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Precision-Driven Advancements in Cancer Treatment: A Review of Emerging Therapies and Personalized Approaches

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A B S T R A C T

Cancer remains a significant global health challenge despite advances in research and treatment. In 2023 alone, statistics documented nearly 19.3 million new diagnoses and 10 million fatalities. While conventional therapies like surgery, chemotherapy, and radiation have demonstrably improved survival outcomes, they often result in systemic side effects, particularly in advanced malignancies. In recent years, the field of oncology has placed more focus on specific molecular and cellular mechanisms that trigger tumor growth. Several treatments, such as targeted therapy and immunotherapy, have evolved from these advancements and work to enhance immune-mediated tumor recognition and destruction while limiting the amount of damage to normal tissue. Furthermore, using drugs like rosiglitazone and MEK inhibitors to cause cancer cells to transdifferentiate into benign adipocyte-like cells represents a novel approach to non-lethal cancer control. Chimeric antigen receptor (CAR) T-cell therapy has demonstrated significant clinical success in treating blood malignancies. In contrast, oncolytic therapy uses genetically modified viruses to infect and kill cancerous cells and stimulate antitumor immunity. Non-invasive technologies like histotripsy use focused ultrasound waves to mechanically disrupt cancerous cells. This review study summarizes comprehensively the latest innovative developments in oncology by incorporating all of the most recent promising techniques currently available. A new era in cancer care is being signaled by these developments, which not only assist patients respond better to cancer treatment but also enhance their quality of life. More technological and scientific advancements will be required to give patients new, creative cancer control methods that are more precise and less toxic.

Key words: Cancer therapeutics, Precision oncology, Nanomedicine, Cellular immunotherapy

Introduction

In 2020, about 19.3 million new cancers were reported globally, and nearly 10 million people died from cancer.[1] The most frequently diagnosed types of cancer and their location are determined by numerous factors; however, worldwide, lung cancer is the leading cause of cancer deaths, followed by liver, gastric, and colon cancers. Common treatment options for cancer typically include surgery, chemotherapy, and radiation therapy; all of these traditional therapies have played in improving patient outcomes.[2] However, all of these medical treatments also have limitations and may not work well for advanced stages of cancer. Even with substantial advancement in traditional therapies including surgery, chemotherapy, and immunotherapy, clinical outcomes for many patients remain unsatisfactory. Such therapies are often limited by systemic toxicity, the emergence of drug resistance, and issues associated with effectively targeting the tumor microenvironment (TME).[3]

Advanced cancer therapies target specific cellular and molecular changes, offering hope for metastatic disease. Targeted therapies have significantly improved the management of several cancers, including non-small cell lung cancer, HER2-positive breast cancer, and BRAF-mutant melanoma, by selectively targeting key molecular alterations.[4] Over the past decade, targeted cancer therapies have transformed the field of oncology, shifting away from low-specificity cytotoxic chemotherapy to strategies that selectively target molecular

pathways critical for tumor growth and survival.[5] This paradigm shift has further evolved into more precise theragnostic, which integrates targeted delivery, cytotoxic action and non-invasive imaging in a single clinical feedback loop that provides clinicians continuously customizable options depending on tumor biology and dynamic reactions to treatments.[6] Immunotherapy has transformed the treatment of several malignancies, including melanoma, non-small cell lung cancer, and renal cell carcinoma.[7]

Advanced cancer therapies are cutting-edge approaches to treating metastatic or advanced malignancies. These modern approaches specifically focus on specific alterations that cancer cells undergo to continue their proliferation, providing more directed, effective, and less toxic treatment measures. The key features of advanced cancer therapies are summarized in Table 1, and their mechanisms of action are illustrated in Figure 1.

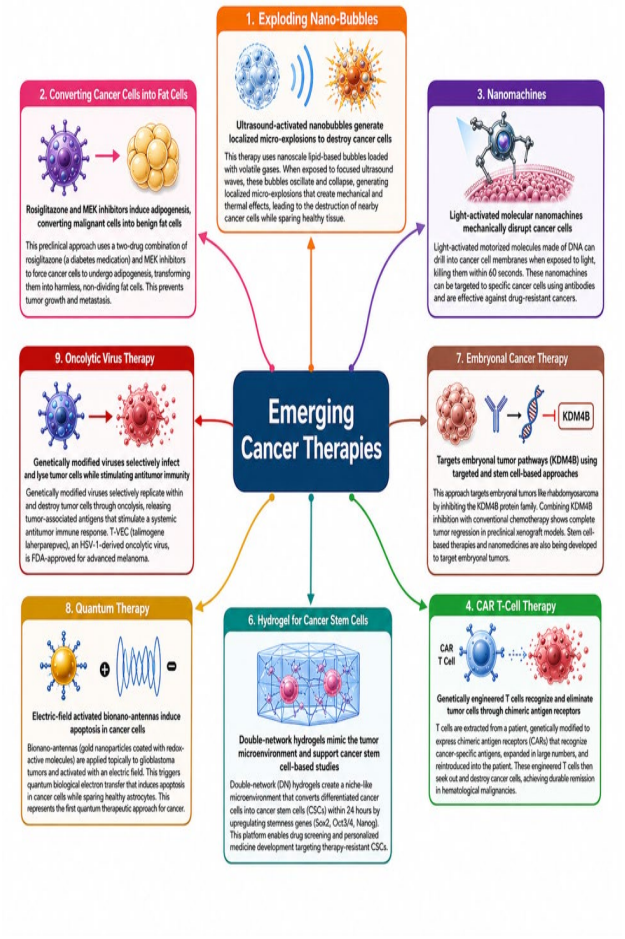

Figure 1. Schematic overview of the mechanisms and therapeutic strategies of emerging cancer therapies. The figure illustrates the principal mechanisms of action of the novel therapeutic approaches discussed in this review, including exploding nano-bubbles, conversion of cancer cells

TREATMENT OF CANCER BY EXPLODING CANCER CELLS

Exploding cancer cells represents a novel, early-phase targeted therapy. The concept of exploding cancer cells was first introduced in 2017 by researchers at the Karolinska Institute in Sweden. Their discovery revealed that a naturally occurring compound, Vacquinol-1 (extracted from mountain ash tree berries), could induce cancer cells to burst and die.[8] Since this initial breakthrough, further research has led to the development of additional methods for causing cancer cell explosion, utilizing various compounds and technologies. For example, a team at the University of California, Berkeley, has devised a method that employs gold nanoparticles and laser light to achieve this purpose.[9]

Mechanism of the Method

Nanobubbles encapsulate volatile gases under focused ultrasound, generating micro-explosions that destroy cancer cells.[10]

Treatment Efficacy

Prostate For instance, in prostate cancer therapy, nanobubbles encapsulating chemotherapeutic agents are guided to the tumor site using imaging modalities, followed by focused ultrasound-mediated drug release for selective tumor cell destruction.[11]

Treatable Cancer Types

The exploding nano-bubble method has shown promising efficacy in solid tumors, including breast, prostate, and pancreatic cancers.[12] Its therapeutic application in hematologic malignancies, including leukemia and lymphoma is under investigation.[13]

Prolonged Treatment and Experimental Success Rate

Recent studies have demonstrated that nanoparticle-assisted photothermal therapy effectively reduces tumor burden while enhancing treatment precision in breast cancer, highlighting its promising clinical potential.[14, 15]

Advantages and Disadvantages

The exploding nano-bubble method offers precise tumor targeting, reduced collateral damage, fewer systemic side effects, and reduce resistance compared to conventional chemotherapy. Additionally, its localized approach minimizes the likelihood of treatment resistance.[16]

TREATMENT OF CANCER BY CONVERTING CANCER CELLS INTO FAT CELLS

A study by researchers at the University of Basel in Switzerland described the conversion of cancer cells into fat cells using rosiglitazone and a MEK inhibitor.[17] MEK inhibitors block a

Table 1. Comparative summary of emerging cancer therapies

Therapy	Mechanism of Action	Advantages	Limitations	Clinical Status	Key Indications
Exploding Nano-Bubbles	Ultrasound-activated nanobubbles generate localized micro-explosions to destroy cancer cells	Precise targeting; reduced collateral damage; fewer systemic side effects.	Specialized equipment; high cost; limited accessibility; challenges with deeply seated tumors.	Preclinical/Early clinical	Solid tumors (breast, prostate, pancreatic)
Converting Cancer Cells into Fat Cells	Rosiglitazone and MEK inhibitors induce adipogenesis, converting malignant cells into benign fat cells.	Non-toxic strategy; uses FDA-approved drugs; reduces metastatic potential.	Limited preclinical evidence; MEK inhibitor resistance; cardiovascular risks of rosiglitazone.	Preclinical	Breast cancer
Nanomachines	Light-activated molecular nanomachines mechanically disrupt cancer cells.	Rapid action; potential against resistant tumors.	Early-stage development; delivery challenges; no clinical trials.	Preclinical	Various cancers
CAR T-Cell Therapy	Genetically engineered T cells recognize and eliminate tumor cells through chimeric antigen receptors.	Durable responses; high efficacy in hematological malignancies.	Cytokine release syndrome; neurotoxicity; high cost; limited efficacy in solid tumors.	FDA-approved	Leukemia, lymphoma, multiple myeloma
Histotripsy	Focused ultrasound creates acoustic cavitation to mechanically destroy tumor tissue.	Non-invasive; non-ionizing; precise ablation; real-time imaging.	Acoustic accessibility limitations; specialized equipment.	FDA-cleared for selected liver tumors	Liver and selected solid tumors
Hydrogel for Cancer Stem Cells	Double-network hydrogels mimic the tumor microenvironment and support CSC-based studies.	Useful for drug screening and personalized medicine	Experimental; mechanisms not fully understood.	Preclinical	Cancer stem cell reserach
Embryonal Cancer Therapy	Targets embryonal tumor pathways (including KDM4B) using targeted and stem cell-based approaches.	Novel therapeutic target; promising preclinical results.	Early-stage research; resistance remains a challenge	Preclinical	Embryonal tumors (e.g., rhabdomyosarcoma, medulloblastoma)
Quantum Therapy	Electric-field activated bionano-antennas induce apoptosis in cancer cells.	Highly selective targeting; minimal damage to normal cells.	Early-stage technology; requires further validation.	Preclinical	Glioblastoma
Oncolytic Virus Therapy	Genetically modified viruses selectively infect and lyse tumor cells while stimulating antitumor immunity.	Dual mechanism; selective tumor killing; potential for combination therapy.	Delivery challenges; antiviral immunity; variable response.	FDA-approved/Clinical trials	Melanoma and other advanced solid tumors

signaling pathway necessary for cancer cell survival and growth.[18] Adipogenesis is a complex process regulated by various factors such as hormones and growth factors.[19] Rosiglitazone is known to induce adipogenesis, while MEK inhibitors have been shown to block signaling pathways that suppress it.[20]

Mechanism of Method

The drugs induce the differentiation of cancer cells into non-proliferative adipocytes, thereby inhibiting tumor growth and metastasis. PRC2 inhibition in malignant tumors induces adipocyte differentiation via the PPARγ and C/EBPα pathways.[21]

How it Treats Cancer

MEK inhibitors block the MAPK pathway, demonstrating efficacy in breast cancer, melanoma, and non-small cell lung cancer.[18,21] Rosiglitazone promotes adipogenesis in cancer cells, while MEK inhibitors block proliferation, leading to reduced cancer cell viability.[21]

Prolonged Treatment Efficacy and Reverts Cancer Cells

In preclinical study models of breast cancer, treatment with rosiglitazone and a MEK inhibitor resulted in significant conversion of cancer cells into adipocytes, suppressed tumor growth, and prevented metastasis.[17]

Advantages and Disadvantages

The Preclinical studies showed that PPARγ agonists and MEK inhibitors induce adipogenic transdifferentiation, suppressing breast cancer growth and metastasis. Nonetheless, MEK inhibitor resistance and cardiovascular risks associated with rosiglitazone remains concerns that require careful patient selection.[21]

TREATMENT OF CANCER BY USING NANOMACHINES TO DESTROY CANCER CELLS IN JUST 60 SECONDS

Nanomachines are devices with very small size, which can be programmed to deliver drugs at specific targets. The molecular machines can be used for the purpose of delivering medicines against cancer biologically.[22]

Mechanism of Method

A 2017 study developed light-activated molecular machines that pierced cancer cell membranes and killed cancer cells. Tumor-targeting ligands directed these molecular machines to cancer cells.[23]

Treatment Efficacy

The Motorized molecular machines can be selectively targeted to cancer cells using tumor-targeting ligands or antibodies.[24] For breast cancer, tumor-targeting molecules can selectively bind HER2 receptors, improving treatment specificity.[25]

Percentage of Cancer Cells to Revert and Experiment Success Rate

The Preclinical studies have demonstrated that light-activated molecular machines rapidly disrupt cancer cell membranes, resulting in efficient cancer cell death and highlighting their potential as a novel anticancer strategy. However, clinical trials have not yet been conducted.[23]

Advantages and Disadvantages

Nanomachines selectively target cancer cells while minimizing damage to healthy tissues and show potential to overcome drug resistance.[26] They also support personalized therapy by targeting specific cancer biomarkers and are currently under clinical evaluation.[27]

CAR T-CELL THERAPY

Immune and inflammatory responses can potentially eliminate tumors through "immune surveillance," where the immune system recognizes and targets tumor-associated antigens (TAAs). Coley's 1891 work laid the foundation for cancer immunotherapy, and the discovery of T cells in 1967 advanced its modern development. The concept behind CAR T cell therapy originated in 1989 with the development of chimeric antigen receptors (CARs) by Zelig Eshhar. CARs are engineered molecules that allow T cells to recognize specific antigens on cancer cells, independent of the way healthy immune system cells normally identify targets. This discovery laid the groundwork for the creation of genetically altered T cells from patients that target specific antigens on cancer cells. In the 1990s, researchers began to investigate the use of these engineered cells to treat cancer.[7]

Mechanism

CAR T cell therapy involves harvesting patients' T cells via leukapheresis, genetically modifying them ex vivo to express chimeric antigen receptors (CARs) that recognize tumor-specific antigens. After lymphodepleting chemotherapy, the expanded CAR T cells are reinfused, where they activate, proliferate, and destroy target cancer cells.[7,28]

Advantages

CAR-T cell therapy provides short treatment duration, and MHC-independent antigen recognition for efficient tumor destruction.[29]

Limitations of CAR-T cell therapy

Solid tumor efficacy is limited by poor T-cell trafficking, antigen escape, and immunosuppressive microenvironment.[30]

DESTRUCTION OF CANCER CELLS USING SOUND WAVES

In this technique, researchers used ultrasonic waves, high-frequency sound waves (ultrasound; >20 kHz), for the eradication of cancerous cells. The use of ultrasound in medicine dates back to the early 20th century, with the development of ultrasound imaging techniques. In the 1950s, researchers began exploring the therapeutic potential of ultrasound, leading to the development of focused ultrasound therapy. These high-frequency sound waves propagate through the body, oscillating at varying pressures based on the delivery method, and induce the transfer of energy along a targeted path, ultimately leading to the destruction of cancer cells.[28]

Ultrasound can modulate gene expression and influence cell proliferation, migration, and apoptosis. It also targets the tumor stroma, including the extracellular matrix, immune cells, cancer-associated fibroblasts, endothelial cells, and neuronal cells, thereby enhancing drug delivery and complementing chemotherapy.[31]

Histotripsy: A method of destroying sound waves to cure cancer cells

In 2004, the University of Michigan coined the name "histotripsy" from the Greek terms "histo," which means "tissue," and "tripsy," which means "crushing." Contrary to thermal HIFU, which uses extended ultrasound exposure at moderate intensities and high

duty cycles (>10%), histotripsy employs microsecond-scale ultrasound pulses at a low duty cycle (≤1%) to minimize thermal effects. This technique focuses on generating higher peak pressure amplitudes to cause acoustic cavitation in the presence of pre-existing gas pockets in the targeted tissue.[32]

Mechanism

Histotripsy is a non-invasive, non-thermal ultrasound technique that uses cavitation to mechanically disrupt tissues while generating acellular debris. This technique is particularly effective in eliminating and removing the most superficial layer of tissue, especially in areas where two fluids converge such as the surface of atrial septum, or a clot of blood. It allows a gradual process of tissue degradation that begins at the surface and progressing to perforation or erosion with the formation of a tract for liquid flow.[33]

Histotripsy Treatment

In a prospective canine study, histotripsy ablation of spontaneous osteosarcoma was safe and feasible, with CT imaging demonstrating successful tumor ablation.[34]

Applicability to Other Cancer Types

The ultrasound-based histotripsy technique has demonstrated potential in treating various solid tumors.[31,34] Evidence indicates that histotripsy has demonstrated promising efficacy in treating several solid tumors, including prostate, liver, and bone tumors.[33] Histotripsy has also been shown to induce immunomodulation and stimulate anti-tumor immune responses, potentially enhancing control of the primary tumor.[35] However, current evidence is insufficient to determine the effects of histotripsy on tumor recurrence and metastasis following tumor ablation.[36] Ongoing research is investigating the in vivo feasibility of histotripsy for additional cancer types.

Advantages

Histotripsy is a non-invasive, non-ionizing ablation method that eliminates the need for surgical incisions, reducing risks of bleeding and tumor spread. It allows precise tissue disruption while preserving critical structures like blood vessels and bile ducts.[33]

Limitations

However, histotripsy is limited by acoustic accessibility challenges, as gas-containing organs (lung, gastrointestinal tract) pose collateral damage risks, and ultrasound penetration is restricted in deep tissues and obese patients.[33]

EMBRYONIC CANCER THERAPY

Embryonic tumors are characterized by the uncontrolled proliferation of cells in the brain, involving embryonic cells that persist from fetal development. These tumors represent a type of malignant brain cancer, signifying their potential to invade brain tissue and damage healthy cells. Additionally, they can be disseminated through the cerebrospinal fluid that bathes the brain and spinal cord. Embryonic tumors can occur at any age, however they typically occur in newborns and young children and come in a diverse form.[37]

Mechanism of Action

Rhabdomyosarcoma, a sarcoma type that refers to tumors of muscle cells, is one of the various types of embryonal cancers. Chemotherapy using vincristine, actinomycin, and cyclophosphamide is typically used to treat rhabdomyosarcoma.[38] Researchers at St. Jude Children's Research Hospital recently identified a novel risk factor for aggressive forms of rhabdomyosarcoma. This approach treats alveolar rhabdomyosarcoma brought on by PAX3-FOXO1 gene fusions by focusing on KDM4 proteins. By the use of genetic technologies and a KDM4B inhibitor, the researchers were able to substantially halt tumor growth. According to the research, chemotherapy becomes more effective when KDM4B targeting is integrated with regular chemotherapy treatment. Notably, despite the tumors' resistance to chemotherapy treatments, the study showed that the treatment can result in total tumor elimination when given to preclinical xenograft models.[39]

Chemotherapy is regarded as the most effective and well-known treatment option. This also applies to embryonal tumors.[39] For example, children with medulloblastoma and other embryonal CNS malignancies typically receive chemotherapy orally or intravenously. This makes it possible for the medications to enter the bloodstream and target cancer cells throughout the body. Treatment involves chemotherapeutic drugs that act on brain tumor cells by crossing the blood-brain barrier.[37]

Despite having unique characteristics, stem cells have the capacity to inhibit immune system activity, migrate to cancerous tumors, and secrete physiologically active substances. These characteristics help overcome limitations of gene therapy techniques and increase tumor targeting. Stem cells facilitate the targeted delivery of anticancer medications by traveling to solid tumors and micro metastases. In addition, stem cells can be altered to continuously produce various anticancer medications, removing the issues associated with the short half-lives of conventional chemotherapy.[40]

The application of cell treatments and nano medicinal medicines can be seen as an optimistic approach. Because of their use, nanoparticles can identify diseased cells and swiftly administer medication to them, minimizing harm to healthy tissues. A

treatment that employs immune or stem cells to combat malignant cells is known as cell therapy. The techniques are presently undergoing clinical testing and have already demonstrated their efficacy in studies.[41]

TURNING CANCER CELLS INTO CANCER STEM CELLS

Researchers have created a hydrogel that allows the use of medications by turning cancer cells back into cancer stem cells, making medication use possible in a day. Cancer stem cells found in tumors have the ability to proliferate and differentiate into several cancer cell types. Cancer stem cells can hide in tissues and cause tumors to regrow given their resistance to conventional cancer treatments like radiation and chemotherapy. Because it works like biological tissue and contains two chemicals combined with water, this new gel is known as dual network gel. The interaction of cancer cells with a double network gel causes these cells to aggregate into spheres and produce certain molecules which are markers of cancer stems cells. This hydrogel can stimulate the development of a range of anticancer drugs, including anticancer stem cell agents and medications tailored to a specific individual, according to validation experiments using six different types of human tumors.[42]

Conversion of cancer cells into stem cells utilizing hydrogel

Double network (DN) gel, a modern hydrogel developed by researchers at Hokkaido University, transforms differentiated cancer cells into cancer stem cells. It is anticipated that this advancement will encourage the development of novel cancer therapies and tailored medications aimed at treating cancer stem cells. Hydrogels, a wide variety of materials applied in biomedical engineering and related domains, have garnered particular attention in academic discussions, particularly double-network hydrogels for their ability to swiftly reprogram differentiated cancer cells into cancer stem cells (CSCs).[43]

Mechanism of Action of Hydrogels and Treatment

By increasing the expression of stemness-related genes (including Sox2, Oct3/4, and Nanog) and inducing tyrosine kinase phosphorylation, double-network hydrogels transform cancer cells into cancer stem cells. Additionally, they create a microenvironment similar to tumor settings, which permits the niche to contribute to the formation of cancer stem cells.[43]

Advantages

The physiochemical properties of these hydrogels enable them to mimic biological tissues, thereby making them potential for targeted cancer therapy and modulation of the pathways for stemness processes.[43]

Disadvantages

The hydrogels' interactions with stem cells are complex and poorly understood, and factors like porosity, stiffness, and degradation influence the results of reprogramming.[43]

Hydrogels offer a promising approach for CSC research and personalized medicine, though further studies are required to fully understand their mechanisms.

CANCER CELLS HIDE INSIDE EACH OTHER

Cancer cells evade immunotherapy by forming 'intracellular' structures that protect them against immune attack.[38] Killer T cells trigger this hiding mechanism; blocking these signals prevents concealment and improves immunotherapy efficacy.[44]

1. QUANTUM THERAPY

Glioblastomas are being treated with quantum therapy employing bionano-antennas, which are gold-based nanoparticles that contain redox-active particles. These antennas have the ability to specifically induce apoptosis in cancerous cells while sparing healthy cells when exposed to an electric field.[45]

CANCER THERAPY THROUGH ONCOLYTIC VIRUS

Oncolytic viruses are a promising class of cancer immunotherapy that utilizes the ability of certain viruses to infiltrate and destroy tumor cells while preserving non-neoplastic cells. These viruses are emerging as powerful tools in the fight against cancer, offering several advantages over traditional cancer therapies.

Mechanism of Action

OVs selectively replicate within tumor cells, causing them to burst and release new virus particles. This process, known as oncolysis, directly destroys tumor cells and releases tumor antigens that can stimulate an anti-tumor immune response.[46] Furthermore, OVs can also trigger immunogenic cell death (ICD), a type of cell death that stimulates release of damage-associated molecular patterns (DAMPs), further increasing the antitumor immune response.

Advantages of Oncolytic Viruses

Because oncolytic viruses (OVs) selectively grow in malignant cells while sparing healthy tissues, their systemic side effects are not fully known.[41] Similarly, the use of modified adenovirus in oncolytic immunotherapy is successful in eliminating cancer cells and generating a potent anti-tumor immune response.[42]

Furthermore, oncolytic immunotherapy, specifically using engineered adenovirus, has demonstrated effectiveness in directly destroying tumor cells and eliciting a robust anti-tumor immune response.[42] Tumor cells are destroyed, and tumor

antigens are released as the OVs replicate inside the cancer cells, a process known as oncolysis. These tumor antigens are thot to be significant immune system stimulants that initiate the activation of cytotoxic T lymphocytes (CTLs) with the goal of eliminating any residual cancer cells. The ability of OVs to both directly kill tumor cells and stimulate immunity against them is a two-in-one impact that demonstrates their effectiveness against a variety of malignancies.[46]

Oncolytic viruses, or OVs, have also shown their long-lasting effectiveness by remaining in tissues over extended periods of time. OVs offer long-term benefits that may assist delay or prevent recurrence due to their prolonged operation.[53] Furthermore, oncolytic viruses are thot to be superior to other conventional treatments. Oncolytic adenoviruses also work in concert with traditional cancer treatments such chemotherapy, radiation, and immunotherapy.[43]

In conclusion, because oncolytic viruses (OVs) can be delivered intratumorally or systemically, they offer a practical mode of administration. OVs can be administered systemically through intravenous infusion, which distributes them to tumors present throughout the body. On the other hand, intratumoral administration allows for the local therapy of malignancies by infiltrating OVs directly into the malignant spot. OVs are a suitable therapy option for a number of malignancies due to their adaptability.[47]

Challenges and Future Directions

Overcoming the key challenges include anti-tumor immunity through integrated strategies and adjusting selectivity to minimize off-target actions.[48]

Discussion

The cancer therapeutic approaches discussed include cellular immunotherapies, nanomedicine-based methods, and physical ablative procedures like histotripsy which can revolutionize today's oncology. However, a critical analysis of the existing data reveals numerous challenges with their clinical use. Addressing the therapeutic and clinical challenges such as limited clinical evaluation, safety concerns, manufacturing and regulatory obstacles will be important to fully realize the therapeutic and clinical benefits of these innovative approaches. A significant obstacle for all nanomedicine-based strategies, including exploding nanobubbles and nanomachines, is the ongoing gap between preclinical promise and clinical reality. According to a seminal study that examined the literature from 2005 to 2015, in total, only 0.7% (median) of the injected dose (ID) of intravenously administered nanoparticles accumulates in tumours".[44] This finding was supported by a subsequent study, which reported that the process of delivering nanoparticles to solid tumors has remained unchanged over the last decade, recording a median tumor accumulation rate of 0.7% of the dose administered.[49] Nevertheless, for the exploding nanobubble and nanomachine platforms discussed in this review, systematic evaluation of delivery efficiency and further optimization of targeting strategies remain critical to improving their translational and clinical potential.[44] The immunosuppressive tumor microenvironment represents a significant barrier for CAR T-cell therapy and oncolytic virotherapy. Recent studies have shown that the mutations in KEAP1, SMARCA4, and PTEN can help the tumor evade detection from the immune system that can ultimately lead to aggressiveness of the tumor, resistance to treatments, and disturbance of the pathways involved in oxidative stress, chromatin remodeling, and cell signaling. These changes correlate with poor clinical results regardless of tumor mutation burden or PD-L1 expression. These findings were primarily reported from research concerning immune checkpoint inhibitors, and these factors might also influence responses to CAR T-cell therapy and oncolytic virotherpy. Hence, future investigations should study the impact of these factors on treatment efficacy and develop strategies to overcome mutation-driven resistance.[45]

The techniques described in this study, such as as adipogenic conversion, KDM4B suppression, and hydrogel-based cancer stem cell (CSC) regulation, which target basic biological processes independent of the tissue of origin, are supported by the effectiveness of tissue-agnostic therapies. Recent literature confirms that tissue-agnostic therapies have revolutionized oncology by targeting tumors with particular molecular changes instead of their anatomical origin. However, there are still significant issues, particularly intratumoral heterogeneity and the development of resistance mechanisms that restrict the efficacy of treatment.[48]

Recent studies suggest that next-generation approaches of CAR engineering may help in solving the limitations of the traditional therapies based on CAR T-cell therapy. Xu et al. created fluorinated lipid nanoparticles for CAR-macrophage engineering in vivo by using the properties of macrophages that allow them to obtain homing in the tumors and perform both phagocytosis and tumor microenvironment remodeling. In the study, the leading lipid nanoparticles (formulation A1F5C5) were able to provide effective delivery of mRNA to macrophages both in vitro and in vivo thus allowing for efficient production of CAR-macrophages using the technology of engineering. However, further preclinical validation and clinical studies are required to establish its safety and efficacy.[50] Future research should aim to optimize nanomedicine performance,

discover predictive biomarkers, and develop strategies to mitigate treatment resistance.

Conclusion

Nanomedicine platforms (nanobubbles, nanomachines), cell immunotherapies (CAR-T, oncolytic virotherapy), tissue agnostic approaches, and histotripsy are emerging cancer therapies with promising potential to revolutionize oncology, but limited clinical translation. The delivery of nanomedicine into the tumor is still limited with a median tumor accumulation of only 0.7% of the injected dose, and immunosuppressive tumor microenvironments and mutations in KEAP1, SMARCA4 and PTEN induce resistance to immunotherapies. Intratumoral heterogeneity and adaptive resistance are challenges for the tissue-agnostic approach. Examples of innovations in development include in vivo engineered CAR-macrophages (A1F5C5) for adoptive transfer therapy, which should be further validated as next-generation therapies. However, achieving clinical benefit from such therapies will require enhanced delivery efficiency, identification of predictive biomarkers, resistance, and safety, manufacturing and regulatory issues.

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