holding recovery; the survival of UV-irradiated bacteria was enhanced (and mutagenesis was suppressed) upon nutrient deprivation for a period following the irradiation, later considered to provide a "window" for repair while other DNA transactions were suppressed [16–19]. The idea of "dark repair" was also supported by the isolation of mutants affecting UV sensitivity of bacteria [20–25]. The ubiquitous pathway of nucleotide excision repair (NER), discovered in 1964 in *Escherichia coli*, utilizes the redundant genetic information in duplex DNA. A stretch of nucleotides containing a CPD or other lesion in one strand can be excised, and the resulting gap can be filled by repair replication using the intact complementary strand as template [26–28]. Polynucleotide ligase, discovered in 1967 [29], joins the newly-synthesized patch to the contiguous parental DNA strand. Evidence for NER in humans was initially reported as "unscheduled DNA synthesis" following UV irradiation of non-S-phase cells [30], and later validated as repair replication [31]. In the course of evolution some organisms, including humans, have lost the capability for photoreactivation to eliminate CPDs, evidently in favor of NER, which is highly efficient, more versatile and not constrained by requiring sunlight. The excision-repair modes of BER and mismatch repair (MMR) were reported in the mid-1970's [32,33].

With respect to excision-repair, early concern was raised about the complication created if an advancing replication fork encountered the lesion site following the excision step but before completion of the repair patch. The likely outcome, illustrated in Fig. 1, is a complicated sort of double-strand break (with only one duplex end), which probably would be lethal. A bacterial culture in which DNA replication had been synchronized by the inhibition of protein and RNA synthesis to allow completion of the cycle without new initiations was strikingly resistant to UV in comparison to an asynchronous culture in exponential growth. In

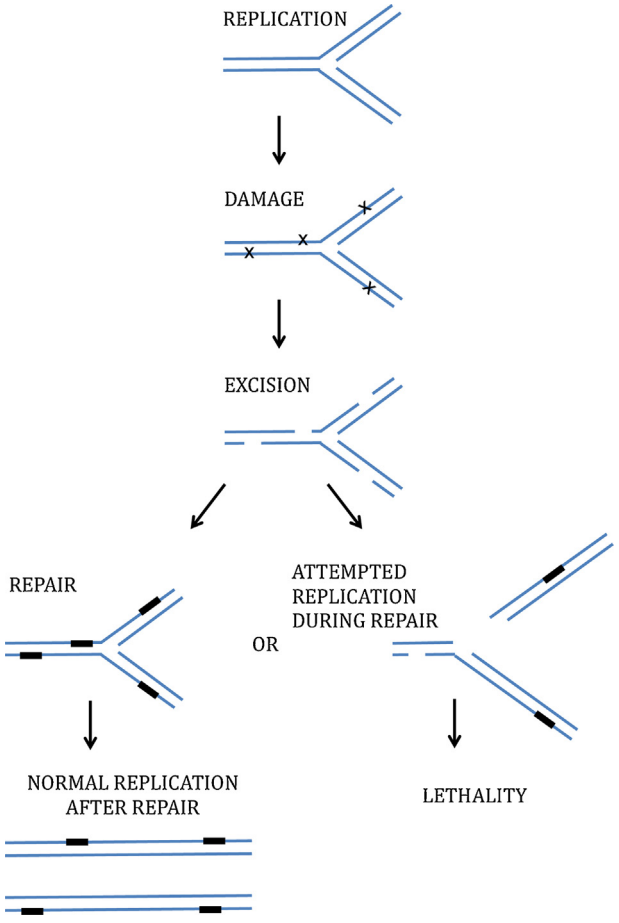

Fig. 1. Early model for the expected consequence if a replication fork encountered a single strand break in the DNA template strand. This was presented after the discovery of repair replication but prior to the discovery of Okazaki fragments and discontinuous lagging strand synthesis.
Source: Adapted from Hanawalt [34].

contrast, the NER deficient strain, *E. coli* B_{S-1}, was equally sensitive to UV during exponential growth or when the DNA replication cycle had been completed, implying that NER was essential for the enhanced resistance in the wild-type cells [34]. Repair replication was documented at the restrictive temperature in several temperature-sensitive strains of *E. coli*, unable to carry out chromosomal replication at the restrictive temperature [35]. Nearly identical UV survival curves were reported for *E. coli* strain TAU irradiated in stationary phase or after starvation for the required arginine and uracil [36]. It was concluded that the remarkable UV resistance of stationary phase cells results from the completion of DNA repair in the absence of chromosomal DNA replication; this emphasizes the importance of completing repair to avoid collisions of replication forks with lesions or intermediates in their repair [34].

3. Inducible responses to DNA damage and replication fork arrest

The enzymes required to detect damaged DNA can sometimes attack undamaged DNA, and such gratuitous events might be deleterious. (Any DNA strand break potentially puts the cell at risk.) A hierarchy of NER activity in extracts of *E. coli* and human cells was shown to act on various lesions with different affinities, and this included "undamaged DNA" at a low level [37]. The situation is also complicated by the fact that some natural DNA sequences can