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# The Effects of Anticancer Agents on DNA

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**Abstract**

DNA-targeting anticancer agents play a pivotal role in modern oncology by inducing structural and functional damage to DNA, thereby inhibiting cellular proliferation and promoting apoptosis. This review explores the mechanisms by which various classes of chemotherapeutic agents such as alkylating agents, platinum compounds, antimetabolites, and topoisomerase inhibitors interact with DNA and disrupt essential cellular processes like replication and transcription. Emphasis is placed on the types of DNA damage induced, including single-strand breaks, double-strand breaks, and cross-links, as well as the activation of the DNA damage response (DDR) and cell cycle checkpoints. The roles of critical molecular regulators such as p53 and repair mechanisms like homologous recombination (HR) and non-homologous end joining (NHEJ) are discussed in relation to cell fate determination. Moreover, the development of therapeutic resistance, driven by enhanced DNA repair capacity, p53 mutations, and drug efflux mechanisms, presents significant clinical challenges. Future perspectives highlight the potential of targeted therapies, particularly PARP inhibitors, nanotechnology-based drug delivery, and personalized medicine, in overcoming resistance and improving treatment outcomes. A comprehensive understanding of DNA damage pathways and resistance mechanisms is essential for optimizing therapeutic strategies and advancing the effectiveness of cancer treatment.

*Keywords:* DNA damage, Anticancer agents, DNA repair mechanisms, Therapeutic resistance, Targeted therapies

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## 1. Introduction

DNA (Deoxyribonucleic Acid) is the primary genetic material found in the cells of living organisms and carries hereditary information (Campbell & Reece, 2008). DNA possesses a double helix structure and is composed of structural units called nucleotides, which contain four nitrogenous bases: adenine (A), thymine (T), guanine (G), and cytosine (C). These bases pair according to specific base-pairing rules: adenine pairs with thymine, and guanine pairs with cytosine (Watson & Crick, 1953). Before cell division, DNA can replicate itself, ensuring that genetic information is wholly and accurately transmitted to newly formed cells (Campbell & Reece, 2008). Furthermore, DNA plays a key role in protein synthesis by encoding the necessary instructions, thereby maintaining cellular function and the integrity of the organism (Campbell & Reece, 2008).

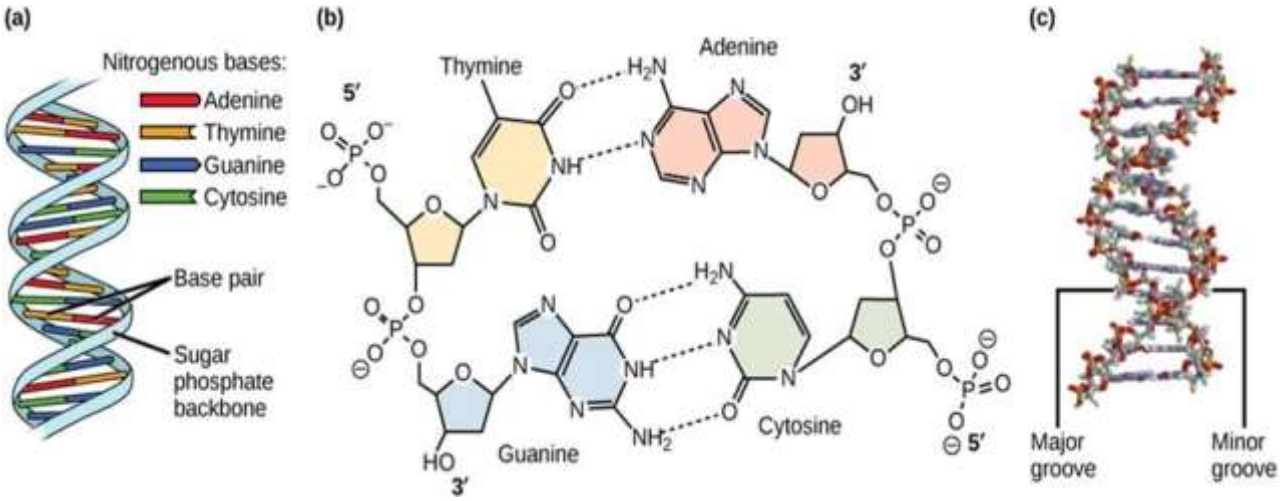


**Figure 1**. DNA has (a) a double helix structure and (b) phosphodiester bonds. The (c) major and minor grooves are binding sites for DNA binding proteins during processes such as transcription (the copying of RNA from DNA) and replication (Green *at al.*, 2010; Arjmand *at al.*, 2014).

## 2. The Role of DNA During Cell Division

*Preservation and Transmission of Genetic Information:* DNA carries the genetic instructions that determine cellular functions. During cell division (mitosis or meiosis), this information must be wholly and accurately transmitted to daughter cells to ensure continuity of genetic material (Campbell & Reece, 2008).

*DNA Replication:* Before division, DNA undergoes replication, producing an identical copy of itself. This ensures that each newly formed cell receives the duplicate genetic content as the parent cell (Watson & Crick., 1953; Campbell & Reece, 2008).

*Role in Mitosis and Meiosis:*

- *Mitosis* occurs in somatic cells, where DNA is duplicated precisely, preserving the genetic identity of the cells (Campbell & Reece., 2008).
- *Meiosis* takes place in gametes, reducing the DNA content by half and introducing genetic variation, which is crucial for biological diversity (Campbell & Reece, 2008).

*Instruction for Protein Synthesis:* Following division, DNA continues to serve as a template for protein synthesis, guiding the production of proteins necessary for the cell's structure and function (Campbell & Reece, 2008).

Cancer is a group of genetically based diseases characterized by mutations in genes that regulate the cell cycle and proliferation mechanisms (Hanahan & Weinberg, 2011). These genetic alterations are often rooted in DNA damage, deficiencies in repair mechanisms, and genomic instability. As DNA is the fundamental carrier of cell proliferation and viability, most anticancer agents act directly or indirectly on DNA (Helleday *et al.*, 2008; Waring *et al.* 2002). In particular, chemotherapeutic agents aim to induce apoptosis in cancer cells by disrupting DNA replication, transcription, and repair. These agents fall into various categories, including alkylating agents, platinum-based compounds, topoisomerase inhibitors, and antimetabolites (DeVita *et al.*, 2019).

Anticancer agents that target DNA are generally most effective during the S (synthesis) and G2/M phases of the cell cycle, where they halt cellular proliferation and trigger apoptosis (Kroemer *et al.*, 2009).

For instance, alkylating agents create covalent cross-links between DNA bases, disrupting the double-helix structure and inhibiting replication (O'Connor., 2015). Similarly, platinum derivatives such as cisplatin form covalent bonds with DNA, thereby impeding both replication and transcription processes (Galluzzi *et al.*, 2012). Antimetabolites block DNA synthesis by inhibiting enzymes involved in nucleotide biosynthesis. The structural damage caused by these agents, if left unrepaired, typically leads the cell to undergo programmed cell death (apoptosis). Understanding these mechanisms is of great importance for the development of next-generation anticancer drugs that are more targeted and exhibit reduced toxicity.

In this paper, the DNA-targeting mechanisms of anticancer agents will be examined in detail, and the implications of these effects on therapeutic strategies will be discussed.

## 3. Classification of DNA-targeting Anticancer Agents

DNA-targeting anticancer agents can be broadly classified into several categories based on their mechanism of interaction with DNA. The most prominent classes include alkylating agents, platinum-based compounds, antimetabolites, and topoisomerase inhibitors. Alkylating agents, such as cyclophosphamide and ifosfamide, exert their effects by transferring alkyl groups to nucleophilic sites

on DNA, particularly at the N7 position of guanine bases. This reaction leads to cross-linking of DNA strands, mispairing, and ultimately, inhibition of DNA replication and transcription (DeVita et al., 2019). Because these agents are not phase-specific, they can act throughout the cell cycle, although they are most cytotoxic during the S phase when DNA is actively synthesized.

Platinum-based compounds, such as cisplatin, carboplatin, and oxaliplatin, form covalent bonds with purine DNA bases, resulting in intrastrand and interstrand DNA cross-links. These cross-links distort the DNA helix, preventing replication and transcription, and thereby triggering cell cycle arrest and apoptosis (Galluzzi et al., 2012). Antimetabolites, including 5-fluorouracil (5-FU), methotrexate, and cytarabine, interfere with nucleotide biosynthesis or mimic natural nucleotides, leading to their incorporation into DNA or RNA and causing chain termination or faulty transcription (Longley et al., 2003). Meanwhile, topoisomerase inhibitors, such as etoposide (Topoisomerase II inhibitor) and irinotecan (Topoisomerase I inhibitor), interfere with the enzymes responsible for relieving DNA supercoiling during replication and transcription. This leads to DNA strand breaks and genomic instability, ultimately promoting apoptosis (Pommier., 2006).

## 4. Mechanisms of DNA Damage

Anticancer agents disrupt cellular proliferation and induce programmed cell death (apoptosis) by causing various structural and functional damages to DNA. These damages include single-strand breaks (SSBs), double-strand breaks (DSBs), DNA crosslinks, base modifications, and replication fork collisions (Jackson & Bartek., 2009). Among these, DSBs are considered the most cytotoxic type of damage, as unrepaired DSBs can lead to chromosomal fragmentation, mitotic errors, and ultimately apoptosis.

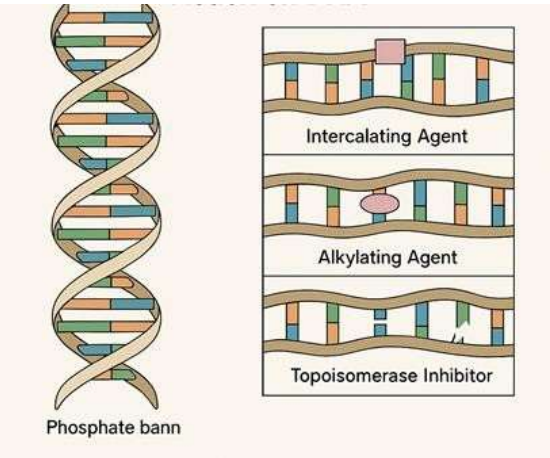


**Figure 2.** Anticancer drugs act on DNA: intercalating agents insert between base pairs, alkylating agents form covalent bonds with DNA bases, and topoisomerase inhibitors block enzymes that relieve supercoiling, causing strand breaks.

For example, alkylating agents cause covalent modifications in DNA bases, while platinum-based compounds create interstrand crosslinks that disrupt the helical structure. Topoisomerase inhibitors induce DNA strand breaks by blocking the enzymes responsible for relieving DNA supercoiling during replication and transcription.

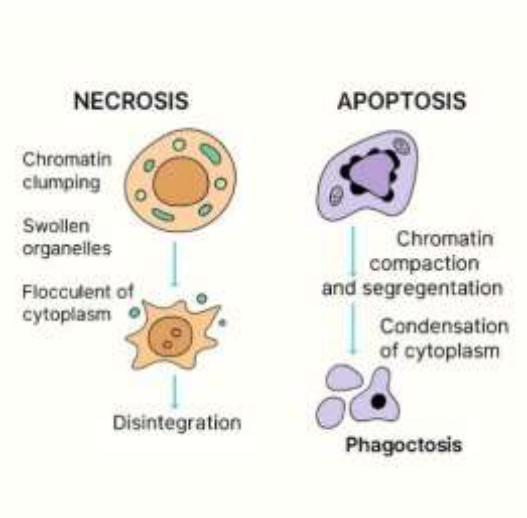


**Figure 3.** This figure provides a comparative illustration of two distinct types of cell death: necrosis and apoptosis.

**NECROSIS – Left Side:**

Initiation: Intracellular structures (organelles) swell, chromatin clumping occurs, and the cytoplasm becomes flocculent (fragmented).

Progression: The cellular structure disintegrates.

Outcome: Intracellular contents are released uncontrollably, triggering an inflammatory response. Therefore, necrosis is generally considered a pathological process that can damage surrounding tissues.

**APOPTOSIS – Right Side:**

Initiation: The cell membrane forms blebs, chromatin condenses, and the cytoplasm becomes dense.

Progression: The membrane develops more pronounced blebs, the nucleus fragments, and the cell breaks into apoptotic bodies.

Outcome: The resulting apoptotic bodies are cleared by phagocytic cells through phagocytosis. Since this process occurs in a controlled and non-inflammatory manner, it is typically considered a physiological event.

The cellular outcome of DNA damage is largely determined by the DNA damage response (DDR), a coordinated network responsible for detecting damage, transmitting signals, halting the cell cycle, and activating repair mechanisms (Ciccia & Elledge., 2010). Cells utilize base excision repair (BER) and

nucleotide excision repair (NER) for single-strand breaks, whereas homologous recombination (HR) and non-homologous end joining (NHEJ) are employed to repair DSBs. If the extent of DNA damage exceeds the repair capacity of the cell, the apoptotic pathway is triggered. Therefore, not only the level of DNA damage but also the cell's repair proficiency is a crucial determinant of treatment response in anticancer therapy.

The cellular response to anticancer agents depends not only on DNA repair capacity but also on the integrity of cell cycle checkpoints. The G1/S and G2/M checkpoints temporarily halt the cell cycle upon detection of DNA damage, allowing time for repair mechanisms to be activated (Bartek & Lukas., 2007). The tumor suppressor protein p53 plays a central role in orchestrating the cellular response to DNA damage. Depending on the extent of damage, p53 either facilitates cell cycle arrest or initiates irreversible pathways such as apoptosis. Therefore, in cancers with mutated p53, the response to DNA damage is impaired, often leading to therapeutic resistance (Vousden & Lane., 2007).

Moreover, cancer cells with impaired or completely inactivated DNA damage response (DDR) pathways often become more dependent on specific DNA repair mechanisms. This biological vulnerability enables the development of targeted therapies based on the principle of synthetic lethality. For instance, in tumors with BRCA1 or BRCA2 mutations, homologous recombination repair is deficient; thus, agents such as PARP inhibitors, which block single-strand break repair, exhibit selective cytotoxicity (Bryant et al., 2005; Farmer et al., 2005). Consequently, DDR pathways are not only crucial for cellular defense but have also become key targets in modern anticancer treatment strategies.

## 5. Cellular and Molecular Consequences of DNA-targeting Anticancer Agents

DNA damage poses a serious threat to the cell, which responds by activating various molecular mechanisms depending on the extent and type of damage. Primarily, DNA damage triggers cell cycle checkpoints, leading to cell cycle arrest. These checkpoints, especially at the G1/S and G2/M transitions, provide the cell with time to repair the damage (Kastan & Bartek., 2004). Cell cycle arrest also helps to prevent replication stress. However, when DNA damage is severe and irreparable, cells are directed towards irreversible fates such as apoptosis, senescence, or mitotic catastrophe.

At the molecular level, the p53 protein stands out as a key regulator of the DNA damage response. Activated following DNA damage, p53 plays a critical role in both halting the cell cycle and initiating apoptosis (Vousden & Prives., 2009). Among its target genes, p21 mediates cell cycle arrest to allow repair processes, while pro-apoptotic genes such as BAX and PUMA activate the mitochondrial apoptosis pathway. Additionally, DNA damage signals are transmitted through ATM/ATR kinases, which facilitate the recruitment of repair proteins (e.g., BRCA1, RAD51) to the nucleus. This promotes

high-fidelity repair mechanisms such as homologous recombination.

However, tumor cells may develop resistance to DNA damage, reducing treatment efficacy. Notably, mutations in p53 abolish apoptotic responses, allowing damaged cells to survive (Soussi & Beroud., 2001). Likewise, upregulation of DNA repair pathways (e.g., NER, HR) or structural alterations in target proteins contribute to therapeutic resistance. Therefore, modern treatment strategies aim not only to induce DNA damage but also to target DNA damage response pathways. For instance, PARP inhibitors suppress DNA repair pathways, thereby enhancing cancer cell death.

## 5.Treatment Resistance and Future Perspectives

The efficacy of DNA-targeting anticancer agents is often limited by the development of treatment resistance during the disease course. Resistance arises through multiple mechanisms, including enhanced DNA repair capacity of cancer cells, reduced drug uptake, mutations in drug target proteins, and inhibition of apoptotic pathways (Holohan et al., 2013). Notably, mutations in p53 weaken the apoptotic response to DNA damage, contributing to resistance. Moreover, overactivation of DNA repair systems allows cancer cells to more effectively repair drug-induced DNA damage, diminishing the effects of chemotherapeutic agents (Lord & Ashworth., 2012).

Future therapeutic strategies focus on molecular targets to increase the efficacy of DNA-targeting agents and overcome resistance mechanisms. Agents that inhibit DNA repair pathways, such as PARP inhibitors, exhibit high selectivity in tumors with homologous recombination deficiencies, providing effective treatment based on the principle of synthetic lethality (Lord & Ashworth., 2017). Furthermore, combining DNA-damaging agents with immunotherapy and targeted therapies is believed to enhance treatment success in resistant cancer types. Nanotechnology-based drug delivery systems and personalized medicine approaches are considered revolutionary advances in future cancer therapy.

Treatment resistance fundamentally stems from the ability of cancer cells to adapt to DNA damage. Overactivation of DNA repair mechanisms, in particular, reduces the effectiveness of chemotherapeutic agents. For instance, mutations in the BRCA1 or BRCA2 genes involved in homologous recombination repair increase the efficacy of PARP inhibitors in some tumors, but compensatory shifts to alternative repair pathways can lead to resistance development (Lord & Ashworth., 2012). Additionally, the overexpression of efflux pumps belonging to the multidrug resistance protein (MDR) family decreases intracellular drug concentrations, resulting in treatment failure (Gottesman., 2002).

Future treatment approaches aim to develop personalized and multi-target strategies to overcome resistance. Advanced genomic analyses allow for molecular profiling of tumors to identify the most appropriate drug combinations (Garraway & Lander., 2013). Moreover, nanotechnology-based drug

delivery systems enable targeted delivery of drugs directly to tumor cells, minimizing damage to healthy tissues (Shi et al., 2017). The development of new inhibitors targeting DNA repair mechanisms will further weaken the repair capacity of cancer cells, enhancing drug efficacy.

## Conclusion

The effects of anticancer agents on DNA remain a fundamental strategy in cancer treatment. While genetic alterations underlying cancer largely arise from DNA damage and insufficient repair mechanisms, these agents target the DNA structure to halt cellular proliferation and induce apoptosis. Drugs from different classes, including alkylating agents, platinum-based compounds, antimetabolites, and topoisomerase inhibitors, induce various types of structural damage on DNA, leading to cancer cell death. Understanding these molecular interactions plays a critical role in enhancing therapeutic efficacy. DNA damage mechanisms and cellular responses to such damage directly influence treatment outcomes. Cell cycle checkpoints and DNA damage response (DDR) systems enable DNA repair, with the balance between insufficient or excessive repair capacity determining therapy success. Key regulators such as p53 have a crucial role in determining cell fate. Cells attempt to prevent tumor progression by eliminating irreparably damaged DNA through irreversible processes such as apoptosis. However, this balance may be disrupted by cancer cells developing resistance mechanisms.

Treatment resistance is one of the major clinical challenges limiting the effectiveness of DNA-targeting agents. Multiple mechanisms including hyperactivation of DNA repair pathways, mutations in p53, and increased expression of multidrug resistance proteins adversely affect treatment success. This reduces patients' response rates and complicates disease prognosis. Therefore, strategies aimed not only at damaging DNA but also targeting repair pathways must be developed to overcome resistance.

In the future, personalized approaches and molecularly targeted drug combinations will become more prominent in DNA-targeted therapies. Agents inhibiting DNA repair, such as PARP inhibitors, have shown significant success in tumors with homologous recombination deficiencies. Moreover, integration of nanotechnology and advanced genomic analyses enables targeted drug delivery directly to tumor cells, enhancing therapeutic efficacy. These advancements will pave the way for more effective and less toxic treatment strategies in cancer therapy.

In conclusion, detailed investigation of the molecular and cellular effects of anticancer agents on DNA forms the basis for optimizing treatment strategies. Understanding and overcoming resistance mechanisms will improve treatment outcomes and patient quality of life. Therefore, ongoing research and new therapies are crucial in the fight against cancer.

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