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The Intricate Relationship between DNA Repair Mechanisms and Cancer

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DESCRIPTION

The integrity of our DNA is paramount for the proper functioning of cells and the prevention of diseases such as cancer. DNA repair mechanisms are critical for maintaining this integrity by correcting damage caused by environmental factors, metabolic processes, and errors during DNA replication. However, in the context of cancer, these repair mechanisms can become a double-edged sword. While they usually protect against cancer by preventing mutations, they can also contribute to cancer development and resistance to therapy when they malfunction or are hijacked by cancer cells. This article explores the intricate relationship between DNA repair mechanisms and cancer, highlighting key pathways and their implications for cancer treatment. DNA damage can occur due to a variety of internal and external factors. Internally, reactive oxygen species generated during metabolism can cause oxidative damage. Externally, ultraviolet light, ionizing radiation, and chemical agents can inflict direct harm to DNA. To counteract this, cells have evolved several DNA repair pathways, each specialized in correcting specific types of damage. Base Excision Repair is the primary pathway for correcting small, non-helix-distorting base lesions, such as those caused by oxidative damage. Enzymes called glycosylases recognize and remove damaged bases, creating an abasic site that is subsequently processed by endonucleases, DNA polymerase, and DNA ligase to restore the correct sequence.

Nucleotide Excision Repair deals with bulky, helix-distorting lesions, including those induced by UV light. NER involves the recognition of DNA damage, excision of a short single-stranded DNA segment containing the lesion, and synthesis of the correct sequence using the undamaged strand as a template. Mismatch Repair corrects replication errors such as base-base mismatches and small insertions or deletions that escape the proofreading activity of DNA polymerases. Proteins like MutS and MutL recognize and initiate the repair process, ensuring replication fidelity. Homologous Recombination and Non-Homologous End Joining are the major pathways for repairing double-strand breaks. HR is an error-free process that uses a sister chromatid as a template to accurately repair breaks, predominantly occurring during the S and G2 phases of the cell cycle. NHEJ, on the other hand, is an error-prone process that directly ligates the broken ends without a template, functioning throughout the cell cycle. The role of DNA repair mechanisms in cancer is multifaceted. On one hand, they prevent cancer by repairing DNA damage that could lead to mutations and genomic instability. On the other hand, defects in these pathways are a hallmark of many cancers, contributing to their development and progression.

The interplay between DNA repair mechanisms and cancer has significant therapeutic implications. Targeting DNA repair pathways in cancer cells can enhance the efficacy of existing treatments and overcome resistance. PARP inhibitors are a prime example of exploiting DNA repair deficiencies in cancer therapy. PARP (poly ADP-ribose polymerase) is involved in BER, and its inhibition is particularly effective in cancers with BRCA1 or BRCA2 mutations. These cancers are already compromised in HR, so inhibiting PARP leads to an accumulation of DNA damage, ultimately causing cell death. This synthetic lethality approach has shown promise in treating BRCA-mutated breast and ovarian cancers. Another emerging strategy involves inhibiting NHEJ to enhance the effectiveness of radiotherapy. Since NHEJ is error-prone, its inhibition forces cancer cells to rely on the less efficient HR pathway, which can be overwhelmed by the high levels of DNA damage induced by radiation. Furthermore, immune checkpoint inhibitors have shown that DNA repair deficiencies can increase the mutational burden of tumors, making them more recognizable to the immune system. Tumors with high microsatellite instability, a result of defective MMR, respond well to these immunotherapies, highlighting the potential of leveraging DNA repair defects to enhance anti-tumor immunity.

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CONFLICT OF INTEREST

The author's declared that they have no conflict of interest.

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