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Exploring DNA Repair Mechanisms and their Role in Resistance to Nucleoside Analogues

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Introduction

Cancer remains one of the leading causes of death worldwide, with over 10 million deaths reported in 2020 alone. Despite advancements in cancer treatment, resistance to therapy still poses a significant challenge to successful treatment outcomes. Understanding the mechanisms that contribute to cancer treatment resistance is therefore critical in the development of effective cancer therapies. In particular, identifying the role of DNA repair mechanisms in cancer cells canhelp shed light on potential resistance mechanisms. This essay aims to explore the identification and analysis of DNA repair mechanisms that contribute to resistance against nucleoside analogues. The essay will cover the following points: Carcinogenesis and Cancer Treatment Resistance, Mechanisms in Cancer Cells, 3.0 Nucleoside Analogues, Purine nucleobases and purine nucleoside analogues, Deoxyadenosine derivatives, Deoxycytidine analogues, Topoisomerases, and The MRN complex. By examining these points, we can better understand the mechanisms involved in cancer treatment resistance and identify potential targets for developing more effective therapies.

Carcinogenesis and Cancer Treatment Resistance

In the past, cellular DNA was considered to be an inert substance, but recent molecular research has shown that it is much more dynamic than previously thought. DNA is continuously subjectedto damage and repair processes, and this occurs due to various internal and external sources. Some of the external factors include mutagenic environmental agents such as chemicals found infood and by-products of human industry, among others. To maintain the balance of these mutations, multiple repair mechanisms within the cell act to repair and proofread DNA using DNA polymerase. However, due to the high frequency of mutations, some of them may go unnoticed during the repair process and become integrated into the DNA. This process can

initiate carcinogenesis, making it a crucial step in the development of cancer (Loeb and Loeb 2000).

At present, there are 346 known genes that are associated with the development of cancer, and this number is constantly expanding. The mutations of these genes are found in cancer cells, butnot in normal cells, while in other cases, genes exhibit significant levels of deregulation. Both ofthese processes have the potential to significantly reduce the effectiveness of certain genes, leading to alterations in pathways within the cancer cell and the body itself (Huang et al. 2006). This implies that mutations are a critical component of cancer formation. In fact, human cancersseem to exhibit thousands of diverse mutations by the time they are initially detected.

Furthermore, the fact that cancer can be inherited from one generation to the next suggests thatsome of these mutations can be passed down through genes (Loeb and Loeb 2000). Cancer is characterized by a high level of clonal expansion of somatic cells, which are not subjected to the normal growth regulatory components of the cell cycle. This enables them to proliferate beyond the typical constraints of tissue, and the controls over apoptosis are also evaded (Evan and Vousden 2001). Most tumours that develop in the human body exhibit significant heterogeneity, indicating that multiple mutations occur within human cancers, driving the formation of tumors and the alteration in function between normal and cancerous cells (Loeb et al. 2003). Thus, cancer can be viewed as a disease or a collection of diseases resulting from genetic abnormalities that accumulate within cells (Huang et al. 2006). In each generation of cancer cells, significant mutations occur within different cells, and those cells that develop mutations that promote cancer growth are selected for, leading to an increase in their prevalence. These mutations may be subtle, such as changes in the nucleotide sequence, or more significant,

such as changes in the chromosomes themselves (Wang et al. 2002).

A significant factor in the resistance of cancer to treatment is that therapeutic interventions, while causing cancer to go into remission, may also select for resistance to treatment. This can lead to the progression of tumour growth, with cells that are not susceptible to the same treatment (Blagosklonny 2005). Another form of resistance that can arise is linked to the cell's position in the division cycle. Cancer therapy is most effective on cells that are replicating rapidly, and resistance to treatment may be stronger in some stages of the cell cycle than others(Schwartz and Shah 2005).

It is an ironic observation that carcinogenesis plays a significant role both in cancer developmentand in cancer therapy. Cancer can arise due to exposure to cytotoxic agents, which may then be used to treat the cancer. This is because genetic instability is a factor that can speed up tumour progression and make an individual more susceptible to cancer. Genetic instability can be causedby various factors, including exposure to carcinogens or errors in DNA repair. However, inhibiting DNA repair is also a known method for treating cancer (Blagosklonny 2005).

Similarly, errors in DNA replication cause the mutations that drive carcinogenesis. Yet, once cancer forms, high-fidelity DNA replication allows the mutant cells to continue dividing and growing efficiently. This is a crucial factor that needs to be considered in depth when examining resistance to cancer treatment, as it shows that the most logical processes are not always the mosteffective ones.

Mechanisms of Cancer Cells

Understanding the molecular mechanisms underlying cancer development is crucial for developing effective cancer therapies. Cancer is often viewed as a collection of distinct diseases

rather than a single entity, with different types of cancer requiring different treatment approaches (Evan and Vousden 2001).

Normal cells in the body rely on mitogenic signals to regulate their proliferation, and can only divide during the G1 phase of the cell cycle. Mitogenic signaling is limited under normal circumstances, imposing significant constraints on cell growth. Apoptosis, or programmed cell death, is the natural process that eliminates unwanted or damaged cells from the body. This process is regulated by two distinct pathways: the extrinsic pathway, which is activated by death receptors on the surface of the cell, and the intrinsic pathway, which is regulated by the mitochondria within the cell (Igney and Krammer 2002).

Most current drugs that are used for treating cancer do so by targeting the mitotic cycle, however, this is not a precise form of targeting. Instead, cancer treatments act by directly interfering with the machinery involved in cell division and DNA replication (Evan and Vousden 2001). One class of drugs that is becoming increasingly useful in the treatment of cancer are nucleoside analogues (NAs). Nucleoside analogues have the potential to inhibit the repair and replication of DNA within the cancer cells (Milas et al. 2002).

Nucleoside Analogues in Cancer Treatment

Targeting the mitotic cycle is the current approach used by most cancer drugs, but it is not a precise method of targeting. Instead, cancer therapies directly interfere with the machinery involved in cell division and DNA replication (Evan and Vousden 2001). A class of drugs that is gaining popularity in cancer treatment is nucleoside analogues (NAs). These drugs have the ability to inhibit the repair and replication of DNA within cancer cells (Milas et al. 2002).

A recent development in cancer treatment involves nucleoside analogues, a class of antimetabolites that can inhibit the repair and replication of DNA within cancer cells, including solid tumours. This family of molecules includes analogues for both purine and pyrimidine DNA particles and is transported into cells through membrane transporters. Once inside the cell, they interfere with a number of cellular processes, such as cytotoxicity (Hajdo et al. 2010). Different types of nucleoside analogues are used for treatment depending on the type of cancer, with 5-fluorouracil (5-FU) being widely prescribed for various cancer types. Nucleoside analogues were among the first methods of therapy introduced for cancer treatment and are currently prevalent throughout treatment for many forms of cancer. Understanding how these molecules affect cellular processes is crucial for increasing the specificity and efficiency of cancer treatment. The mechanism by which NAs operate varies depending on the specific NA used. Some NAs prevent the synthesis of nucleotides, while others must be integrated into the DNA chain during replication. Upon entering the cell, NAs are phosphorylated to activate them. When integrated into DNA, they halt the replication machinery by preventing further bases from being added. To continue replication, the cell must first remove the NA from the DNA chain. However, this can lead to treatment resistance if the repair mechanism is able to efficiently remove the NA from the chain, allowing replication to continue despite treatment (Zhu et al. 1998).

NAs are effective cancer treatments because human cells are able to incorporate pre-made pyrimidines and purines from their environment into their DNA. Roughly 20% of all cancer drugs are NAs based on purines or pyrimidines. Ongoing research aims to develop new and effective ways of inhibiting cancer cell replication using NAs (Parker 2009). These analogues areusually based on pyrimidine or purine structures and mimic the structure of DNA

bases. The replication machinery must recognize the compound as a component of DNA for it to be incorporated (Galmarini et al. 2001).

1. **Purine nucleobases and purine nucleoside analogs:** Purine NAs are crucial in the treatment of cancer, with significant developments made in this area over the past 50 years. Ongoing research continues to create new purine NAs, with potentialfor more efficient and effective methods of cancer treatment (Parker et al. 2004). Many types of purine NAs exist, each with different methods of action, requirements for activation, and biological activity (Plunkett and Saunders 1991). While primarily affecting actively proliferatingcells, purine NAs can also affect non-proliferating cells (Robak et al. 2005). Examples of such drugs include tiasofurin, heplanocin A, and 3-deazaguanosine.
2. **Deoxyadenosine derivatives:** Purine NAs are designed to mimic the structure of either adenosine or deoxyadenosine. Thederivatives typically involve a substitution or addition of a chemical group. For instance, cladribine involves the substitution of hydrogen with chlorine in deoxyadenosine. Deoxyadenosine derivatives share many commonalities in their chemical structure, such astransport into cells and dephosphorylation by a 5'-nucleotidase (Robak et al. 2005). Many currently used cancer drugs are deoxyadenosine derivatives (Kantarjian et al. 2003).
3. **Deoxycytidine analogs:** Gemcitabine is a deoxycytidine analogue commonly used to treat non-small cell lung cancer. It has low toxicity and can be administered to a wide range of patients, including the elderly and those with weakened immune systems (Shepherd et al. 1997). The low toxicity of this drug alsomakes it effective when used in combination with other forms of cancer treatment (Bunn Jr 1999). When activated in a cell, gemcitabine can be incorporated into the DNA chain, inhibitingDNA chain

elongation, DNA repair, and DNA synthesis. However, patients can develop resistance to this drug (Kang and Saif 2008). Therefore, research is ongoing to develop moreefficient NAs and decrease resistance that cancer cells develop.

Topoisomerases

Topoisomerases play a vital role in regulating the winding of DNA during replication and transcription by creating small cuts in the DNA backbone to unwind it. Without topoisomerases, DNA replication and cell proliferation would not be possible. Therefore, topoisomerases are a prime target for cancer treatment since inhibiting their function can prevent further cell proliferation and eventually lead to cell apoptosis. The drug doxorubicin is an example of a drug that specifically targets DNA topoisomerase II-alpha, which is highly prevalent in rapidly replicating cancer cells (Pommier et al. 2010).

The homodimeric enzyme topoisomerase II has two isoforms, topoisomerase II-alpha and topoisomerase II-beta. The former plays a crucial role in DNA replication, making it a target for many cancer drugs. These drugs trap the enzyme in a complex, restricting it from performing its function. Targeting topoisomerase II-alpha specifically helps to increase the specificity of the drug's use since it is present during cell replication and highly prevalent in cancer cells (Lynch et al. 1997).

The MRN Complex

Consisting of Mre11, Rad50, and Nbs1, MRN complex is a crucial protein complex involved inDNA repair in humans and other mammals. MRN is one of the first compounds to respond to double-strand breaks within the cell and has a role in cell-cycle signaling cascades (Williams etal. 2007). It acts as a sensor for DNA damage, recruiting specific molecules to repair the DNA. The presence of a high-fidelity DNA repair mechanism, such as MRN, has the

potential to decrease the effectiveness of cancer treatments that rely on including NA into the growing DNAchain to halt replication. The repair mechanism can remove the NA from the DNA chain, reducing the treatment's effectiveness and increasing the cell's resistance to treatment. Therefore,it is essential to examine the role of MRN and DNA repair mechanisms as a whole in the effectiveness of cancer treatments (Schwartz and Shah 2005).

Conclusion

The identification and analysis of DNA repair mechanisms that contribute to resistance against nucleoside analogues is a critical area of research in cancer treatment. The mechanisms discussedin this essay, such as topoisomerases and the MRN complex, play important roles in DNA replication, repair, and signaling. Nucleoside analogues, such as purine nucleobases, deoxyadenosine derivatives, and deoxycytidine analogues, have proven effective in cancer treatment, but resistance is a significant challenge. Understanding the mechanisms by which cancer cells resist treatment is crucial in developing new strategies to overcome resistance and improve patient outcomes. This essay provides a comprehensive overview of the key mechanisms involved in cancer treatment resistance, highlighting the importance of continued research in this area. By exploring these topics, we can further our understanding of the complex nature of cancer and work towards more effective treatments in the future.

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