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DNA Damage Response: Cancer Hallmarks and Therapeutic Avenues

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Introduction

DNA damage response (DDR) pathways are indispensable for maintaining genomic integrity, and their dysregulation is a recognized hallmark of cancer, contributing significantly to both the initiation and progression of the disease [1]. Aberrant DDR signaling can promote uncontrolled cell proliferation, facilitate evasion of apoptosis, and drive genomic instability, thereby fueling tumorigenesis [1]. Understanding these intricate pathways offers promising therapeutic opportunities, particularly through synthetic lethality approaches that selectively target DDR-deficient cancer cells for elimination [1]. Genomic instability, a pivotal driver of cancer development, is frequently exacerbated by defects in DNA repair mechanisms [2]. Deficiencies in crucial pathways such as homologous recombination (HR) and mismatch repair (MMR) can lead to an accumulation of mutations that drive oncogenesis [2]. These insights have significant implications for the development of targeted therapies, including the use of PARP inhibitors in HR-deficient cancers [2]. The intricate interplay between DNA damage response (DDR) and the tumor suppressor p53 is fundamental to cancer prevention [3]. P53 acts as a guardian of the genome, orchestrating DDR to halt cell cycle progression or induce apoptosis in response to DNA damage [3]. However, when p53 is mutated or inactivated, as is common in cancer, this critical protective mechanism fails, allowing damaged cells to propagate and leading to tumor growth [3]. Aberrant signaling within the Fanconi anemia (FA) pathway, which plays a key role in DNA cross-link repair, is implicated in the pathogenesis of various cancers [4]. Defects in the FA pathway can contribute to genomic instability and promote the development of certain hematological malignancies and solid tumors, underscoring its importance as a therapeutic target [4]. The concept of synthetic lethality, where the combined defects in two genes result in cell death, represents a particularly promising avenue for cancer therapy [5]. This approach exploits deficiencies in DNA damage repair pathways, such as those involving ATM or ATR, in cancer cells that already possess other DNA repair defects, thereby enabling selective tumor eradication [5]. The clinical success of PARP inhibitors in BRCA-mutated cancers serves as a prime example of this therapeutic strategy [5]. ATM (ataxia-telangiectasia mutated) and ATR (ataxia-telangiectasia and Rad3-related) kinases are central regulators of DNA damage response pathways, responsible for sensing DNA breaks and initiating signaling cascades that lead to cell cycle arrest and activation of repair mechanisms [6]. Dysregulation of ATM and ATR signaling is directly linked to increased genomic instability and cancer development, positioning them as attractive therapeutic targets [6]. The integrity of telomeres, the protective caps at the ends of chromosomes, is crucial for preventing genomic instability and oncogenesis [7]. Telomere dysfunction, coupled with associated DDR pathways, contributes to cellular senescence and plays a role in both the initiation and progression of cancer, with cancer cells often exploiting telomere maintenance mechanisms [7].

DNA double-strand breaks (DSBs) represent particularly dangerous forms of DNA damage, and their repair is primarily managed through two major pathways: non-homologous end joining (NHEJ) and homologous recombination (HR) [8]. The choice between these repair pathways significantly influences genomic stability, and their dysregulation is a contributing factor to cancer development, highlighting their potential as targets for therapeutic intervention [8]. The tumor microenvironment can profoundly influence the DNA damage response of cancer cells, impacting their susceptibility to therapy and their propensity for progression [9]. Factors such as hypoxia and inflammation within the tumor microenvironment can alter the efficacy of DNA repair pathways, potentially leading to increased resistance to treatment [9]. Understanding this complex crosstalk is vital for developing more effective cancer therapies [9]. Mismatch repair (MMR) deficiency is a critical factor in the development of several cancers, including prominent forms of colorectal and endometrial cancers [10]. Defects in MMR lead to microsatellite instability and a high mutational burden, which can, in some instances, sensitize tumors to immunotherapy [10]. These findings have significant implications for personalized cancer treatment strategies based on MMR status [10].

Description

DNA damage response (DDR) pathways are critical for maintaining the stability of the genome, and their malfunction is a characteristic feature of cancer, contributing to both the initial development and the advancement of the disease [1]. When DDR signaling becomes aberrant, it can foster uncontrolled cell proliferation, allow cancer cells to evade programmed cell death (apoptosis), and induce genomic instability, all of which drive the process of tumorigenesis [1]. Furthermore, a deeper comprehension of these pathways unlocks potential therapeutic strategies, particularly through the concept of synthetic lethality, where targeting cancer cells deficient in DDR mechanisms can lead to their selective demise [1]. Genomic instability, a fundamental driver of cancer, is often exacerbated by failures in DNA repair mechanisms [2]. Consequently, deficiencies in important DNA repair pathways like homologous recombination (HR) and mismatch repair (MMR) result in an accumulation of genetic mutations, thereby fueling oncogenesis [2]. This understanding also informs the development of targeted therapies, with PARP inhibitors being a notable example for treating HR-deficient cancers [2]. The crucial relationship between the DNA damage response (DDR) and the function of the tumor suppressor p53 is fundamental to preventing the development of cancer [3]. P53 acts as a guardian of the genome by coordinating the DDR to halt cell cycle progression or initiate apoptosis when DNA damage is detected [3]. However, in many cancers, p53 is mutated or inactivated, leading to the failure of this essential protective mechanism, allowing damaged cells to proliferate and contributing to tumor growth [3]. Aberrant signaling within the Fanconi anemia (FA) pathway, which

is vital for repairing DNA cross-links, has been implicated in the development of a range of cancers [4]. Defects in the FA pathway can contribute to genomic instability and promote the onset of specific hematological malignancies and solid tumors, highlighting the pathway's significance as a potential therapeutic target [4]. The principle of synthetic lethality, where the combined loss of function of two genes leads to cell death, is an emerging and highly promising strategy in cancer therapy [5]. This approach involves exploiting pre-existing defects in DNA repair pathways, such as those involving ATM or ATR, within cancer cells that already harbor other DNA repair deficiencies, thereby achieving selective eradication of tumor cells [5]. A prominent illustration of this strategy is the clinical success observed with PARP inhibitors in cancers with BRCA mutations [5]. ATM (ataxia-telangiectasia mutated) and ATR (ataxia-telangiectasia and Rad3-related) function as master kinases in DNA damage response pathways [6]. They play critical roles in sensing DNA breaks and initiating signaling cascades that arrest the cell cycle and activate repair mechanisms [6]. Alterations in ATM and ATR signaling are associated with increased genomic instability and cancer development, making them compelling targets for therapeutic intervention [6]. The integrity of telomeres, which are protective caps located at the ends of chromosomes, is essential for preventing genomic instability and the onset of oncogenesis [7]. Telomere dysfunction, along with the engagement of associated DNA damage response pathways, contributes to cellular senescence and plays a role in both cancer initiation and progression [7]. Cancer cells often develop mechanisms to maintain their telomeres, which can be exploited therapeutically [7]. DNA double-strand breaks (DSBs) represent one of the most dangerous forms of DNA damage, and their repair is primarily accomplished through two main pathways: non-homologous end joining (NHEJ) and homologous recombination (HR) [8]. The choice between these repair pathways has significant consequences for genomic stability, and their aberrant function contributes to cancer development, underscoring their potential as targets for cancer therapy [8]. The tumor microenvironment can exert a substantial influence on how cancer cells respond to DNA damage [9]. Various factors present within this microenvironment, such as hypoxia and inflammation, can alter the effectiveness of DNA repair pathways, potentially leading to increased resistance to cancer treatments and promoting tumor progression [9]. Understanding this complex interplay is crucial for designing more effective cancer therapies [9]. Deficiency in the mismatch repair (MMR) system is a critical factor in the development of several types of cancer, most notably colorectal and endometrial cancers [10]. Defects in MMR lead to a state of microsatellite instability and a high mutational burden, which can sometimes render tumors more susceptible to immunotherapy [10]. This observation has important implications for tailoring cancer treatments based on an individual patient's MMR status [10].

Conclusion

DNA damage response (DDR) pathways are crucial for maintaining genomic integrity, and their dysregulation is a hallmark of cancer, driving uncontrolled cell proliferation and tumor progression. Aberrant DDR signaling can be therapeutically targeted through synthetic lethality approaches. Genomic instability, fueled by defects in DNA repair mechanisms like homologous recombination (HR) and mismatch repair (MMR), drives oncogenesis and informs targeted therapies such as PARP inhibitors. The tumor suppressor p53 plays a vital role in orchestrating DDR, and its inactivation promotes cancer growth. The Fanconi anemia (FA) pathway and its defects are implicated in various cancers. ATM and ATR kinases are central regulators of DDR, and their dysregulation contributes to cancer. Telomere integrity is essential for preventing genomic instability, and telomere dysfunction is linked to cancer. DNA double-strand break repair pathways (NHEJ and HR) are critical, and their dysregulation contributes to cancer. The tumor microenvironment can influence DDR and treatment resistance. Mismatch repair (MMR) deficiency leads to microsatellite instability and can sensitize tumors to immunotherapy.

Acknowledgement

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Conflict of Interest

None.

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