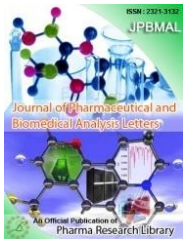

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Novel Therapeutic Options for Prevention and Management of Cancer

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A B S T R A C T

The high incidence of cancer may be caused by several factors, such as genetic mutations, environmental factors, insufficient physical activity, diverse lifestyles, unstable behaviors related to diet, smoking, and alcohol consumption. The current treatment methods for different stages of various cancers include chemotherapy, radiation therapy, and surgical procedures for solid tumors, or a combination of the above. Although these different treatment modalities can effectively reduce cancer, patients may also experience side effects. Radiation therapy runs the risk of causing DNA damage in surrounding healthy cells, which could potentially lead to new incidences of cancer. Similarly, although surgical intervention the primary treatment for solid tumors significantly improves patient survival, its success rate depends on the expertise of the surgeon and the availability of screening methods, including hospital imaging equipment. The introduction of chemotherapy was a milestone in cancer treatment. However, prolonged use of chemotherapy drugs, especially those affecting tumor cell metabolic pathways and signal transduction, can influence tumor occurrence, metastasis, drug response, recurrence, drug resistance, and cancer stem cells (CSCs). Traditionally, drug development involves preclinical research and clinical trials. Preclinical studies involve testing the efficacy, toxicity, pharmacokinetics, and pharmacodynamics of drugs in human tumor cells and animal models. Once the therapeutic efficacy of a drug has been determined, the drug moves into the clinical trial phase, which includes Phase I, II, and III human clinical trials, to determine the safety and effectiveness of the drug. As such, it takes 10–15 years and costs $1–2 billion to produce a new drug approved for clinical use.

Keywords: Cancer, chemotherapy, tumor occurrence, metastasis, clinical trials, DNA damage.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Cancer cells can arise in any organ of the body, and their cells of origin vary depending on the tissue type. In addition, any single tumor, independently of its location of origin, is not homogeneous itself, rather consisting of cells with diverse biological traits. To make matters worse, patients with the same diagnosis may have different molecular profiles of their tumor. Such heterogeneity poses a challenge for diagnosis, prognosis, and treatment of cancer, as it makes the tumor more adaptable, aggressive, and resistant. In the last decades we have developed novel precision-oncology protocols that are starting to be adopted in routine clinical practice. However, despite major advances, the dream of converting solid tumors into a chronic disease is still unfulfilled, and long-term remission

eludes us. Some of the current challenges in oncology deal with: (i) Identifying the molecular profile of each patient's tumor and tailoring the therapeutic approach, rather than using a one-size-fits-all approach; (ii) Exploiting the tumor microenvironment (TME), the most tumor-intermingled organ that lives symbiotic to cancer cells in order to enhance drug delivery and efficacy of treatment; (iii) Harnessing the power of immunotherapy to activate the body's own defense system against cancer; (iv) Identifying new biomarkers and diagnostic tools to monitor treatment response and predict prognosis; (v) Combining different modalities of therapy to achieve synergistic outcomes, optimize benefits and minimize side effects.

This Special Issue (which was so well received that we also launched a 2.0 version) explored the latest advances in precision-oncology for solid tumors to tailor personalized and effective strategies for oncology patients by exploiting cancer cell vulnerabilities. This scientific anthology highlights the importance of understanding tumor heterogeneity, evolution, and recurrence, as well as developing novel therapeutic strategies. These strategies encompass addressing how RNA molecules, proteins, vesicles, and channels can modulate cancer progression and dissemination. They also cover how these components can be targeted or manipulated to bypass cancer cell's growth and drug resistance by adopting different modalities, such as immunotherapy, metabolic inhibition, targeted therapy, epigenetic modification, and RNA regulation/modulation. The 15 papers in this collection offer a valuable insight into the molecular mechanisms and therapeutic potential of these emerging approaches in cancer treatment[1-4].

Another element that plays a role in tumor development and progression is quiescence, a state of dormancy in which cells stop dividing but remain viable. Quiescent cancer cells (QCCs) are non-dividing and resting cells that can escape most anti-cancer drugs and cause cancer recurrence. QCCs are prevalent and diverse in different types of solid tumors, and they can switch between quiescence and proliferation depending on the environmental cues, leading to cancer growth, recurrence, and metastasis. Another challenge for cancer treatment is acquired drug resistance (ADR), which occurs when tumor cells become resistant to anti-neoplastic drugs after exposure.

Singh et al. review the current knowledge on how STAT3, a signaling molecule that is often activated in malignant cells, contributes to the development of ADR to numerous anti-cancer therapies, such as chemotherapeutic agents, targeted kinase inhibitors, anti-hormonal drugs and monoclonal antibodies. STAT3 suppresses the immune system, interferes with autophagy and anoikis, and alters the function of p53 and NNMT, thus favoring tumor survival and growth. The authors suggests that using a STAT3 inhibitor along with other anti-cancer agents could prevent or reverse resistance and improve treatment outcomes by restoring normal cell death processes, correcting molecular dysfunctions, and enhancing immune system function.

Cancer is a complex disease that involves the cooperation of various factors that promote its growth and survival. One such factor is their notorious ability to evade cell death. One of the mechanisms that tumor cells use to escape cell death is by altering their mitochondria, the organelles that produce energy and regulate cell survival. One such alteration can affect the mitochondrial permeability transition pore (mPTP), a channel located in the inner mitochondrial membrane. The opening of the mPTP can trigger apoptosis, or programmed cell death, by releasing cytochrome c and other pro-apoptotic factors from the mitochondria into the cytosol, where they activate the caspase cascade. Normal cells open the mPTP in response to high mitochondrial Ca^{2+}, oxidative stress, and depolarization. However, cancer cells prevent or limit the mPTP opening and avoid apoptosis by altering their mitochondrial structure and function[5-9].

Malignant cells can communicate with other cells through extracellular vesicles (EVs), which are small membrane-bound particles that can carry various cargo, such as proteins, nucleic acids, lipids, and metabolites, from the originating cell to a recipient cell. EVs can modulate many biological processes, such as cell communication, immune response, and tissue repair. However, EVs can also contribute to cancer development and progression by promoting drug resistance; consequently, they can facilitate tumor growth and spread. The paper by Yi et al. provides an informative synopsis of the oncogenic signaling mediated by EVs derived from cancer cells and their potential as a novel target for anti-cancer therapy. In this review, they also point out the obstacles of this approach: the heterogeneity of EVs, the lack of specific markers, and the difficulty of isolating and characterizing them. Using triple-negative breast cancer cells as an example, they suggest ways to prevent EVs from being pro-tumorigenic, such as by blocking their uptake, secretion, or cargo, and enhancing the immune response against cancer-EVs. Another emerging approach in tumor intervention is to use small molecule therapy, a type of targeted therapy that uses compounds that can enter the cells and interfere with their function or survival.

Lithocholic acid-based imidazolium salts (LCA-IMSs), against colon cancer cells. They synthesized different LCA-IMSs with varying carbon chain lengths, and evaluated their cytotoxicity in vitro and in vivo. They found that the length of the carbon chain influenced the efficacy of the LCA-IMSs, and that one of them (S6) had a superior antitumor activity compared to the conventional chemotherapeutic agent 5-fluorouracil (5-FU) in a mouse xenograft model: S6 induced apoptosis and cell cycle arrest in colon cancer cells, and significantly reduced tumor volume and weight in mice. Therefore, this study suggests that LCA-IMSs are promising compounds for the treatment of colon cancer, and that S6 is a potential candidate for further development and clinical trials. RNA molecules are versatile and dynamic regulators of gene expression and cellular functions. By binding to other RNA molecules or proteins, they can modulate RNA fate and function.

Abnormal interactions can lead to tumor development and progression, by affecting various aspects of cancer biology, such as metabolism, proliferation, invasion, angiogenesis, and drug resistance. Therefore, one of the emerging strategies for cancer treatment is RNA therapy. In this Special Issue, several research articles explore the role and potential of RNA-based intervention in different types of tumors, using various approaches and techniques. One of the RNA-binding proteins (RBPs) that has attracted considerable attention in recent years, Insulin-like growth factor 2 mRNA-binding protein 3 (IGF2BP3), is a component of the m6A reader complex, which recognizes the m6A modification on RNAs. m6A methylation is the most common and reversible RNA modification in eukaryotes, and it affects various aspects of RNA biology such as: stability, splicing, translation, and localization. However, RNA-binding proteins are not the only molecules that can influence cancer development and progression. Another factor that can modulate gene expression and cellular functions in tumor cells are microRNAs (miRNAs). These molecules are small non-coding RNAs that can regulate gene expression by binding to messenger RNA and preventing its translation into protein. They influence various cellular functions via their dynamic and complex interactions, including cancer initiation, progression, and metastasis. Therefore, another emerging method for oncological treatments is microRNA therapy, which aims to modulate the expression and function of microRNAs in tumor cells. The microRNA strategy has two main approaches: miRNA replacement and miRNA inhibition. Cancer treatment was limited to only a few options for patients. These included surgery and radiation therapy for solid localized tumours, and chemotherapy for blood-related cancers and solid metastatic tumours.

These therapies have been used as single treatments or in combination for a long time. Recently, with the advent of targeted therapies, a big emphasis has been put on the biological mechanisms underlying response/resistance to targeted agents. As a result, our understanding of the many pathways involved in cancer progression and the ways in which they can be targeted has improved dramatically, with combinatorial strategies involving multiple targeted therapies or "traditional" chemotherapeutics, such as the taxanes and platinum compounds, being found to have a synergistic effect. However, while conventional therapies, such as targeted therapies, radiation therapy and chemotherapy, mainly target epithelial cancer cells, we now know that cancer progression is not exclusively due to changes in cancer cells, but also involves the tumour microenvironment (TME), as well as alterations in cellular metabolism and immune response, offering new avenues for cancer therapies. The use of immune therapy in the treatment of cancer has gained traction over the last few years, culminating in the recent Nobel Prize for Physiology or Medicine to Prof. James Allison and Prof. Tasuku Honjo for their seminal work in this field. Their work has established negative immunomodulation through the inhibition of immune checkpoint proteins, such as Cytotoxic T-lymphocyte-associated Protein 4 (CTLA-4) and Programmed Cell Death Protein 1 (PD-1), as a cornerstone of modern cancer treatment. Immune checkpoint inhibitors, including ipilimumab (anti-CTLA-4) and pembrolizumab (anti-PD-1), are in trial in multiple cancer types, moving from single agent studies to combinatorial studies with other immune checkpoint inhibitors and more classical chemotherapies. Epigenetics drugs such as 5-Azacytosine have now established their presence in the clinic for blood-related malignancies and can be used in combination with traditional treatments in solid tumours where they re-sensitize cancer cells to certain types of chemotherapy.

2. Cancer and Immune Metabolism

Prof. David Finlay's group from Trinity College Dublin (TCD) has focused on understanding how cellular metabolism and the fuels available in the microenvironment control NK cell metabolism and facilitate their effector function. Studies by Prof. Finlay's group have shown that the cellular fuels available to immune cells have a big impact on their function. They found that in cytokine-activated NK cells, robust induction of glycolysis and oxidative phosphorylation (OXPHOS) are essential for effective NK cell anti-cancer functions. Their group identified the key metabolic regulators of this response to be mammalian target of rapamycin complex 1 (mTORC1), cMyc and sterol regulatory element-binding protein (SREBP).

In cancer and other diseases, impaired cellular metabolism can lead to dysfunctional NK cells. In cancer, low levels of glucose may result in direct or indirect inhibition of NK cell metabolism through alteration in the activity of nutrient-sensing signalling pathways. In a metabolically restrictive tumour microenvironment where tumour cells consume large quantities of fuels, the anti-tumour immune response is suppressed. New strategies have been introduced to modulate NK cell function in the tumour microenvironment through modulation of its metabolic requirements.

One strategy is the use of chemotherapy/radiotherapy alongside immunotherapies to reduce the number of fuel-consuming tumour cells, by inducing tumour cell death and increasing glucose levels required for the anti-tumour response of the NK cells. On the other hand, inhibition of glutaminase will reduce glutamine consumption and increase the glutamine available for the metabolic activity of NK cells. Other strategies involve the use of metabolic agents in combination with checkpoint inhibitor antibodies. These include the use of anti-PD-1, anti-CTLA-4, or anti-PD-L1, resulting in reduced T-cell glycolysis and increased glucose levels in the TME and, in particular, an increase in NK cells' anti-tumour effect. Depletion of other nutrients can also have an effect on the glycolytic rate of the immune cells. Expression of the enzymes indoleamine-pyrrole 2,3-dioxygenase (IDO) and arginase-1 by tumour cells results in the depletion of tryptophan and arginine, which can inhibit T-cell and NK cell function, and therefore inhibition of these enzymes with metabolic agents can result in an increased antitumour immune response[10-18].

3. Epigenetic Therapies

The 5-azacytosine DNA methyltransferase inhibitors (DNMTis) have established a presence in the clinic for the treatment of myelodysplastic syndrome and acute myelogenous leukaemia. These agents act as S-phase specific inhibitors of the DNA methyltransferase enzymes and cause global decreases in DNA methylation. Haematological patients respond to DNMTis as monotherapies, but the reasons for doing so are not entirely clear. It will be important to determine the exact mechanism(s) of action of these epigenetic agents in order to increase their efficacy and broaden their scope within solid tumours. Additionally, the use of DNMTis in solid tumours requires the use of combination therapies to increase patient responses. Professor Peter Jones, Chief Scientific Officer at Van Andel Research Institute Grand Rapids, Michigan, U.S., and a pioneer in the field of epigenetics, discussed some of the potential mechanisms by which DNMTis function to cause responses. Traditionally, the main explanation for the effects of epigenetic therapies was that they upregulate the expression of abnormally silenced tumour suppressor genes, thus resulting in the restoration of growth control to treated cells. Most recently, Professor Jones' team has become interested in the roles of sequences constitutively methylated in both normal and cancer cells as targets for DNMTis. For example, the removal of DNA methylation from gene bodies can result in decreased transcription, leading to lower levels of transcription factors such as MYC proto-oncogene, which are commonly upregulated in cancer. This results in substantial downregulation of proto-oncogenes in the MYC pathway [18].

DNMTis are also powerful inducers of human endogenous retroviruses (ERVs). ERVs are a class of transposable elements that are acquired when retroviruses infect germ cells during evolution. The main mechanism for silencing these ERVs is DNA methylation. Therefore, activation of the ERVs through demethylating agents can lead to a state of viral mimicry in which the treated cancer interprets the induced ERV expression as being due to an infection by an exogenous virus and mounts an innate immune response, leading to production of type I and type III interferon and other cytokines. This results in decreased cancer cell fitness and attraction of cytotoxic T lymphocytes (CTLs) to the TME. These infiltrating immune cells also show epigenetic abnormalities and can therefore be targeted by epigenetic drugs. For example, the CTLs become exhausted when continuously stimulated by the TME. The exhausted phenotype is characterised by aberrant DNA methylation of genes involved in T-cell effector function; therefore, DNMT is may be used to reprogramme the CTLs into an effector phenotype. This important mechanism of action of epigenetic drugs highlights the potential for combining these agents with the use of checkpoint inhibitors in solid tumours to capitalize on the viral-defense pathways induced[19-27].

The combination of various agents which might increase the efficacy of DNMTi treatment directly such as the inclusion of Vitamin C in the treatment regimen was also discussed. While Vitamin C deficiency is rare in the general population, cancer patients show low levels of it, suggesting that Vitamin C supplements could be beneficial for cancer patients. The role of Vitamin C in enhancing the viral mimicry resulting from epigenetic treatments [24] is due to the fact that Vitamin C is an essential cofactor for the ten-eleven translocation (TET) enzymes, which are actively involved in DNA demethylation. Experimental evaluation of the combination of Vitamin C with 5-aza-2'-deoxycytidine in preclinical models [24] suggested that a strong synergy could be expected in patients [26], and clinical trials designed to test this are currently underway.

A qualitative sub-study, as part of the above pilot study, investigated the effects of the pre-operative exercise programme on perceived wellbeing and HRQoL in the prostate cancer group. Following completion of the exercise programme (within 1 week before surgery), 11 participants took part in a semi-structured interview which covered four broad HRQoL domains, including physical, psychological, social and spiritual wellbeing. Findings showed that engagement in the pre-operative exercise programme provided participants with: (1) a teachable moment; (2) acted as a vehicle to recovery; (3) a sense of optimism and (4) social connectedness. This qualitative study showed that the exercise programme enhanced wellbeing and improved perceived HRQoL. Further research is required to explore this in a larger, adequately-powered sample.

In keeping with the theme of the importance of physical exercise in the cancer journey, Dr. Gillian Prue and her team from Queen's University Belfast (QUB) adopt a precision oncology approach utilising exercise as an anti-cancer treatment. There is sufficient evidence demonstrating the favourable effects of exercise on symptom control and quality of life (QOL) in prostate cancer, such as in countering the effects of androgen deprivation therapy. Epidemiological studies have suggested that exercise may improve disease-specific and overall survival in prostate cancer; however, this has yet to be demonstrated in a clinical population.

Many exercise oncology trials adopt a generic, linear approach to training (i.e., low to medium intensity gradually increasing over time), but to maximise outcome, the 'principles of training' traditionally used for athletes should be applied to exercise prescriptions. The use of generic exercise prescription, though successful in some cases, has led to homogenous exercise programmes being prescribed for largely heterogeneous populations, not taking into consideration the unique needs and preferences of the individual. This may mask the full therapeutic potential of the exercise programme, prompting calls for the potentially more effective non-linear models which focus on individualisation, specificity, progressive overload and recovery. This approach involves manipulating intensity, duration and occasionally the frequency of training sessions to allow the training volume to continually increase across the entire programme. As there is considerable

heterogeneity in cancer progression and treatment, exercise programming should be equally individualised, to promote safety and optimise the efficacy of treatment for the individual.

In addition, to provide evidence on the feasibility of exercise interventions in patients for whom high intensity exercise is not suitable, Dr. Prue's team are currently running a parallel Northern Ireland-specific study based upon an exercise intervention (Exercise for Advanced Prostate Cancer: a Multicomponent Feasibility Trial (EXACT) and CRC trial) developed and recently tested in CRC survivors by colleagues from Ulster University. Exact-Mcrpc (Exact-metastatic castrate-resistant prostate cancer) offers the benefits of participating in a multicomponent physical activity programme to those men with MCRPC who are ineligible for the Interval programme that contains high intensity exercise. The aim is to ensure that all men have the opportunity to capitalise on the benefits of increased physical activity by offering a lower intensity lifestyle physical activity intervention. This is the first of its kind in this advanced and unwell population. This feasibility study is providing preliminary evidence on the acceptability, feasibility and efficacy of moderate intensity physical activity among men with very advanced cancer, and setting the benchmark for all other cancer patients.

Multi-Omics as a Novel Tool for Discovering New Therapeutics for Cancer: Human biological processes are driven by a complex network of events leading to specific functional phenotypes. These include genomic, epigenomic, transcriptomic, epi-transcriptomic and proteomic networks that cooperate together to deliver a specific biological function. New technologies stated that as well as advances in analytical techniques, have revolutionized 'omic' science and allowed for a more in-depth and integrative understanding of biological processes that lead to various diseases including cancer. The European Association for Cancer Research (EACR) Senior Investigator Award Winner, Dr. Sara Charmsaz from the Endocrine Oncology Research group (EORG) in Royal College of Surgeons Ireland, described their efforts in integrating 'omic' data to identify new therapeutic targets for treatment of endocrine-resistant breast cancer. Dr. Charmsaz presented studies that integrated proteomic and transcriptomic data to identify new therapeutic targets, as well as novel companion diagnostics tools, for Estrogen Receptor (ER)-positive breast cancer. Two main targets were identified, A Disintegrin And Metalloprotease domain 22 (ADAM22) as a potential new therapeutic and S100 calcium-binding protein β S100β as a companion diagnostic for early identification of patients at risk of developing metastasis. S100β as a companion diagnostic is used to identify patients at risk of developing metastatic disease and suggests a src-kinase inhibitor (Dasatinib) as a potential new therapeutic used in combination with endocrine therapy in patients with elevated levels of S100β.

Treatment and Therapy

The dendritic cells are presented with the nano-vaccines, which are porous silicon particle discs loaded with immune stimulating molecules and tumor antigens. These activated cells are then injected back into the host to stimulate an anti-tumor response.

Traditional cancer treatments are currently limited to surgery, radiation, and chemotherapy, all of which carry the risk for damaging normal tissues or incomplete eradication of the cancer. Nanotechnology offers the means to target therapies directly and selectively to cancerous cells and neoplasms, guide surgical resection of tumors, and enhance the therapeutic efficacy of radiation-based treatments. Nanotechnology also presents a unique set of tools to overcome drug resistance and enable the use of novel immunotherapies as one exemplified in the right image. Collectively, these advancements can add up to a decreased risk to the patient and an increased probability of effective treatment[28-33].

Research on nanotechnology cancer therapy goes beyond drug delivery, extending to the creation of new therapeutics available only through the use of nanomaterial properties themselves. First, some physical properties of nanoparticles, such as energy absorption and re-radiation, can be used to disrupt diseased tissue, as seen in laser ablation and hyperthermia applications. Second, nanoparticles are small enough to accumulate at the tumor sites, whereas they are large enough to encapsulate many therapeutic compounds, like radionuclides and active pharmaceutical ingredients. Third, their ample surface area can be functionalized with ligands including DNA or RNA strands, peptides, aptamers, or antibodies, which can actively direct their destination in vivo. Furthermore, nanostructured architectures are innovatively utilized to design artificial antigen presenting cells and create in vivo depots of immunostimulatory factors for sustained anti-tumor activity. Altogether, these applications empower efficient drug delivery, multi-modality treatment, and theranostics.

Nanotechnology's role in cancer therapeutics has been to improve the pharmacokinetics and reduce the systemic toxicities of chemotherapies by selectively targeting and delivering anticancer drugs to tumor tissues. Nanosized carriers can increase the overall therapeutic index of delivered drugs through nanoformulations, where chemotherapeutic is either encapsulated or conjugated to the surface of nanoparticles. The selective delivery of nanotherapeutic platforms primarily depends on the passive targeting of tumors through the enhanced permeability and retention (EPR) effect, although other mechanisms were also proposed. The EPR phenomenon relies on tumor microenvironment defects like lymphatic drainage and increased tumor vasculature permeability, which facilitate the accumulation of nanoparticles (<200 nm) in the tumor. Additionally, the timing or site of drug release can be controlled by the use of external or internal trigger mechanisms such as ultrasound, pH, heat, or material composition itself. Several researchers are working towards developing nanomaterial-based delivery platforms to enhance chemotherapy's effectiveness while reducing its

toxicity. For example, they are developing a strategy for photodynamic therapy, specifically tailored for bone marrow application (Alexander Zheleznyak, Monica Shokeen, and Samuel Achilefu, *WIREs Nanomedicine and Nanobiotechnology*, 2018), an area usually inaccessible to external radiation sources. Others are investigating the fundamental interactions between nanomaterials and biological systems to advance cancer diagnostics and therapeutics. This involves a focus on nanoparticle-based delivery systems that can penetrate physiological barriers to achieve targeted access to specific tumors, utilizing methods like mechanical particle deformation or using a synergistic approach for the delivery of paclitaxel and gemcitabine chemotherapeutics in mesoporous silica nano-constructs.

Delivering or Augmenting Radiotherapy

Roughly half of all cancer patients receive radiation therapy as part of their treatment regimen. This therapy uses high-energy radiation to shrink tumors and kill cancer cells by inducing cellular apoptosis. Radiation therapy achieves this by either directly damaging DNA or generating charged particles (atoms with an odd or unpaired number of electrons) within the cells that can in turn damage the DNA. Most types of radiation used for cancer treatment are X-rays, gamma rays, and charged particles. Given their inherent toxicity to all cells, not solely cancer cells, these radiation treatments are administered at dosages balancing the effectiveness and safety, aiming to be potent while preventing excessive harm to surrounding tissue or organs near the tumor mass. This compromise considers factors like tumor type, tumor location, and stage.

Nanotechnology-specific research has been focusing on radiotherapy, elevating capabilities of this treatment modality through the unique properties of nanoscale materials. Specifically, most of the nanotechnology platforms designed for radiotherapy treatments rely on the interaction between X-rays and nanoparticles, driven by the inherent atomic level properties of the materials. The nanoparticles with high atomic number can enhance the Compton and photoelectric effects of conventional radiation therapy, thus increasing efficacy while reducing the existing radiotherapy dosage and its subsequent toxicity to the surrounding tissue. Other platforms make use of nanoparticles that release drug upon X-ray radiation, enabling localized drug delivery at tumor site and sensitizing cancer cells to radiotherapy.

Another type of therapy that benefits from external electromagnetic radiation is photodynamic therapy (PDT). It is an effective anticancer procedure for superficial tumors that relies on tumor localization of a photosensitizer followed by its light activation to generate cytotoxic reactive oxygen species (ROS). Upon X-rays irradiation, some nanoparticles that contain lanthanide or hafnium can emit visible light photons locally at the tumor site to generate ROS for tumor destruction. This approach serves as an alternative therapy for cancer cells that have become radiotherapy resistant. Moreover, certain nanomaterials can function as dual agents, facilitating both PDT and enhanced radiation therapy. In addition, some platforms utilize Cherenkov radiation for localized photon emission, acting as a trigger for local PDT in deep-tissue targets.

Nano-enabled Immunotherapy

Immunotherapy is a promising modality in cancer treatment, encompassing various approaches such as checkpoint inhibitors, lymphocyte-promoting cytokines, engineered T cells, and cancer vaccines. However, a key challenge in the widespread implementation of cancer immunotherapy is the precise regulation of the immune system, as these treatments can lead to serious adverse effects including autoimmunity and nonspecific inflammation. Understanding of tumor-host immune system interactions is pivotal for improving efficacy and controlling these adverse effects. New technologies for molecular and functional analysis of single cells are being used to interrogate tumor and immune cells, shedding light on molecular indicators and functional immune responses to therapy. To this end, nano-enabled devices and materials are strategically employed to efficiently sort, image, and comprehensively characterize immune cells.

Depiction of the complex pathway involved in cancer immunotherapy. Nanoparticle delivery vehicles can play a role in multiple steps of activation of immune system to suppress cancer. Nanoparticle-based therapeutics can induce tumor cell death and in turn increase neo-antigen release from this tumor. Nanoparticles can be utilized to improve antigen presentation and T cells activation. They can also deliver pro-immune/pro-inflammatory agents to tumors and tumor microenvironments to enhance the cancer immunotherapy response.

Credit: Alberto Gabizon and Ninh La-Beck, Texas Tech University Health Sciences Center

Nanotechnologies are also being investigated to deliver immunotherapy while reducing toxic side effects, as illustrated in the figure above. This includes use of nanoparticles for delivering immunostimulatory or immunomodulatory molecules in combination with chemo- or radiotherapy, or as adjuvants to other immunotherapies. Nanoparticles are also used to capture antigens shed from tumors following radiotherapy. Furthermore, nanoparticle-based vaccines (as exemplified in the image below) are being designed for raising T cell responses through antigen-adjuvant co-delivery, multi-antigen activation of dendritic cells, and continuous antigen release, as exemplified by the image below. Other applications of nanotechnology here include in situ vaccination with artificial antigen presenting cells or immune depots placed near tumors. These strategies will advance and be refined as our understanding of cancer immunotherapy deepens.Vaccine-based immunotherapy from novel nanoparticle systems. This scanning electron microscope image shows dendritic cells, pseudo-colored in green, interacting with T cells, pseudo-colored in pink. The dendritic cells internalize the particles, process the antigens, and present peptides to T cells, guiding immune responses.

Credit: Victor Segura Ibarra and Rita Serda, The Methodist Hospital Research Institute

Delivering Gene Therapy

The value of nanomaterial-based delivery has become apparent for new types of therapeutics, particularly those

using nucleic acids. Nuclei acids are highly unstable in systemic circulation and sensitive to degradation. These include DNA and RNA-based gene therapeutics, such as small interfering RNAs (siRNAs), messenger RNAs (mRNAs), and microRNAs (miRNAs), which have been reported to have significantly extended half-lives when delivered either encapsulated or conjugated to the surface of nanoparticles. These therapeutics are frequently used to target 'undruggable' cancer proteins. Additionally, the increased stability of genetic therapies delivered via nanocarriers, often combined with controlled release, has been shown to prolong their effects.

4. Conclusion

The novel therapies described in this Special Issue have shown promising results for treating a variety of different solid tumors. However, there are still many challenges and obstacles to overcome before these therapies can be widely applied in clinical practice. Future research should focus on improving the safety, specificity, and durability of these therapies; in addition to exploring the synergies among these novel agents, as well as their combination with treatments that are already available34. Combining repurposed therapeutic drugs with approved anticancer drugs can achieve synergy and improve therapeutic effectiveness and safety. In addition, as with other drug strategies for cancer treatment, new drug delivery technologies are necessary for treating cancer cells. In this regard, nanotechnology represents a potential strategy to improve the current prognosis and treatment of tumors. Currently, large clinical studies are examining the use of established safety nanomedicines such as nab-paclitaxel (Abraxane), liposomal DOX, liposomal verteporfin (Visudine), and gadolinium nanoparticles (AGuIX)379 in cancers such as pancreatic cancer,380 advanced squamous NSCLC,381 breast cancer,382 platinum-refractory metastatic urothelial cancer,383 and gastrointestinal cancer. However, many components (materials) of the nanocarriers that have exhibited excellent tumor targeting and therapeutic properties in a xenograft tumor model have not been tested for safety and their long-term toxicity is not known. This has resulted in few clinical trials of nanoparticles loaded with repurposed drugs for cancer treatment.

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