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An Overview of Targeted Therapy Applications in Cancer Treatment

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ABSTRACT

Cancer remains one of the most important health challenges of modern societies, prompting extensive global research efforts aimed at its control and eradication. Although numerous therapeutic strategies have been developed over time to combat cancer, the persistent issue of resistance exhibited by cancer cells—even against conventional chemotherapy—continues to hinder the success of treatment. Many of these therapeutic interventions fail to produce the desired outcomes due to the adaptability and survival mechanisms of malignant cells. To address this challenge, especially over the past twenty years, researchers have focused on designing more advanced and intelligent methods to overcome cancer resistance. A promising strategy that has emerged involves identifying and targeting the specific vulnerabilities or weak points inherent within neoplastic cells for drug development. Exploiting these molecular weaknesses increases the likelihood of effective elimination of cancer cells while reducing their capacity to develop resistance. Targeted cancer therapy generally uses two primary methodologies. The first approach involves the development of specialized drugs that interact directly with specific molecular targets in cancer cells. The second strategy is the precise delivery of these therapeutic agents specifically to tumor cells, thereby minimizing damage to healthy tissues and reducing adverse side effects. The ultimate objective of these research efforts is to advance personalized medicine—tailoring treatment plans to the unique genetic and molecular characteristics of each patient's cancer. This patient-centered approach signifies a transformative shift in medical science towards individualized care. In this review, by utilizing credible and up-to-date sources, the various therapeutic targets used in targeted cancer treatment will be discussed, along with the rationale behind their selection and the relevant drugs developed from these approaches.

Keywords: Targeted cancer treatment, Targeted therapy, Resistance, Cancer treatment, Chemotherapy

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Introduction

Cancer has long posed a significant threat to human health, ranking as the second most common cause of mortality globally, following cardiovascular diseases [1]. This disease represents a highly intricate disorder influenced by genetic, epigenetic, and environmental factors, displaying remarkable diversity across tissues, tumors, and cellular structures—often resulting in challenges in selecting effective treatment strategies [2, 3]. Cancerous cells disrupt the natural regulatory mechanisms of the body, bypassing the controls of normal cell division and proliferating unchecked.

The rate at which tumors develop is largely influenced by an individual's biological profile, immune system response, genetic background, and environmental exposure. With the growing identification of numerous genes, particularly tumor suppressor genes and molecular signaling pathways involved in cancer progression, the complexity of this disease continues to expand [4, 5]. Nonetheless, research findings indicate that many of the factors predisposing individuals to cancer extend beyond mutations within protein-coding regions of the genome. A prominent example is the discovery of long non-coding RNAs (lncRNAs), which are RNA molecules exceeding 200 base pairs in length and have been shown to play key roles in cancer development and tumor formation [6].

Cancer-related mutations are thought to arise through a gradual, multi-step process that involves the accumulation of genetic alterations across different regions of the genome. Consequently, advancing methods for precise diagnosis and optimized treatment have become a critical area of research. However, cancer cells have demonstrated remarkable adaptability, often leveraging the body's defense mechanisms to survive and resist therapeutic interventions [4, 7-9].

For this reason, modern oncology research is increasingly focused on designing personalized treatment strategies that align with the unique mutational profile of each patient's cancer. By identifying the specific genetic drivers responsible for the onset and progression of cancer in each individual, it is possible to minimize chemotherapy-associated side effects while improving therapeutic effectiveness. Crucially, these treatment approaches aim to target "driver" mutations—the primary genetic alterations fueling cancer development—rather than "passenger" mutations, which are incidental and widespread across various cancer types [9-11].

To achieve these goals, two principal strategies have been proposed: (1) comprehensive genomic analysis of an individual's cancer cells, particularly in the early stages of the disease before metastasis occurs, to detect key mutations and select appropriate targeted therapies; and (2) developing advanced delivery systems capable of transporting chemotherapy drugs directly to tumor sites at optimal concentrations, thereby maximizing treatment efficacy while limiting harm to healthy tissues [12].

In this review, by utilizing credible and up-to-date sources, various therapeutic targets employed in targeted cancer treatment will be discussed, along with the rationale behind their selection and the corresponding drugs developed from these approaches.

Results and Discussion

The main goals of targeted cancer therapy

Cell signaling routes

One of the critical factors contributing to carcinogenesis is the disruption and dysregulation of cellular signaling pathways, which results either in uncontrolled cell division or the inability of cells to cease proliferation at the appropriate time.

Among the various signaling pathways implicated in cancer, the epidermal growth factor receptor (EGFR) pathway stands out as a major tyrosine kinase signaling cascade. As its name implies, this pathway plays a vital role in stimulating cellular growth and division. In a study focusing on patients diagnosed with non-small cell lung carcinoma (NSCLC) [13], researchers examined the second functional loop involving 47 genes out of a total of 58 known human tyrosine kinase genes. The study revealed that within the EGFR protein, a range of genetic alterations had occurred—notably, deletions in exon 19 as well as specific missense mutations located in the activator loop (L858R) and the P-loop (G719S).

This research was conducted on patients who exhibited remarkable clinical responsiveness to AstraZeneca's drug Gefitinib (commercial name: Iressa 21839). Further analysis demonstrated that this drug exerts its therapeutic effect by inhibiting the phosphorylation of downstream signaling components within the EGFR pathway. As a result, it became evident that gefitinib is most effective in patients whose tumor cells harbor these specific primary mutations. Consequently, the drug's prescription has become highly selective, targeting only patients with these genetic profiles, since its administration to other patients may lead only to adverse effects without significant therapeutic benefit over the long term.

Nevertheless, subsequent investigations indicated that even within this carefully selected patient population, some individuals eventually developed resistance to gefitinib [14]. This resistance was attributed, in part, to the presence and activity of cancer stem cells within the heterogeneous tumor mass. To address this challenge, another therapeutic strategy was employed—the use of a monoclonal antibody known as DMC-C225 Erbitux (cetuximab). This antibody operates through a more specific mechanism, binding to the second extracellular domain of the EGFR, triggering receptor internalization, and effectively halting signal transduction.

An additional noteworthy observation from this study was the significantly higher prevalence of the aforementioned EGFR mutations in the Japanese population compared to the American population. This finding suggests that ethnic or genetic background may play an influential role in cancer development and mutation frequency.

About the RAS signaling pathway, which is situated downstream of EGFR, numerous mutations have been identified, prompting the development of diverse inhibition strategies and targeted therapeutic agents [15]. For example, the proper function of the RAS protein depends on a post-translational modification process whereby a

farnesyl group is attached to the protein. To interfere with this critical step, several drugs have been developed—these are known as farnesyl transferase inhibitors (FTIs).

However, some compounds from the ISIS drug family, despite successfully preventing farnesyl group attachment, have demonstrated limited therapeutic efficacy when used alone. This limitation arises from multiple factors, including the possibility that blocking this modification may prompt the alternative attachment of a geranyl-geranyl group to the protein, resulting in unpredictable changes in protein function. Therefore, while identifying the target pathway is essential for drug development, it is equally important to anticipate how the drug will interact within the highly intricate and dynamic environment of the human body.

Furthermore, another potential target for pharmaceutical intervention within the RAS signaling cascade involves the kinase activity of RAS pathway proteins, providing an additional avenue for therapeutic control [16].

Angiogenesis

A critical feature of tumor progression that researchers have heavily focused on regulating is angiogenesis—the process by which new blood vessels form to supply growing tumors. Among the signaling pathways involved, the vascular endothelial growth factor (VEGF) pathway plays a central role, primarily through its interaction with two key receptors, FLT1 and FLK1. Targeting this pathway, the monoclonal antibody bevacizumab (marketed by Genentech as Avastin) was developed, representing the first anti-angiogenic agent approved by the FDA for clinical use. Additionally, compounds like 9006-43-Bay and 011248-SU are currently being evaluated for their therapeutic potential, particularly in renal cell carcinoma treatment strategies.

Another approach to disrupting the VEGF pathway involves small-molecule inhibitors such as SU5416 and SU6668, which act by competitively binding to the tyrosine kinase domain of the receptors, effectively blocking their activity. Furthermore, advancements have led to the development of multi-targeted agents like SU011248, which can inhibit several receptors simultaneously, making it suitable for patients with advanced-stage malignancies or widespread metastatic disease [17].

Beyond the VEGF pathway, hypoxia-inducible factor (HIF-1), particularly the HIF-1α subunit, represents another significant regulator of angiogenesis. Under hypoxic conditions, this factor promotes both angiogenesis and cellular adaptation for survival. Efforts to block the activity of HIF-1α have mainly centered around the use of small-molecule inhibitors [18]. The mechanisms by which these inhibitors function are diverse—many act indirectly by suppressing molecules that stabilize or enhance HIF-1α activity [19]. Interestingly, drugs commonly classified as topoisomerase inhibitors or microtubule polymerization inhibitors have demonstrated the ability to downregulate HIF-1α, although their effects are not considered highly specific or targeted in this context.

Moreover, HIF-1α stability is dependent on the molecular chaperone HSP-90, suggesting that inhibition of HSP-90 offers another therapeutic avenue for restricting angiogenesis [12]. An alternative strategy involves targeting the mammalian target of rapamycin (mTOR), which regulates HIF-1α at the translational level via the PI3K/AKT signaling cascade. Consequently, mTOR inhibitors have emerged as a valuable class of anti-angiogenic agents [19-21].

More recently, new therapeutic candidates such as PT2399 have been designed specifically to target HIF-2α, a related hypoxia-responsive factor. These agents are still in the early phases of pre-clinical investigation but hold promise for expanding future therapeutic options [22, 23].

Genome stability

Loss of genome stability is a key factor in the formation of neoplastic cells. In targeting this vulnerability, one of the effective therapeutic approaches is the use of drugs that induce genomic damage in cells with impaired DNA repair mechanisms [24]. In this method, only abnormal cells are eliminated, while healthy cells survive due to their intact DNA repair ability. Alkylating agents are among the main drugs applied for this purpose. Another important class includes platinum-based compounds. A more advanced strategy involves combination therapy, where cancer cell repair pathways are first inhibited, followed by the use of DNA-damaging agents like alkylating or platinum-containing drugs. This method allows broader application of these drugs but may also increase chemotherapy-related side effects [24, 25].

Targeted transfer methods

One of the key approaches in targeted cancer therapy is the direct delivery of drugs to cancer cells, minimizing the impact on healthy cells and reducing the side effects of chemotherapy. This strategy, although challenging in

practice, involves three primary methods: The first, and most commonly utilized, involves antibodies engineered to bind to specific cancer cell surface markers. These antibodies can be categorized into two types. The first category consists of monoclonal antibodies that act directly as drugs, referred to as functional antibodies. These antibodies remain inactive in the bloodstream but become lethal upon binding to the target cells. While the number of these drugs is limited, they are often combined with chemotherapy or radiation therapy, and in some cases, radioisotopes are attached to enhance their efficacy. In the second category, antibodies serve as carriers, transporting drugs to the target cancer cells. Upon binding to specific receptors, they are internalized, allowing the drug to enter the cell. Drugs are typically attached to the lysine amino groups in the constant regions (FC regions) of the antibodies [26].

Careful adjustment of the drug molecule quantity is necessary to prevent interference with the antibody's solubilization properties and to avoid excessive cytotoxicity. Initial efforts in this field led to the development of first-generation drugs, where the antibodies were mouse or human-mouse chimeras. These drugs required a binding agent to detach from the acidic properties of endosomes. However, due to the allogeneic nature of these antibodies, they can provoke immune responses, limiting repeated treatments. Subsequently, second-generation drugs with fully human antibodies and disulfide linkers were developed, reducing immune reactions. Methotrexate and doxorubicin are examples of first-generation Toxoids, while second-generation drugs have improved efficacy [26].

The second targeted method takes advantage of the leaky vasculature found in rapidly growing tumors. Due to the rapid synthesis of new blood vessels, these vessels often have incomplete structures, allowing drugs to be absorbed more readily by tumor cells than by healthy cells. Nanoparticles with hydrophilic surfaces and a diameter of about 100 nm are designed to evade the reticuloendothelial system, allowing the drug to remain in the bloodstream longer. When these nanoparticles are coated with antigens targeting cancer cell surface markers, they provide an efficient drug delivery system. This method is also used for gene transfer, such as the delivery of mutated Raf genes to mouse tumors, which inhibits signaling pathways and reduces tumor growth. This approach is being further explored for various cancer types [27-29].

A promising new avenue in cancer therapy involves the use of non-coding RNAs, particularly miRNAs, to regulate or inhibit signaling pathways. miRNAs are short RNA sequences (19-21 nucleotides) that affect mRNA stability and regulate gene expression. These miRNAs, after undergoing several precursor stages with enzymatic help, become active and bind to target mRNAs, leading to the suppression of gene expression depending on the match between the sequences [30].

Other mechanisms for miRNA function have been suggested, some of which involve enhancing gene expression through miRNA binding [31, 32]. Despite the complexity, miRNAs hold great promise as therapeutic agents. Researchers have identified several miRNA sequences that, if proven effective in clinical trials, could become key tools in cancer treatment. For instance, increasing the expression of miR-193a has been suggested as a target for treating AML patients with mutations in the C-gene [33]. Additionally, the miR-29 family has been identified as a potential therapeutic sequence to suppress AML progression in mouse models [34].

Small interfering RNAs (siRNAs) are another group of non-coding RNAs showing therapeutic potential. These synthetic sequences, around 21-23 nucleotides long, function similarly to miRNAs by inhibiting target gene expression. siRNAs have already been employed in treating certain cancers [35].

Conclusion

Cancer remains one of the most intricate health challenges faced by humanity, placing significant financial and emotional burdens on societies each year. The adaptive capabilities of cancer cells to resist treatment highlight the ongoing necessity for improved drug development. A promising approach involves designing chemotherapy drugs that exploit the vulnerabilities of cancer cells, allowing for personalized treatments tailored to maximize efficacy while minimizing adverse effects. Advances in targeting specific cellular signaling pathways, such as EGFR and RAS, the angiogenesis pathway, and the genome repair pathway, have already yielded promising outcomes. Additionally, targeted drug delivery methods, including the use of nanoparticles, miRNAs, and siRNAs, are showing potential to improve therapeutic precision and efficiency.

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