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A REVIEW ARTICLE ON THE NOVEL MECHANISMS FOR DELIVERY OF CANCER THERAPEUTICS

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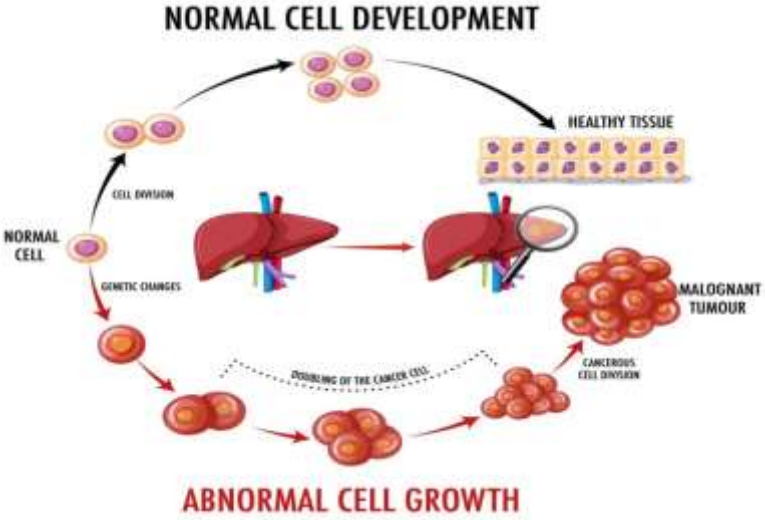
ABSTRACT

The majority of cancer treatments used today focus on surgically removing the tumour mass. The rapid proliferation of malignant cells is significantly slowed down by physical and chemical therapies like radiotherapy and chemotherapy. Additionally, these treatments have a high level of toxicity and severe side effects, which decrease patient compliance. To improve treatment indices, new approaches to conventional cancer therapeutics, including cancer stem cell therapy, triggered release, intracellular drug targeting, gene delivery, magnetic drug targeting, ultrasound mediated drug delivery and photodynamic therapy have added new techniques for treating cancer. These methods have aided in the selective detection of cancerous cells, enabling their eradication with the fewest possible negative effects. This review discusses cutting-edge methods for administering chemotherapy more effectively in an effort to improve cancer prognosis.

KEYWORDS - *cancer stem cells, photodynamic therapy, gene therapy, triggered release*

INTRODUCTION



Cancer is a group of diseases involving uncontrolled growth and spread of abnormal cells. Such cells undergo transformations to obtain inexhaustible replication and thus traverse to other organs leading to malignancy. Cancer is becoming the second biggest cause of mortality worldwide due to the alarming increase in cancer incidence and treatment abnormalities. The overall annual economic toll of cancer is significant and rising. The causes of increased morbidity and death, in addition to the absence of effective curative treatments, include adverse treatment-related side effects, drug resistance, and tumour recurrence. The survival rate has substantially increased in the meantime. Wide-ranging improvements in cancer treatment have been made in

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recent years with the goals of preventing cancer, achieving total tumour regression, reducing side effects, enhancing patient quality of life, and preventing tumour recurrence.(1)

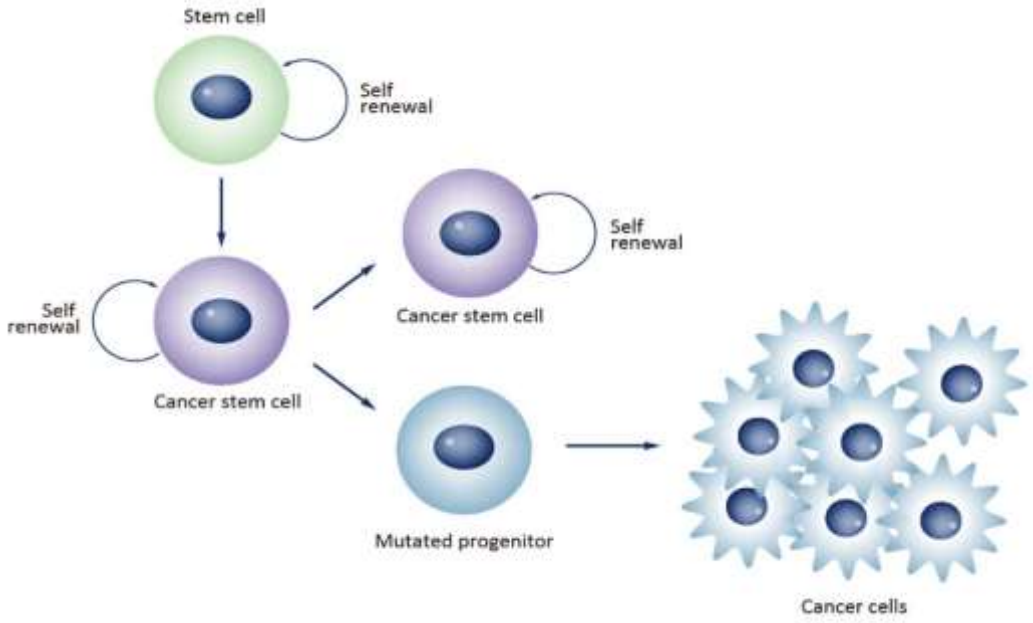
PHOTODYNAMIC THERAPY (PDT)

For the treatment of cancer, photodynamic therapy is a minimally invasive, dual-selective, and clinically- approved therapeutic method. Photosensitizer (PS), specific wavelength radiations (often in the visible or near infrared region), and oxygen are the three individually non-toxic components used in the procedure. These straightforward elements can be combined in a specific sequence to have complex cytotoxic effects on cancerous cells. The maximum absorption band (max) of the photosensitizer has the same wavelength as the radiations.3 PDT can have local anti-tumor cytotoxic effects, damage tumour vasculature, and induce systemic immunity by causing acute inflammation depending on the dose and type of photosensitizer used, the oxygen concentration in the tumour, the light dose, and the time interval between the administration of PS and irradiation. Delivering the targeted PS exclusively to the target malignant cells or tissue is made possible by tumour homing ligand grafting. The treatment is dual selective since the radiation is only spatially aimed towards the body's malignant mass area. The first PS for PDT was hematoporphyrin (an endogenous porphyrin), which the FDA approved in. (3)

CANCER VACCINATION

Cancer immunotherapy and cancer immunoprevention, respectively, relate to the use of vaccinations to treat or prevent the development of cancer. Innate (antigen nonspecific) and acquired or adaptive (antigen specific) immune systems interact in a complex way to produce immunity. The immune system's built-in immunity has the power to get rid of malignant cells. Normally occurring neoplastic cells are eliminated by the immune system. When the immune system's defences break down due to genetic and epigenetic abnormalities, cancers form. The essential elements of anticancer immunity are T-lymphocytes, which are capable of differentiating between healthy and malignant cells. Specific antigens or marker peptides are overexpressed by cancer cells as a result of oncogenes or DNA alterations. By identifying and eliminating cancer-specific epitopes attached to the major histocompatibility complex (MHC), activated T-cells can reject the malignancies. Antigen presentation cells (APCs), which identify, bind, and present lymphocytes with cancer-specific epitopes, are necessary for the stimulation of T-lymphocytes. Dendritic cells (DCs) are necessary for the formation of a powerful anticancer response because cancer cells perform poorly as APCs. These cells, which are generated from bone marrow, can recognise cancer antigens and present them to lymphocytes. Highly effective, DCs are known as "natural adjuvants" or "professional APCs" because they provide a connection between innate and adaptive immunity (8)

CANCER STEM CELLS



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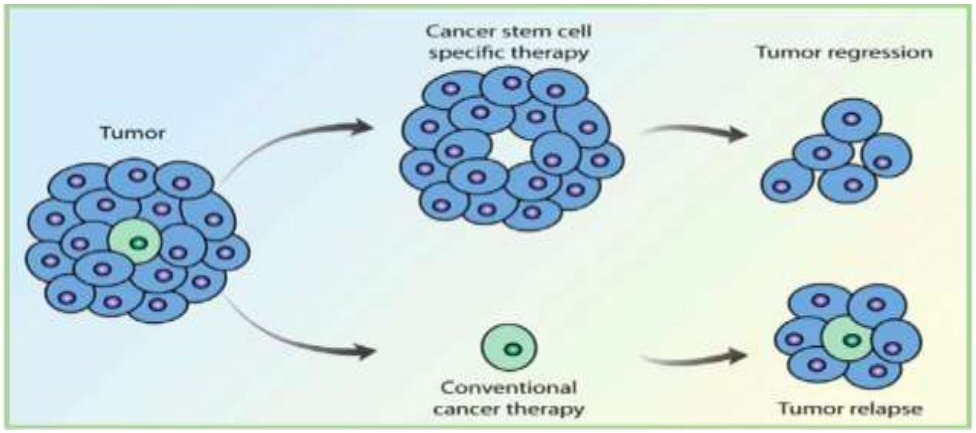

In tumour tissue, there is a clear hierarchy of cancer cells, according to recent studies. According to the cancer stem cell hypothesis, not all tumour cells in cancer are created equal. Cancers can only be started by a tiny population of tumour cells known as "cancer stem cells" (CSCs). This is a subpopulation of "Self-sustaining cells," which are multipotent, capable of self-renewal, and able to form diverse tumour masses. Additionally known as "Tumor starting cells" on occasion. The majority of the tumour is composed of "Transit Amplifying Cells" and "Post Mitotic Differentiated Cells." The former are cells that multiply quickly, whereas the latter are differentiated cells. Both cell types are descended from tumor-initiating cells and are not involved in the development of tumours. The "drivers" of local tumour recurrence and metastatic dissemination, according to current findings, are thought to be tumour initiators or cancer stem cells. Stem cells can be distinguished from the majority of cells in a tumour due to the presence of certain markers on their surface. Examples include the successful use of markers like CD133, CD44, and ALDH (aldehyde dehydrogenase) to identify highly tumorigenic cancer stem cells in HNSCC. Involved in cell adhesion and migration is CD44, a cell surface glycoprotein that serves as a hyaluronic acid receptor. (4)

LIGAND /RECEPTOR BASED TARGETING

Drug delivery via ligand/receptor targeting has proven to be successful. Chemotherapeutic drugs must be introduced into the cytoplasm of tumour cells or to subcellular organelles like the nucleus and mitochondria if they are to be more effective. Such targeting may be accomplished by careful ligand selection, customization, and design. It is important to clearly define the specificity of an antibody that targets an antigen that is overexpressed in cancer cells. In addition, a stable covalent bond must form between the ligand/receptor and the drug if a linker is present, such as in cell penetrating peptide (CPP) drug conjugates. But it's important to understand how drugs are released at the tumour location. Systemic toxicity could occur as a result of premature medication release. To target metastatic cells and prevent migration and invasion, researchers are looking into tumor-targeting ligands such antibodies, aptamers, siRNA, and peptides. The two main types of targeted drug delivery are active and passive. Using a ligand to deliver medication is considered active targeting. These ligands may be surface-attached to a carrier system, such as nanoparticles, liposomes, or nanomicelles, or covalently conjugated to the active ingredient. (1)

GENE THERAPY

When working genes or genetic materials are injected into patients' cells during gene therapy, the damaged genes are either repaired or replaced at the molecular level.The oncogenes p53, bax, and other are mutated in the cancer cells. Gene therapy can therefore be extremely important in the treatment of cancer. Mechanism of gene therapy in cancer treatment includes delivering genetic material to cancer cells is via viral carriers. After being delivered into cells, therapeutic genes work through a variety of ways, including silencing, up- or down-regulation, repair, or alteration of the specific target genes. Suicide genes may result in tumour necrosis or cell death. Cell development and tumour regrowth are inhibited by gene silencing. While gene editing might increase the effectiveness of various combo therapies (e.g. chemotherapy, immunotherapy, or radiation). Gene delivery can be done via Viral and Non-Viral vectors (9)

(i) VIRAL VECTOR

To assure the transport of genetic material, a vector is used as a carrier. The pathogenic portion of viral genes must be removed and replaced with therapeutic genes in order to use a virus as a vector. The therapeutic gene that makes up the viral vector is carried by the remaining non-pathogenic portions of the virus. (1)

(a) **Adenovirus (Ads)** are double-stranded linear viruses that are not enclosed. Ads are a very effective vector for treating glioblastoma multiforme (GBM) because they may cause transduction safely and high transgene expression. Squamous cell carcinoma of the head and neck can be treated with either medication. (1)

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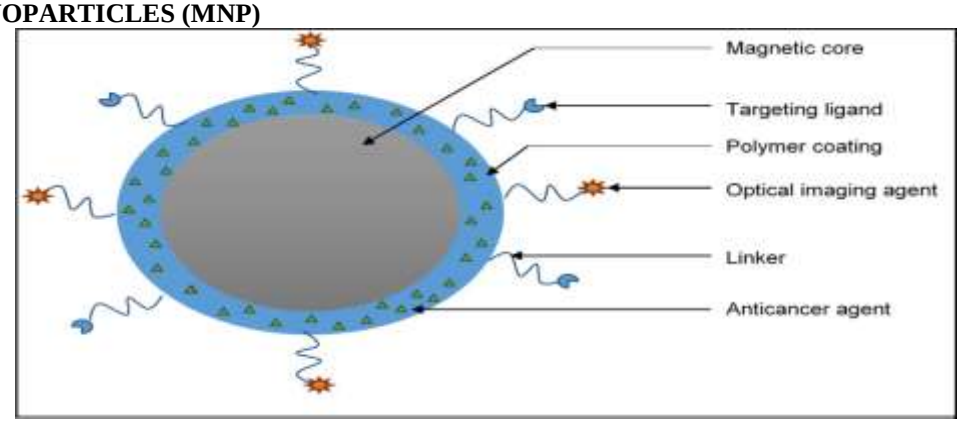
(b) **Adeno-Associated viruses (AAV)** are tiny single-stranded DNA viruses with long-lasting expression, a broad host range, and a minimal immune response since they are not pathogenic. To treat tumours such prostate cancer, glioblastoma, cervical and breast cancer, nasopharyngeal carcinoma, and lung carcinoma, a number of AAV-mediated genes have recently been created. (1)
(c) **Lentiviruses** are superior to conventional viral systems in several ways, including minimal immunogenicity and the capacity to transduce a wide range of cells. Many research teams have used lentivirus-mediated short hairpin RNA to knockdown PPM1D in colorectal cancer and lung.(1)
(d) Herpes viruses are large enveloped DNA viruses that can carry large transgene.

(ii) NON-VIRAL
In comparison to viral approaches, non-viral techniques offer higher levels of transfection efficiency, lower immunogenicity, and superior large-scale production.(7)
(a) **NAKED DNA:** The simplest method of delivering therapeutic genes is directly injecting free DNA into certain tissues, which causes the expression of the genes. DNA can be directly injected into the tumour or the tissues around it during cancer gene therapy to express tumour antigens that may serve as a cancer vaccine. This approach has a lower immunogenicity and is relatively cost-effective. (7)
(b) **ELECTROPORATION** (or electro-permeabilization) is a method that uses an electrical field to increase DNA's ability to enter cells. Numerous benefits of electroporation include precise therapeutic gene transfer, localised gene expression, and fewer side effects. 2004 saw the beginning of the first clinical trial.(7)
(C) **NANOCARRIERS** - These man-made non-bioactive nonviral vectors offer a reliable method of transferring genetic material to cells. Unique benefits of this strategy include low immunogenicity, reduced toxicity, and flexibility for chemical alterations. The fundamental disadvantage of this approach, however, is relatively low transfection efficiency. The preparation of the nano-vectors, such as nanoparticles or nanocapsules, typically uses biodegradable substances. These nanoparticles, which range in size from 10 to 100 nm, combine with genetic materials to produce a nano complex. These nano-vectors fall into two categories: inorganic nano-vectors made of silica, iron oxide, and gold nanoparticles, and polymeric nano-vectors made of dendrimers, lipids, PLGA, and chitosan. The transfection of the targeted genes is both safe and efficient. (7)
(d)**HYDRODYNAMIC** - It works by exerting a physical force that increases intravascular pressure.

MAGNETIC NANOPARTICLES (MNP)



The first magnetic microsphere was used by Widder and colleagues to target anticancer medicines to tumour tissue with the help of an external magnetic field. Magnetic nanoparticles (MNP) are adaptable systems that can be modified in a number of ways for therapeutic and diagnostic purposes. MNP have shown to be excellent magnetic resonance imaging (MRI) contrast agents because of their super paramagnetic properties. These substances are well tolerated and biocompatible. By covering MNPs with polymers, surfactants, inorganic metals, or oxides, this can be readily prevented. Magnetite (Fe_3O_4), maghemite (-Fe_2O_3), iron-based metal oxides ($CoFe_2O_4$, $NiFe_2O_4$, $MnFe_2O_4$), iron alloys (FePt and FeAu), rare earth metal alloys, and transition metals are some of the materials that are frequently utilised to create MNPs. As biomedical agents, cobalt, nickel, and chromium are less favoured due to their high toxicity and need for impervious covering. Materials made of iron oxide and iron alloys are often safer to use.(5)

TRIGGERED RELEASE

A magnetic field, light, ultrasound, or radio-frequency can be the external stimuli. The internal stimulation may be cellular enzymes, pH, temperature, or both. These response-triggered delivery systems allow for not only the precise administration of therapeutic drugs but also the regulation of the timing and volume of medication release into tumour cells. (1)

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(i)THERMO-RESPONSIVE RELEASE

The physical properties of temperature-responsive or thermoresponsive polymers vary with temperature abruptly and discontinuously. These polymers can be functionalized with bind-specific biomolecule-binding groups. A slight temperature change can precipitate the polymer-biomolecules-conjugate out of solution.(1)

(ii)ENZYME RESPONSIVE RELEASE

Enzymes are important tools in the bio-nanotechnology toolbox because they have great bio-recognition abilities and catalytic activities. The resulting enzyme-responsive nanoparticles can be created to function effectively with selectivity for the triggering stimulus by combining certain physical features of nanomaterials. This potent idea has been successfully used in the creation of drug delivery systems that target the tissue of interest by releasing cargo in response to an enzyme's biocatalytic action. The nanomaterial can be configured to distribute pharmaceuticals via enzymatic conversion of the carrier when the enzyme activity linked to a specific tissue is expressed at higher concentrations at the target spot. Magnetic iron oxide nanoparticles (MIONPs) coated with MMP-sensitive PEG-hydrogel were created by Nazli et al.(1)

(iii)pH RESPONSIVE RELEASE

The pH sensitive system has been the most frequently used nano-system in cancer therapy among the many forms of stimuli. It is generally recognised that different tissues and organs, including the stomach and liver, as well as disease states like ischemia, infection, inflammation, and cancer, have drastically variable pH levels. Due to the high rate of glycolysis in cancer cells, tumours' lower pH and aerobic and anaerobic environments can be used to specifically target chemotherapy to these cells. While normal tissue has a pH of 7.4, tumours have been shown to have acidic pH values between 5.7 and 7.8. In order to create pH-responsive medication release, various strategies have been devised. Adding a "ionizable" chemical group, such as amines, phosphoric, or carboxylic acids, among others, to polymeric structures is one of the most widely utilised strategies.

ULTRASOUND

The delivery of anticancer drugs and non-invasive therapy have both been advised for ultrasound as a traditional diagnostic technique. There are three potential ways for how ultrasound can deliver drugs: heat effects, cavitation, and radiation forces. Ultrasound has been used to improve the overall effectiveness of the cytotoxic effects from carriers like microbubbles and nanobubbles as well as to facilitate the intracellular administration of a specific medicine. For the treatment of cancer, ultrasound as a component of a drug delivery system has the potential to be combined with a variety of drug carriers(6)

THERMAL EFFECT

The rate of thermal transport and conversion, ultrasonic intensity and frequency, and energy absorption all play a role in localised tissue heating. Even a slight temperature increase can considerably enhance blood capillary permeability and/or lead to fluidization of cell membranes. The most often researched ultrasound-responsive drug delivery system, temperature-sensitive liposomes, have been used to take advantage of the ultrasound's thermal effect. The administration of different anticancer medications to tumours was enhanced by thermosensitive liposomes when combined with localised hyperthermia under ultrasonography. The phospholipid membrane of liposomes transitions from a gel to a fluid phase, making them more permeable. This method permits non-destructive hyperthermia (39–41 °C) and fast drug release in the target area . (1)

CAVITATION

Under an ultrasonic field in a fluid medium, acoustic cavitation causes small stable gas bubbles to oscillate and collapse. The importance of this non-thermal ultrasonic process is regarded as being the highest. Especially for improving medication delivery, this method has the ability to cause cavitation in biological tissues. Combining gas-filled microbubbles has been shown to significantly improve cavitation. Acoustic cavitation activity can be divided into two categories: non-inertial (or stable) cavitation and inertial (or transient) cavitation. The non-inertial cavitation bubbles may continue for numerous acoustic cycles with stable oscillation. Microbubbles administered systemically cause alternating vascular wall invagination and distention via non-inertial cavitation. In turn, it damages the endothelial lining of the blood artery and briefly increases its permeability. improved distribution to the whole tissue and improved extravasation (10)

CONCLUSION

The leading cause of death in the world today is cancer. Despite being the cornerstone of the fight against cancer, conventional chemotherapy is linked to typical cell damage. Conventional cancer treatments frequently have harmful side effects and toxicities because they lack selectivity. The new cancer treatment is at the centre of such novel approaches. As a result, these innovative technologies present fresh possibilities for cancer prevention and treatment that are less hazardous to normal cells and can be implemented in clinical settings relatively soon. In this study, we explored several cutting-edge strategies for treating cancer cells, including ligand and receptor-based targeting, triggered release techniques and gene delivery. This review paper has covered a wide

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range of contemporary methods for delivering cancer therapeutics, including intracellular drug targeting, cancer stem cell therapy, magnetic drug targeting, and ultrasound-mediated drug therapy. The survival rate has increased significantly, and cancer treatment is continually getting better.

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