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Review

Recent Advances in Cancer Drug Discovery: A Molecular Journey to Precision Medicine

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ABSTRACT

In 1937, President Franklin Roosevelt signed the National Cancer Act, launching a nationwide effort to combat the disease. Eighty-seven years later, despite significant progress, cancer treatment often falls short, with 50 to 80 percent of patients not responding to treatment and more than 600,000 cancer deaths annually in the United States. The challenge lies in the diverse nature of the disease. There are hundreds of different types of cancers, characterized by the specific types of cells from which they originate. Even patients with the same cancer type require personalized treatments due to unique factors like genetic predisposition, lifestyle and immune response. The therapeutic outcomes - from complete remission to resistance to treatment - are unpredictable because cancer cells can develop resistance to drugs through genetic mutations, rendering therapy ineffective.

Ninety-five percent of cancer drugs tested in clinical trials never get approved. Moreover, only 14% of cancer patients in the United States are treated with precision medicine and only 7% benefit—a sobering reality that in large part due to the limited number of cancer drivers that are currently druggable. We've been treating cancer as if it doesn't evolve in response to what we do to it. It is time that we take that evolution seriously, guiding it rather than succumbing to it.

Overall, we need to increase the clinical success rate of the drugs we are developing and to find ways to discover drugs against the so-called 'undruggable' targets. Furthermore, we need to use intelligent combinations of new and old drugs to overcome drug resistance.

Keywords: Cancer, Druggable, Drug resistance, Genetic mutation, Precision medicine

1. Introduction

Cancer encompasses a large group of complex multifactorial diseases, which are characterized by the rapid and uncontrollable proliferation of abnormal cells. Although much progress has been made in recent decades for cancer prevention, diagnosis and treatment, it remains one of the leading causes of death worldwide, accounting for nearly 10 million deaths in 2020[1,2]. As a result, scientists are continuing to look for more effective strategies. This short communication will explore recent cancer drug discovery successes, touching on new biological insights, novel anticancer drug modalities and combinations.

2. New Biological Insights

Generally, advances in drug discovery rely on an understanding of the physiopathology underpinning a particular disease - cancer is no exception. Below we present some of the latest preclinical studies on cancer biology that could lead to the development of new therapies.

2.1. Pancreatic ductal adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) is an extremely aggressive type of cancer that is resistant to current chemotherapy and immunotherapy regimens. In a recent study, researchers found a previously unknown molecular "crosstalk" between cytokine signaling, nucleotide metabolism and a DNA replication stress-response pathway in PDAC cells. They discovered that exposure to a cytokine (type I interferon, IFN) causes the tumor cells to rely on a specific signaling pathway for survival and that inhibition of ATR, the protein mediating this pathway, induces apoptosis. This discovery provides solid ground to further explore cytokine-stimulating therapies in combination with ATR inhibitors (several of which are already under clinical investigation) for the treatment of PDAC tumors[3].

2.2. Breast cancer

Patients with HER2+breast cancer are highly susceptible to developing brain metastases, which can be characterized as synchronous (S-BM), latent (Lat) or metachronous (M-BM). A recent study found that M-MB and Lat cells express higher quantities of xCT - a protein mediating oxidative stress – compared to S-MB cells. Moreover, the study found that xCT inhibition significantly reduces the metastatic activity of M-BM and Lat cells making them more vulnerable to therapeutics. An xCT inhibitor is already being tested in clinical trials for multiple myeloma and its use could potentially be extended to delay brain metastasis in HER2+breast cancer patients[4].

2.3. Cervical cancer

The endogenous lysosomal cysteine protease inhibitor SERPINB3 is elevated in patients with cervical cancer. Researchers discovered that deletion of the SERPINB3 gene from cervical cancer cells, using CRISPR technology, made them more susceptible to chemotherapy and radiation[5]. Drug screening is now being conducted to identify compounds that can aid treatment by inhibiting the expression of this gene[6].

2.4. Brain cancer

Scientists have discovered how a specific genetic mutation, called H3-K27M, causes a childhood brain cancer, known as diffuse midline glioma (DMG). The study highlights the important role of the transcriptional repressor, polycomb repressive complex 2 (PRC2), in DMG and the potential therapeutic benefit of targeting its main enzymatic subunit[7]. Importantly, a suitable inhibitor has already received regulatory approval for the treatment of two types of adult cancer[8] and its use could potentially be extended to treat children with DMG.

3. Novel Drug Modalities

Conventional anticancer treatment approaches, such as surgery, chemotherapy and radiotherapy, are still being used. However, the development of technologies such as structural biology, computer-aided drug design, molecular biology and genomics, have led to significant advances in targeted therapies that inhibit cancer progression causing less damage to healthy cells **(Figure 1)**.

3.1. Small-molecule anticancer drugs

Small-molecule targeted drugs are safer and more efficient than traditional chemotherapy drugs. Yet, these drugs still face some challenges such as drug resistance and off-target effects[9]. One of the latest developments to tackle these challenges are PROteolysis-TArgeting Chimeras (PROTACs), which are heterobifunctional small molecules containing a ligand to the target protein and a ligand to the E3 ubiquitin ligase. Dual targeting allows them to recruit target proteins that are then ubiquitinated and removed by the proteasome[10]. Using this approach, small molecules are not used to inactivate target proteins, but to induce their degradation. Currently, two PROTAC drugs have entered clinical trials for the treatment of patients with prostate and breast cancer[10].

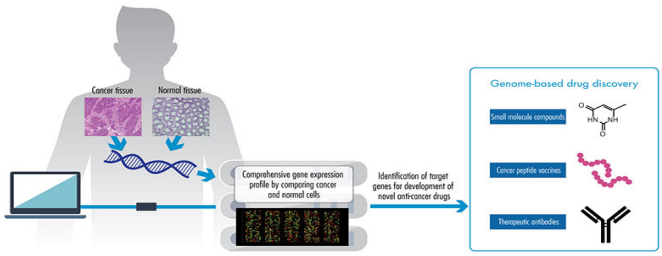

Figure 1: A number of genome-informed approaches that could be applicable for development of molecular-targeted anti-cancer therapies. The type of anti-cancer drugs for specific biomarkers were defined by their functional genomics characteristics, such as differential gene expression, subcellular localization, mode of function and immunogenicity.

3.2. Therapeutic monoclonal antibodies

Therapeutic monoclonal antibodies (mAbs) work by binding to specific targets in cancer cells. Once attached to the target, they can elicit cell death via different mechanisms, including neutralization, antibody-dependent cell-mediated cytotoxicity (ADDC) and complement-dependent cytotoxicity (CDC)[11,12]. The next generation of therapeutic mAbs are those targeting proteins that regulate the immune system, known as immune checkpoints. Checkpoint proteins on the surface of T cells bind partner proteins on cancer cells and activate a pathway that turn off the immune response. Immune checkpoint inhibitors (ICI) work by blocking these proteins allowing the T cells to kill cancer cells.11 To date, the US Food and Drug Administration (FDA) has approved eight ICIs[13,14].

The mAbs can also be conjugated to radioisotopes, toxins, drugs, cytokines or liposomes to deliver cytotoxic agents at higher local concentrations to the affected tissues[12]. The last years have seen the emergence of several Ab-drug conjugates (ADCs), eleven of which have already been granted FDA approval[15].

One of the latest advances in cancer immunotherapy is the emergence of bispecific antibodies engineered to bind two targets (i.e., one binding site targets tumor-associated antigens and the other binds to the immune cell receptor). In this way, the immune response remains focused at the tumor cells[16]. There are three bispecific antibodies approved by the FDA. Rybrevant® (amivantamab), approved in 2021 as treatment for non-small cell lung cancer, comprises yet another innovation as it offers three different mechanisms of action to kill tumor cells. It blocks two receptors that are essential for tumor proliferation and also recruits macrophages and natural killer cells[17].

3.3. Adoptive cell therapy

Adoptive cell therapy (ACT) represents a highly personalized cancer treatment that uses immune cells to attack tumors. There

are three classes of ACTs using T cells: tumor-infiltrating lymphocytes (TILs), genetically modified T cells expressing novel T cell receptors (TCR T cells) and genetically modified T cells expressing chimeric antigen receptors (CAR T cells)[18].

Similar strategies are being explored using other immune cells, such as natural killer (NK) cells [19]. ACTs have shown promising results in various tumor types and multiple clinical trials are being conducted to further optimize this treatment modality[19-21]. However, to date, only two CAR T-cell therapies have been approved to treat leukemia, lymphoma and advanced multiple myeloma[22].

Although CAR T-cell therapy has proved effective against blood cancers, its ability to treat solid tumors is limited by several challenges. For example, most of the proteins responsible for tumor proliferation reside in the nuclei of tumor cells and are generally not accessible to CAR T cells. The recent development of "peptide-centric" chimeric antigen receptors (PC-CARs) allows researchers to target fragments of intracellular oncoproteins exposed on the cancer cell's surface by the major histocompatibility complex (MHC)[23]. This novel method has the potential to target oncoproteins in any type of cancer.

3.4. Therapeutic cancer vaccines

Therapeutic cancer vaccines represent a promising strategy to induce a specific and long-lasting immune response against tumors. Early vaccination strategies targeting tumor-associated antigens (TAAs) were largely unsuccessful[24]. Therefore, the next generation of cancer vaccines focus on tumor-specific antigens (TSAs), such as oncoviral antigens and neoantigens[24]. The majority of neoantigens are unique to an individual's tumor and thus require a personalized vaccine. Currently, there are several personalized neoantigen-based vaccines in clinical development[25]. For example, treatment with PGV-001, which incorporates up to 10 neoantigen peptides, showed potential clinical benefits in patients with diverse types of cancer with high risk of recurrence[26,27]. Nucleic acids vaccine platforms are also being explored. In addition to mRNA-based vaccines, a recent preclinical study, developed the first DNA vaccine platform to target multiple neoantigens for breast and pancreatic cancers[28].

3.5. Oncolytic viral therapy

Oncolytic viral therapy (OVT) is a novel form of cancer immunotherapy that utilizes native or genetically modified viruses to selectively kill tumor cells[29]. Imlygic® (T-VEC) is a modified herpes simplex virus (HSV) indicated for patients with melanoma and it is the only OVT approved by the FDA[29]. Several other OVTs are being assessed in clinical trials[30]. Another promising candidate is the Myxoma virus (MYXV), which selectively infects and kills cancer cells and has a large genome that is amenable to the introduction of genetic modifications[31,32].

3.6. RNA interference therapy

RNA interference (RNAi) is a naturally occurring post-transcriptional mechanism whereby small interfering RNAs (siRNA) inhibit gene expression by binding to messenger RNA and promoting its degradation. siRNAs can be used to silence virtually any gene, showing great potential as a cancer therapy[33]. A variety of therapeutic siRNA-based drugs to treat cancer have been developed and are being clinically evaluated[34]. However, the development of an efficient platform to successfully deliver siRNA inside cancer cells is a challenge that must be overcome. A recent preclinical study explored the use of receptor-targeted nanocomplexes (RTNs) to efficiently deliver siRNAs to neuroblastoma cells. RTNs are nanoparticles formed by integrin-targeting peptides and lipids that encapsulate the siRNA. The study showed that RTN formulations can achieve specific tumor-targeting, with minimal clearance by the liver and the effective delivery of siRNAs to promote gene silencing and tumor retraction[35].

4. Novel Drug Combinations

Combining anticancer drugs or therapies can improve treatment outcomes, minimize off-target effects and reduce the emergence of drug resistance[36]. Several of the latest cancer drug combination "breakthroughs" involve the use of ICI drugs. For example, reports from an early-stage clinical trial reveal that treating bladder cancer patients with two ICI drugs (ipilimumab, an anti-CTLA-4 mAb and nivolumab, an anti-PD-1 mAb) prior to surgical treatment can improve rates of long-term remission[37]. ICI can also be combined with other type of drugs. For example, a recent preclinical study showed that a microparticle-based cancer vaccine was able to partially remove tumors. Yet, due to the natural downregulation of the immune response, the tumors gradually returned 30 days after vaccination. However, tumor remission increased significantly when the vaccine was combined with an ICI (anti-CTLA-4 mAb). This drug combination could be an effective cancer immunotherapy that should be tested in future clinical trials[38]. Likewise, ICIs can be combined with ADCs and cytokines. A recent clinical trial showed that treating patients with advanced non-small cell lung cancer with nivolumab (anti-PD1 mAB) plus TIL therapy resulted in promising anti-tumor activity, with 11 out of 16 patients experiencing tumor regression[39]. Cytokines, such as IL-12, can stimulate the immune system to fight tumors. However, they are highly toxic when administered systemically. In a new preclinical study, scientists found that attaching IL-12 to aluminum hydroxide enables direct delivery to tumor cells. Moreover, intratumoral IL-12 injection combined with nivolumab promoted anti-tumor activity in 50 to 90% of treated mice[40]. Small-molecule combinations can also be effective. A recent preclinical study explored different small-molecule combinations to treat cutaneous T-cell lymphoma (CTCL). The results highlighted the synergistic potential of combining ruxolitinib (a protein kinase inhibitor) with other small-molecule anticancer drugs, such as BCL2, histone deacetylase (HDAC), extra-terminal domain (BET) or proteasome inhibitors. This study lays the groundwork for the clinical assessment of these therapeutic combinations[41].

5. Conclusion

Significant advancements are being made in cancer drug discovery every year, as researchers continue to discover novel molecular targets that fuel the development of precision and personalized medicine. Yet, cancer drug research remains a remarkably challenging field and therapeutic innovations do not always achieve expected clinical results. Novel drug modalities have several advantages over traditional therapies, but frequently lack satisfactory effectiveness. In this scenario, the combination of different therapies has proved to be a worthwhile approach and will likely become more widely adopted in clinical practice in the future.

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