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Review

Alternative end-joining repair pathways are the ultimate backup for abrogated classical non-homologous end-joining and homologous recombination repair: Implications for the formation of chromosome translocations

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ABSTRACT

DNA double strand breaks (DSB) are the most deleterious lesions for the integrity of the genome, as their misrepair can lead to the formation of chromosome translocations. Cells have evolved two main repair pathways to suppress the formation of these genotoxic lesions: homology-dependent, error-free homologous recombination repair (HRR), and potentially error-prone, classical, DNA-PK-dependent non-homologous end-joining (c-NHEJ). The most salient feature of c-NHEJ, speed, will largely suppress chromosome translocation formation, while sequence alterations at the junction remain possible. It is now widely accepted that when c-NHEJ is inactivated, globally or locally, an alternative form of end-joining (alt-EJ) removes DSBs. Alt-EJ operates with speed and fidelity markedly lower than c-NHEJ, causing thus with higher probability chromosome translocations, and generating more extensive sequence alterations at the junction. Our working hypothesis is that alt-EJ operates as a backup to c-NHEJ. Recent results show that alt-EJ can also backup abrogated HRR in G_2 phase cells, again at the cost of elevated formation of chromosome translocations. These observations raise alt-EJ to a global rescuing mechanism operating on ends that have lost their chromatin context in ways that compromise processing by HRR or c-NHEJ. While responsible for eliminating from the genome highly cytotoxic DNA ends, alt-EJ provides this function at the price of increased translocation formation. Here, we analyze recent literature on the mechanisms of chromosome translocation formation and propose a functional hierarchy among DSB processing pathways that makes alt-EJ the global backup pathway. We discuss possible ramifications of this model in cellular DSB management and pathway choice, and analyze its implications in radiation carcinogenesis and the design of novel therapeutic approaches.

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1. Introduction

Together with replication and transcription, repair is a fundamental component of the DNA metabolism. Indeed, maintenance of DNA integrity is essential for the genomic stability of any organism. Importantly, in all organisms, DNA integrity is challenged by multiple internal and external agents and processes that chemically alter, i.e., damage, the DNA building blocks compromising thus their coding fitness. Intracellular sources of DNA damage include base-hydrolysis or deamination from water attack, as well as base- and sugar oxidation from reactive oxygen species generated as byproducts of the cellular metabolism. Extracellular sources include environmental, medical or accidental exposures to ionizing radiation (IR), as well as exposures to ultraviolet (UV) light.

IR and UV-light induce chemical alterations in the DNA that must be recognized and processed by the cellular DNA repair machinery. The vast majority of these chemical alterations is confined locally to one DNA strand and can, in the absence of interference with DNA replication, be readily repaired through lesion excision and subsequent strand restoration. Strand restoration takes advantage of the double-stranded nature of the DNA and readily copies missing segments generated after lesion removal on the damaged strand based on information available on the undamaged strand (Fig. 1A). In this way the vast majority of chemical alterations generated in the DNA by external or internal sources are removed and genomic integrity is maintained. Repair pathways

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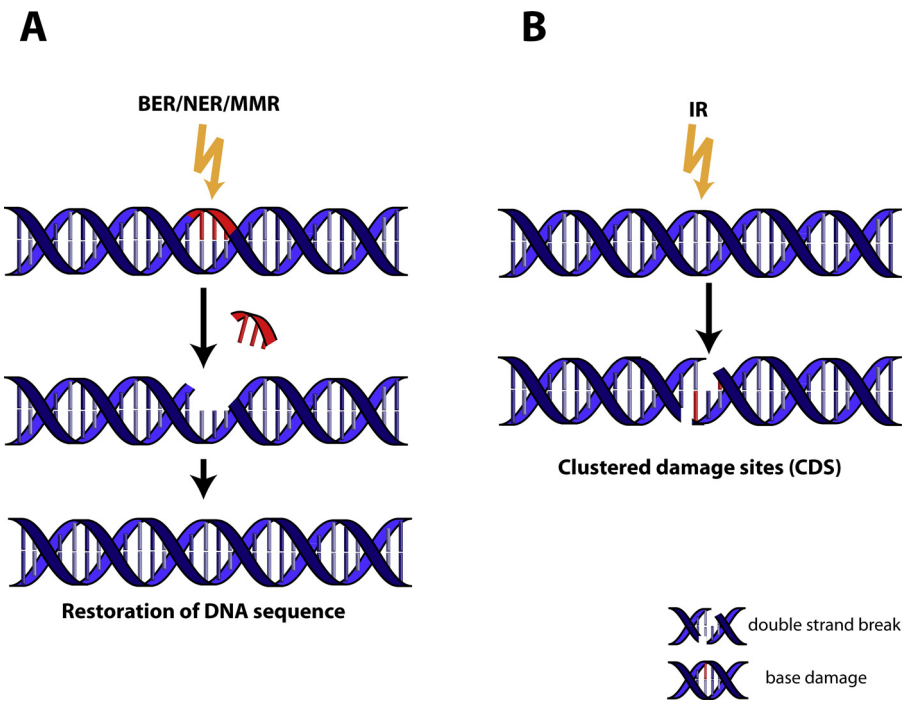

Fig. 1. The special character of IR-induced DNA damage. (A) Lesions induced in only one strand of the DNA can be excised and the missing strand-segment replaced using sequence information available on the intact DNA strand. (B) Ionizing radiation generates clusters of ionizations that induce clustered DNA damage sites (CDS). A CDS can contain multiple lesions distributed on both DNA strands and spaced only a few nucleotides apart. Repair of a CDS is normally not possible with the mechanism outlined in A—it will require other repair mechanisms.

successfully employing this concept include base excision repair (BER), nucleotide excision repair (NER) and mismatch repair (MMR) [1].

1.1. The specific processing requirements of DNA double strand breaks (DSBs)

This fundamental principle of DNA repair is naturally compromised when two or more of the induced lesions (base or sugar damages) are directly apposed in the double-stranded DNA molecule—or lie only a few nucleotides apart (typically less than 10). Restoration of the DNA molecule will in this case not be possible as described above, as an intact template strand is not available. Forms of damage comprising two or more lesions distributed on both DNA strands in close proximity, i.e., within about 10 bp, are commonly termed clustered damage sites (CDS) [2,3] (Fig. 1B).

Endogenous and exogenous sources of DNA damage rarely induce CDS. The best known and most widely used agent able to induce clustered damage in the DNA by virtue of its energy deposition characteristics is IR [3–6], in the form of X-rays or gamma rays, and more pronouncedly in the form of densely ionizing forms of radiation such as alpha-particles emitted from radon gas, or heavy ions present in space or used in advanced centers of cancer therapy. While the total energy deposited by X-rays or gamma-rays is largely deposited in the form of single ionization events that induce single DNA-base-alterations or DNA-single-strand-breaks (SSBs), a small proportion of total energy is deposited in the form of ionization clusters that form clusters of damage in the DNA [7] (Fig. 2).

The DSB is one of the most characteristic and biologically relevant forms of clustered DNA damage, as it severs (cuts, breaks) the DNA molecule. IR-induced DSBs can comprise single sugar damages that disrupt the continuity of the phosphodiester backbones on each of the two DNA strands, but can also be accompanied by extra base and sugar damages that will increase DSB "complexity" [7]. DSBs can also be generated enzymatically in the irradiated DNA from the incision during repair of base-damage sites within a CDS. The possibility of a CDS to present as, or develop to, a DSB is considered its most biologically relevant consequence [7].

DSBs, by affecting both strands of the DNA helix, compromise the fundamental principle utilized by other DNA repair pathways to copy missing information during single lesion processing (Fig. 1A). As a result, they require the development of specific solutions for error-free processing, and, as we discuss below, are associated

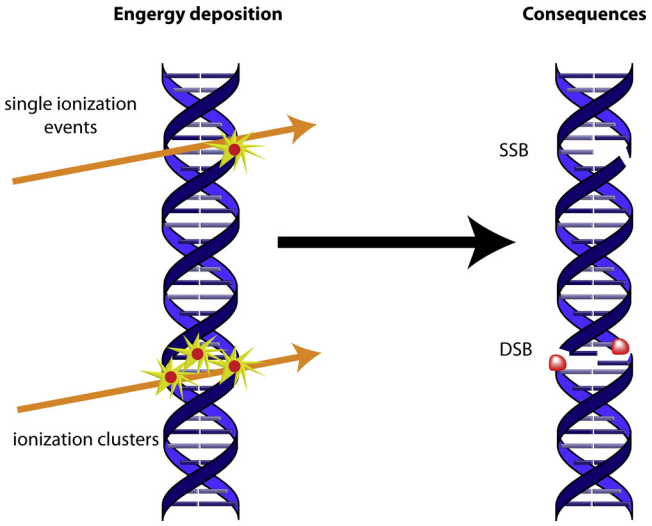

Fig. 2. Energy deposition by IR. Most of the energy deposited by X-rays or gamma-rays is in the form of single ionization events inducing single DNA base or sugar alterations, including DNA single strand breaks (SSB). A small proportion of total energy, however, is deposited in the form of ionization clusters, some of which lead to the formation of DSBs. DSBs forming after IR exposure have damaged bases and sugar moieties at their ends (indicated by the red circles) and need processing before ligation.

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