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Research Paper

Targeting DNA damage response pathways for cancer therapy

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Abstract
Cancer has long been thought to be a cellular disease caused by mutations in genes involved in cell propagation, differentiation, and death, resulting in an aberrant cell mass. Genomic instability is a defining feature across a spectrum of cancers, characterized by the progressive accumulation of DNA damage. Defects in DNA repair pathways facilitate genomic instability, which in turn promotes cancer cell proliferation and survival rates. Nonetheless, cancer cells rely on the remaining capacity of DNA repair mechanisms to shield them from further damage. Targeted cancer therapy may lower cancer cells' DNA damage response by personalizing treatment to patients who lack specific functions. One example where we have a deeper insight into how genetic DDR abrogation impacts therapy responses is in tumors with mutated BRCA1 or BRCA2. In tumors with BRCA1 or BRCA2 mutations, compromised homologous recombination repair makes them vulnerable to PARP inhibitors, which selectively kill these cancer cells. This has become a model for targeted cancer therapy. In this review, we summarize the mechanisms of DNA damage repair associated with targeted cancer therapy, focusing on the specific proteins that become dysfunctional due to extrinsic damage from environmental factors.

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Objective of study

The complexities of intratumor heterogeneity and cancer evolution pose significant challenges to modern medicine, rendering cancer one of the most elusive threats to human life. DNA repair pathways are essential for maintaining genomic stability, yet how cancer cells exploit these pathways to sustain intratumor instability for evolutionary advantage remains largely unexplored. This exploitation leads to diminished DNA repair capabilities, resulting in genomic instability within cancer cells. However, the destruction of one DNA repair pathway by certain agents may prompt compensation by alternative pathways. Identifying and targeting these compensated pathways offers potential avenues for treating cancers with defective DNA repair mechanisms.

DNA repair Pathways

Numerous repair pathways are present, encompassing direct reversal, base excision repair(BER), nucleotide excision repair (NER), mismatch repair (MMR), single-strand break repair (SSB), and double strand break (DSB) repair. MMR system main function is to eradicate mutational intermediates produced by DNA polymerisation errors after replication. NER stands out as the most versatile DNA repair pathway, recognise and eliminate various bulky DNA lesions that destabilize the DNA duplex. Two primary types of pathways for repairing double-strand breaks (DSBs) have been identified: homologous recombination (HR) and non-homologous end joining (NHEJ).

DNA damage and Cancer Evolution

Various types of DNA damage have been documented previously, encompassing single-strand breaks, double-strand breaks (DSBs), base damage, sugar damage, DNA cross-linking, and clustered damaged sites. Among these, DSBs pose the most significant threat to cells, potentially leading to carcinogenesis or cell death if left unrepaired or undergoing error-prone repair. Both environmental factors and endogenous toxic agents like free radicals contribute to DNA damage, compromising genome stability and promoting diseases, notably cancer. Given the substantial DNA damage cells encounter from sources like ionizing radiation or reactive oxygen species (ROS), further investigation into the mechanisms of DNA damage occurrence is imperative. The DNA damage response (DDR) represents a complex network that operates through diverse mechanisms

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targeting various DNA lesions. These include signal transduction, transcriptional regulation, cell-cycle checkpoints, apoptosis induction, damage tolerance processes, and multiple DNA repair pathways.
Several DDR inhibitors have currently come to market or under clinical development. Among them, PARP inhibitors represent the first clinically approved DDR drugs. These inhibitors have been extensively utilized in cancer patients with mutations in BRCA1 and BRCA2 or deficiencies in homologous recombination repair (HRR), demonstrating promising clinical efficacy.

DNA damage response and cancer

Several concepts underlie the targeting of DDR in cancer (i) Utilizing DDR as a target for anticancer drug therapies; (ii) Exploring inhibition targets in remaining DDR pathways, considering the deficiency of certain pathways in most cancer cells; (iii) Investigating cancer replication stress through DDR inhibition; and finally (iv) Using DDR inhibitors in specific DDR-deficient contexts to pave the way for future cancer treatments.

Methodology

Single-cell and spatial transcriptome sequencing, two recently optimized transcriptome sequencing methods, are increasingly used to study cancer and related diseases. Also,deep sequencing and microarrays for cancer genome profilingprovide enhanced insights into the mutations and misregulationsof DNA damage response (DDR)-related genes. Despite these advancements, there remains an urgent need for a deeper comprehension of DDR pathways and the discovery of innovative ideas to enhance cancer treatment.

Whole-genome sequencing

In whole-genome sequencing, fragmented genomic DNA undergoes minimal processing before being directly subjected to massively parallel sequencing, often involving multiple cycles of PCR amplification. This approach enables the identification of various structural abnormalities, including chromosomal translocations, deletions, insertions, and copy number alterations, in a comprehensive manner. Additionally, whole-genome sequencing can unveil the intricate landscape of cancer genomes, revealing tens to hundreds of genomic rearrangements within localized genomic regions, a phenomenon known as 'chromothripsis.'

Single-cell sequencing

Single-cell sequencing (SCS) is an emerging powerful technique that will undoubtedly lead to a better understanding of the complex genetic variability within individual cells. Changes at the RNA level that regulate tumorigenesis and determine differential cell fate and cellular heterogeneity within a tumor remain unclear. Studying individual cell transcriptomes could explain, in a more detailed and reliable fashion, the genetic variations between tumor cells in a single patient. The SCS method not only allows the identification of genetic variability between individual cancer cells but also enables analysis of the evolution of a tumor.SCS methods also have many translational applications in developing anticancer treatments. For instance, the identification and analysis of rare subpopulations of CTCs at an early stage and during follow-up may enable oncologists to track genetic mutations in and make crucial changes in therapeutic treatments to avoid drug resistance.

Deep sequencing

Intratumoral heterogeneity is widely observed in cancers, often serving as a significant factor contributing to tumor recurrence or resistance against anti-cancer treatments. Deep sequencing, particularly in conjunction with whole-genome or exome sequencing, offers the most effective means to assess this phenomenon. By analyzing mutations detected through genome or exome sequencing at greater depths, accurate allele frequencies can be determined, providing valuable insights into intratumoral heterogeneity.As low as 1% of minor alleles could be sensitively detected by target deep sequencing depending on experimental conditions and sequencing platforms. Saha et al. performed deep sequencing (median 20 000 times) of somatic mutations in triple-negative breast cancers detected by whole-exome sequencing, in which existence of subclones with different mutant allele frequencies were clearly demonstrated in most of cases.

Microarrays

Therefore, a microarray measures mRNA transcript levels in a sample, offering a genome-wide perspective on gene expression in cancer due to the presence of thousands of gene fragments on the array. The two most prevalent microarray technologies involve either double-stranded cDNA probes placed on slide surfaces or single-stranded oligonucleotide probes. Typically, a comparative approach is employed to identify significant genes in neoplasia. For instance, tumorous tissue may be compared to normal tissue, or tumors of varying pathological types or grades may be analyzed. For instance, the Her2/neu/ERBB2 positive status in breast cancer is commonly assessed for trastuzumab (Herceptin) treatment, as this gene is the drug's target. Microarrays are now frequently utilized in the quest for such biomarkers.

Targeting DNA damage repair for cancer chemotherapy

Chemotherapy remains a cornerstone of cancer treatment, utilizing drugs to target and kill rapidly dividing cancer cells. The major DNA damage repair pathways include base excision repair (BER), non-homologous end joining (NHEJ), alternative-NHEJ (alt-NHEJ), and homologous recombination (HR). Key proteins in BER are PARP-1, APE1, XRCC1, and DNA ligase III; NHEJ pathway proteins include KU70/Ku80, DNA-PK, Artemis, XRCC4, DNA ligase IV, and XLF; alt-NHEJ involves PARP-1, XRCC1, and DNA ligase III; while HR utilizes RPA, BRCA1, PALB2, BRCA2, and RAD51.

Targeting PARP-1

Following the occurrence of a single-strand break or double-strand break, PARP1 expression is triggered, activating poly (ADP-ribose) (PAR) activity. This activity facilitates the addition of branched PAR chains, thereby enhancing the recruitment of repair proteins to the site of damage. Anticancer therapies often utilize inhibitors targeting PARP-1, which competitively bind with NAD+ to catalyze the PARP active site. Olaparib, classified as a PARP inhibitor, functions by inhibiting PARP enzymes, thereby impeding cancer cells' ability to repair damaged DNA, ultimately leading to their demise.

Targeting XRCC1

Increasing evidence suggests a strong association between XRCC1 mutations and various diseases, such as neurological disorders and cancer. For instance, the XRCC rs25487 AA genotype is linked to a heightened risk of severe radiation-induced lymphopenia in cancer therapy. Additionally, the influence of XRCC1 polymorphisms on the response to chemotherapy agents satraplatin and prednisone was investigated in patients with metastatic castration-resistant prostate cancer. Results indicated that patients with the wild-type allele exhibited prolonged progression-free survival compared to those with XRCC1 polymorphisms.

Targeting DNA-PKcs

DNA-PKcs plays a crucial role in activating ATM (ataxia-telangiectasia mutated) and ATR (Rad3-related protein) in response to DNA damage. In clinical cancer therapy, inhibiting components of the DNA repair machinery shows promise in eradicating cancer cells. DNA-PKcs inhibitors, such as NU7441, nedisertib, AZD7648, VX-984, berzosertib, and ceralasertib, are being explored for this purpose. Among them, AZD7648 stands out as a potent and selective DNA-PKcs inhibitor, demonstrating favorable chemotherapy outcomes and augmenting the activity of olaparib.

Targeting Ligases

The ligase I inhibitor, benzocoumarin-stilbene hybrid, shows potential in decreasing cancer cell proliferation and growth, indicating its promise as a chemotherapy agent for cancer by modulating DNA damage repair pathways.

Targeting homologous recombination

Mutations of BRCA1/2 are the most common source of HR deficiency. When hyperthermia is used to inhibit the HR pathway, BRCA2-deficient cancer cells become more sensitive to radiation treatment. Combining a PARP inhibitor with hyperthermia showed good treatment efficacy for cancers with HR deficiency.

Targeting DNA damage repair pathways to improve radiotherapy responses

Radiotherapy employs high-energy radiation to target and eliminate cancer cells by damaging their DNA or hindering their ability to proliferate. It's often utilized to shrink tumors before surgery or to eradicate residual cancer cells post-surgery. While radiation can disrupt DDR pathways in cancer cells, these cells have developed rescue mechanisms to survive radiation, highlighting the importance of targeting these pathways to enhance radiotherapy efficacy and reduce cancer recurrence. However, radiotherapy faces challenges, including damage to normal tissues and cells, and the development of radiotherapy resistance. Currently, there are no approved radio sensitizers for use alongside neo-chemo- and radiotherapy. Nonetheless, combining most chemotherapeutic drugs with radiotherapy enhances cancer sensitivity to treatment. A recent trial demonstrated that the combination of avelumab and cetuximab with radiation was well-tolerated in patients with advanced squamous-cell cancer. Additionally, combining cisplatin with radiotherapy extended progression-free survival time by three years.

Future perspectives

Chemotherapy can lead to off-target toxicity and adverse effects on healthy tissues in patients. Therefore, chemotherapy strategies should prioritize precision therapy, taking into account individual patient characteristics such as genetic background, environment, lifestyle, diet, culture, and race, which can significantly influence treatment outcomes. Considering the critical role of DNA damage, response, and repair in cancer therapy, it's reasonable to reconsider the categorization of cancers based on their DNA repair deficiency status. This new classification could pave the way for personalized cancer treatments. For instance, patients with DNA repair defects in the non-homologous end joining (NHEJ) pathway might find benefit from

therapy inhibitors targeting the homologous recombination (HR) pathway. The mechanism behind the effectiveness of DNA damage repair inhibitors in cancer therapy remains uncertain, despite several candidates being approved for clinical trials. Solving this puzzle could lead to improved therapeutic outcomes in targeted cancer therapy. Although numerous DNA damage repair inhibitors have entered clinical trials, their precise mechanisms of action remain unclear. Resolving this uncertainty holds the potential to enhance future therapeutic strategies by refining targeted cancer therapies that exploit DNA damage repair mechanisms.

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