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Nanotechnology In Cancer Treatment

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Abstract
Nanotechnology has the potential to increase the selectivity and potency of chemical, physical, and biological approaches for eliciting cancer cell death while minimizing collateral toxicity to nonmalignant cells. Materials on the nanoscale are increasingly being targeted to cancer cells with great specificity through both active and passive targeting. In this review, we summarize recent literature that has broken new ground in the use of nanotechnology for cancer treatment with an emphasis on targeted drug delivery.

Keywords: Cancer, nanotechnology, nanoparticles, tumours

Introduction

The need for an advanced technology to play an important role for cancer treatment is clearly evident in the statistics indicating that cancer incidence, prevalence, and mortality remain at exceedingly high levels[1]. Cancer is one of the leading causes of deaths worldwide with an estimated 7.6 million individuals lost each year and accounting for 13% of all deaths. Cancer-related mortality is expected to rise to 13.1 million by 2030. Cancer is not a single disease but a multitude of diseases with each organ or system developing a distinct set of diseases. Many instances of cancer could be avoided, with some estimates indicating that about 30% of cancer deaths are associated with smoking or other lifestyle factors or dietary practices that could potentially be avoided by changes in human behavior[2–4]. Nonetheless, the majority of cancers cannot be avoided by simple behavioral changes and require technological innovation to improve outcomes.
Nanotechnology may also be able to increase the percentage of cancers that are diagnosed early through improved imaging and this, in conjunction with more aggressive implementation of existing screening technologies, will lead to improved outcomes for cancer patients[5]. Still, for many cancer types, new approaches for treating established disease are required. To address these therapeutic requirements, nano-sized molecular tools capable of distinguishing between malignant and nonmalignant cells as well as delivering a lethal payload should be developed. This review summarizes several of the most innovative technologies that have been reported in recent years and that hold promise for improving outcomes for cancer patients.

Types of tumours

There are two types of tumours

- **Benign:** In benign tumor, neoplastic cells remain clustered together in a single mass and cannot spread to other sites.

- **Malignant:** Neoplastic cells that do not remain localized, encapsulated and become progressively invasive are described as malignant tumors.

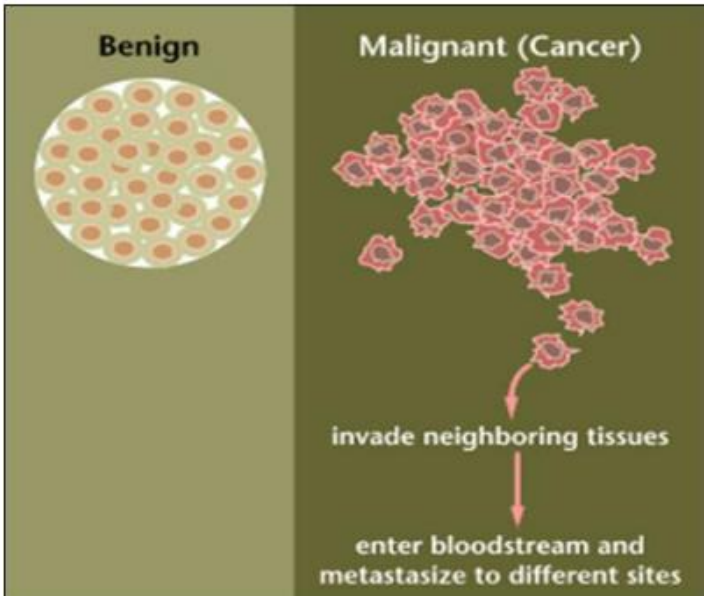

Figure:1 Types of tumours

Conventional therapies for cancer treatment

Surgery: Surgery is an old form of cancer treatment and is a major treatment. In addition to advances in surgical procedures, two thirds of cancer patients have tumors spread across the original site.

Radiation therapy: Radiation therapy is the use of ionizing radiation - X-rays, gamma rays, or subatomic particles such as neutrons - to eliminate cancer cells.

Chemotherapy: Chemotherapy is the administration of chemicals, or drugs, to eliminate diseases in general. The first chemical agent used to fight cancer was mechlorethamine, a mustard compound used in the 1940's to treat Hodgkin's disease and other lymphomas. In the early 21st century, more than a hundred different drugs were used to treat cancer.

Limitations of conventional therapeutics

- Poor water solubility
- Tendency to aggregate
- Lack of selectivity towards cancerous cells
- Systemic toxicity.
- Low therapeutic index (high drug dose).
- Multidrug resistance.
- Susceptible to physiological distribution.
- Low circulation half-life.
- Repetitive administration necessary.

Nanotechnology

The word "Nano" is derived from the Greek word νᾶνος (Nanos) which means little. A nanometer is a billionth meter, that is, about 1 / 80,000 times the width of a human hair, or ten times the width of a hydrogen atom. When Nobel Prize-winning scientist Richard Feynman challenged the scientific

community to think less of his 1959 dissertation, 'There's a lot of room downstairs', he planted the seeds of a new era in science and technologymodern nanotechnology. Nanotechnology is defined as the study and application of structures between 1 nanometer and 100 nanometers in size.

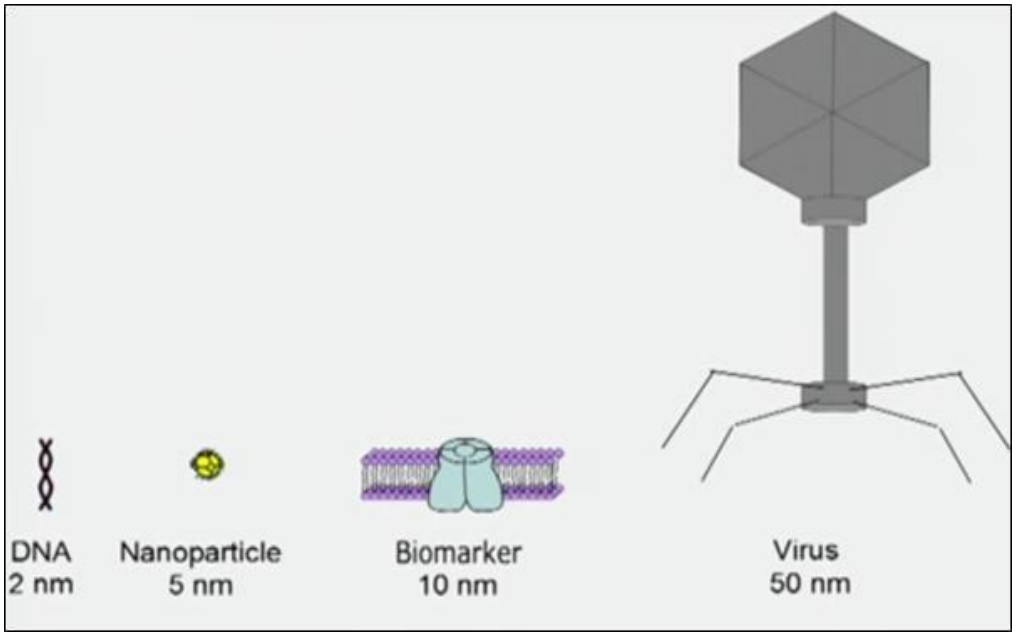

Figure:2 Nanotechnology

Nanotechnology has made a great revolution in selective cancer targeting. Nanoparticles can be designed through various modifications such as changing their size, shape, chemical and physical properties, and so forth, to program them for targeting the desired cells. They can target the neoplastic cells either through active or passive targeting.

Nanoparticles

Nanoparticles (NPs) are technically defined as particles with one dimension less than 100 nm with unique properties usually not found in bulk samples of the same material [18]. Depending on the nanoparticle's overall shape, these can be classified as 0D, 1D, 2D or 3D [19]. The basic composition of nanoparticles is quite complex, comprising the surface layer, the shell layer, and the core, which is fundamentally the central portion of the NP and is usually termed as the NP itself [20]. Owing to their exceptional features like high surface: volume ratio, dissimilarity, sub-micron size, and enhanced targeting system, these materials have gained a lot of importance in multidisciplinary fields. NPs are found to have deep tissue penetration to increase enhanced permeability and retention (EPR) effect. Besides, the surface characteristics impact bioavailability and half-life by effectively crossing epithelial fenestration [21]. For example, NPs coated with polyethylene glycol (PEG), a hydrophilic polymer, decrease opsonization and circumvent immune system clearance [22]. Additionally, it is possible to optimize the release rate of drugs or active moiety by manipulating particle polymer characteristics. Altogether, the distinct properties of NPs regulate their therapeutic effect in cancer management and treatment.

Classification of nanoparticles

Nanoparticles are classified based on their dimensions.

i. In one-dimension One-sided systems, such as small films or structures made or anointed are one idea. Their applications include corrosion resistance, wear, and scratch resistance, hydrophobic and self-cleaning, non-abrasive, antibacterial and anti-microbial, effective and chemically active and synthetic.
ii. In two-dimension Nanotubes, nanowires, Nano fibers and Nano polymers are two dimensional nanoparticles.

a) Carbon Nanotubes Carbon nanotubes are a new form of carbon molecules. Damaged to a six-sided network of carbon atoms, these empty cylinders can have a diameter of about 0.7 nm and reach several millimeters in length Each limit can be opened or closed by a fully charged half-molecule. These nanotubes may have a single layer (like grass) or several layers (such as a poster wrapped in a tube) of coaxial cylinders of growing pores in a standard axis.

iii. In three Dimension Fullerenes, dendimers and quantum dots are three dimensional nanoparticles.

ADME Of Nanoparticles

Several barriers prevent extraneous substances, such as bacteria, viruses from entering the body. These same barriers, which include the pulmonary system, the gastrointestinal tract, and the skin, regulate nanoparticle access. Previously, only tiny lipophilic compounds (600 Da) and metallic ions (such as cobalt and nickel) could pass through the skin barrier. However, due to their tiny size, nanoparticles may be easily absorbed through the dermis of the skin, as well as the pulmonary and gastrointestinal mucosa, positioning these substances for distribution through the vascular circulation to all tissues in the body. The vascular endothelium, with an average pore size of 5 nm in mammals, provides another possible barrier to nanoparticle absorption and distribution, although nanoparticles smaller than this limit pass readily from the blood over the endothelium and into tissue. Furthermore, because the discontinuous endothelium of these organs includes holes of 50-100 nm in diameter, nanoparticles may be able to translocate efficiently from the blood into the liver, spleen, and bone marrow. As a result, techniques for determining the quantity of total external exposure, absorption effectiveness, and tissue biodistribution of nanoparticles are required. However, the excretion of nanoparticles is majorly done by two ways; from renal filteration through urine and hepatobiliary processing. Choi et al. demonstrated that quantum dots are excreted through renal filteration as urine. Another study demonstrated that gold nanoparticles were excreted though hepatobiliary processing.[6,7]

Mechanisms of Cellular Targeting

For effective cancer therapy, it is essential to develop or engineer a drug or gene delivery system that has an excellent ability to target tumor cells sparing the normal healthy cells. It enhances therapeutic efficacy, thereby shielding normal cells from the effect of cytotoxicity. It can be achieved by the well-organized delivery of NPs into the tumor microenvironment (TME), indirectly targeting cancer cells. These nano formulations should pass through numerous physiological and biological barriers. These barriers are complex systems of several layers (epithelium, endothelium, and cellular membranes) and components (mechanical and physicochemical barriers and enzymatic barriers). These facts impose specifications with respect to the size, biocompatibility, and surface chemistry of NPs to prevent unspecific targeting. However, mere cytosolic internalization of an NP drug molecule does not mean it reaches its subcellular target. Specific engineering and optimization are mandatory to enable cellular or nuclear targeting. Several studies have been carried out so far and several more are in progress to discover NP-based drug targeting design. These nanocarriers typically should possess certain fundamental characteristics such as 1) ability

to remain stable in the vascular system (blood) until they reach their target, TME, 2) to escape the reticuloendothelial system (RES) clearance, 3) escape mononuclear phagocyte system (MPS), 4) accumulate in TME via tumor vasculature, 5) high-pressure penetration into the tumor fluid, and 6) reach the target and only interact with tumor cells[8]. The vital aspects such as surface functionalization, physicochemical properties, and pathophysiological characteristics regulate the process of NP drug targeting. Generally, NPs considered apt for cancer treatment have a diameter range of 10–100 nm. In order to understand the process of interaction and crosstalk between NP carriers and cancer cells and tumor biology, it is important to address the targeting mechanisms. The targeting mechanisms can be broadly classified into two groups, passive targeting and active targeting.

Passive Targeting of Nanoparticles

The passive tumor targeting highly depends upon certain factors like tumor microenvironment, punctured tumor vasculature, and the direct local application[9]. It is important to note that the presence of tight junctions between the nonmalignant tissues, results in resistance to the passage of nanoparticles. Specifically in cancer, the neovasculature is leaky and disorganized[10]. This whole scenario allows the extravasation of nanocarriers in the endothelium of the tumor vessels due to the presence of fenestrations. The passive drug targeting also depends upon the accumulation of drug at the targeted site and the half-life of the drug carrier. The therapeutic potential of nanoparticles depends upon the surface charge, solubility, biodegradability, and morphology[11]. A hydrophilic biomaterial's (Polyethylene glycol) covering or coating is used to defend nano-formulation against the attack of macrophages and to enhance the circulation time of nano-formulations. In the passive targeting, the nanoparticles conglomerate in the affected tissues because of their retention and permeability effect. The trafficking of nanoparticles over the neoplastic tissues highly depends upon the surface charge, tumor microvasculature, size, and shape.

Examples of Passive Targeting Taxanes are one of the most successful drug groups that are used in cancer treatment. Paclitaxel has shown great potency against a broad range of cancers. Breast cancer, lung cancer (small cell and non-small cell), and ovarian cancer are the most treated histologies with taxanes. US-FDA, in 2005, approved Abraxane® (albumin-bound paclitaxel, Abraxis Bio-Sciences), which is used for advanced or metastatic breast cancer (MBC).

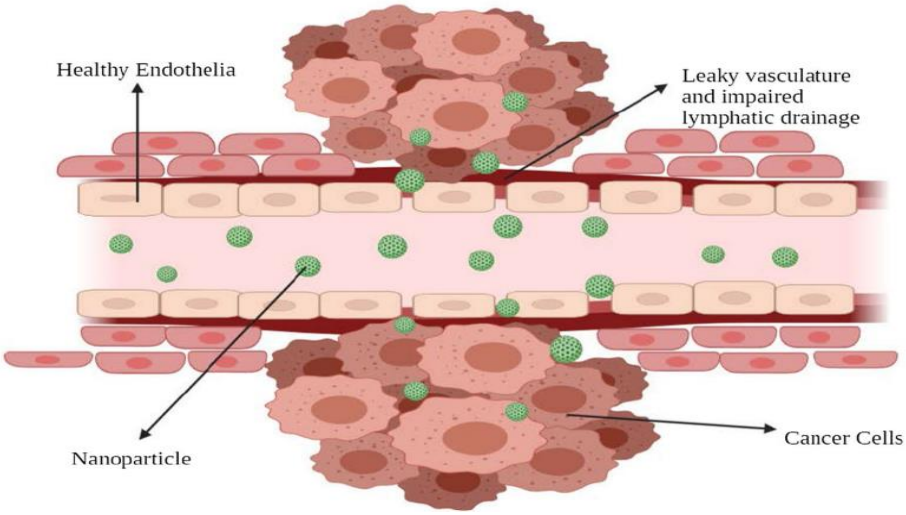

Figure:3 Passive cellular targeting

Active Targeting of Nanoparticles

The active targeting mode of nanoparticles depends upon the utilization of certain ligands like folate and transferrin, which bind to the proteins that are over-expressed or somewhat expressed on the target cellular sites[12]. This instigates the inbound folding of membranes and incorporates the nanoparticles into the cells through a phenomenon named receptor-mediated endocytosis. Under the non-alkaline conditions of the endosome, the encapsulated drug is released from the nanoparticles and sets foot in the cytoplasm after that it acts on the cellular target[13]. The strategies of tumor-targeting are classified into three classes. i) Angiogenesis-associated targeting through the growth factor receptors of vascular endothelial, matrix metalloproteinase receptors, vascular cell adhesion molecule-1 andαvβ3 integrins. ii) Tumor cell targeting for targeting colorectal cancer, for targeting lungs cancer, for targeting breast cancer, for targeting prostate cancer, etc., and iii) the targeting of uncontrolled cellular proliferation through human folate receptors, endothelial receptors, and transferring receptors[14]. Scientists have reported the active targeting of tumor cells by using the multi-functional dendritic nanodevice attached with folic acid which contained Methotrexate as a chemotherapeutic agent. In addition, the Rapamycin-loaded epithelial growth factor antibody-conjugated nanoparticles reported increased efficacy in MCF 7 breast cancer cells.

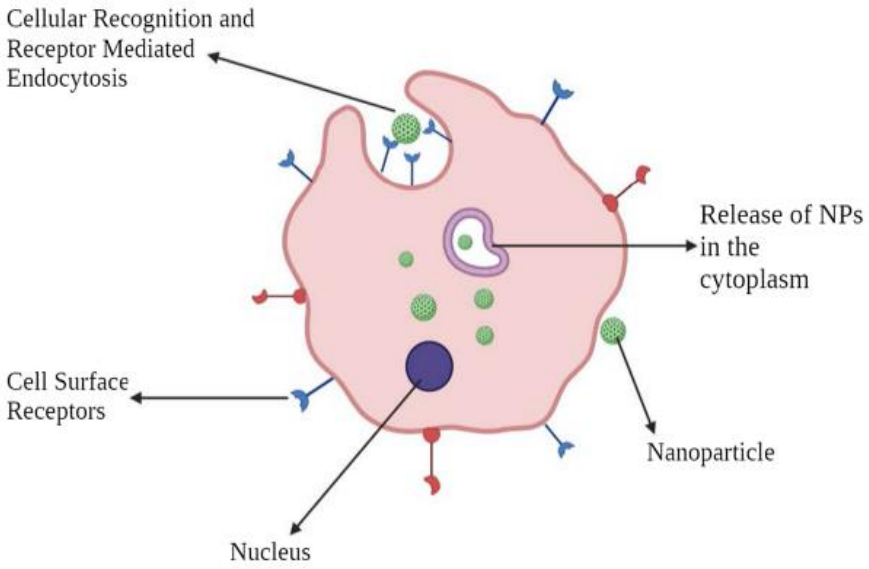

Figure4: Pictorial representation of active cellular targeting

Examples of Active Targeting

EGFR, a member of the ErbB family of tyrosine kinase (TK) receptors, is overexpressed in various types of cancer, especially with squamous cell histology. Gold NPs with anti-EGFR-PEG-AuNPs and anti-IgG-PEG-Au nanoparticles can be used to target the human SCC [48]. Herceptin® is a therapeutic drug that targets human EGF receptor-2 (HER2) that is overexpressed on breast cancer cell surfaces. HER2-targeted PEGylated liposomal doxorubicin was developed to reduce cardiotoxicity, a known side effect of anthracyclines [49]. The surface of the tumor endothelium expresses a glycoprotein known as vascular cell adhesion molecule-1 (VCAM-1) that is involved in the process of angiogenesis. A study has highlighted NPs that target VCAM-1 in the breast cancer model, indicating its potential role [50]. Folic acid, also known as vitamin B9, is vital in nucleotide synthesis. Folic acid is internalized by the folate receptor that is expressed on the cells. However, tumor cells overexpress FR-α (alpha isoform of folate receptor), while FR-β is overexpressed in liquid cancer cells [51].

Nanoparticles in Cancer Therapy

NPs used extensively in drug delivery systems include organic NPs, inorganic NPs, and hybrid NPs.

Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) are well-defined as "colloidal macromolecules" with specific structural architecture formed by different monomers[20]. The drug is either entrapped or attached to NPs'exterior, creating a nanosphere or a nanocapsule to achieve regulated drug release in the target [21]. Initially, PNPs were made up of non-biodegradable polymers such as polyacrylamide, polymethylmethacrylate (PMMA), and polystyrene. However, the accumulation of these led to toxicity due to difficulty in eliminating these from the system. Biodegradable polymers such as polylactic acid, poly(amino acids), chitosan, alginate, and albumin are now being used and are known to reduce toxicity and enhance drug release and biocompatibility. Proven research has reflected that by coating PNPs with polysorbates and by using polysorbates surfactant effect. Exterior coating enhances NPs' interactions with the endothelial cell membrane of the blood–brain barrier (BBB) [22].

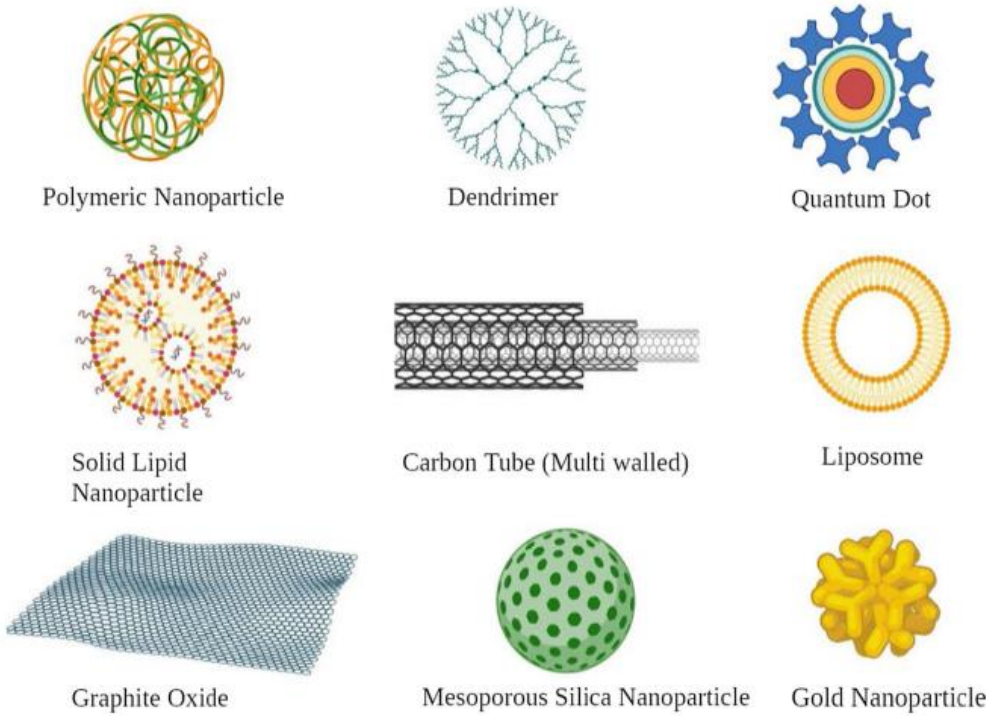

Figure: 5 Various types of nanomaterials used in cancer therapy

Dendrimers

Dendrimers are spherical polymeric macromolecules with defined hyperbranched architecture. Highly branched structures are the characteristic feature of dendrimers. Typically, the synthesis of dendrimers is initiated by reacting an ammonia core with acrylic acid. Tis reaction results in forming a "tri-acid" molecule that further reacts with ethylenediamine to yield "triamine," a GO product. This product further reacts with acrylic acid to give rise to hexa-acid, which further produces "hexa-amine" (Generation 1) product and so on [23]. Typically, the size of the dendrimers ranges from 1–10 nm. However, the size may reach up to 15 nm [24]. Given their specific structure like defined molecular weight, adjustable branches,

bioavailability, and charge, these are used to target nucleic acids. Some dendrimers that are widely used are polyamidoamine (PAMAM), PEG (poly(ethylene glycol)), PPI (polypropylenimine), and TEA (triethanolamine). A PAMAM dendrimer was initially designed to achieve MDR management. DNA assembled PAMAM dendrimers have been described extensively. As compared with animals treated with single-agent chemotherapy, the synthesized dendrimers significantly delayed the growth of epithelial cancer xenografts[25].

Quantum Dots

Quantum dots are semi-conduction nanoparticles. They elicit some unique characteristics like broad absorption spectrum, higher photostability, broad ultraviolet excitations, narrow emission bands, and brighter fluorescence[26]. The narrow emission bands and wider absorption spectrum grant only one wavelength of light to instigate a cluster of quantum dots of many sizes which reciprocally discharge multiplex imaging at different wavelengths. To cope-up with limitations regarding imaging in the visible spectral region, quantum dots that fluoresce in the near-infrared spectral region (700-1000 nm) have been reported. The near-infrared region quantum dots have been experimented with for lymphatic mapping in various animal studies. In 2004, Gao at el. reported that the quantum dots can be effective against cancer targeting in animal models. Another group of scientists Bagalkot et al. investigated quantum dots aptamer – doxorubicin couple for targeting the prostate cancer cells. The prepared nanoparticle couple demonstrated the sensitivity and specificity for cancer therapy and imaging. In the near past, Liu et al. reported a biological activity of conjugated molecules of alyl isothiocyanate and silicon quantum dots, the scientists find out that this conjugation showed identical anticancer properties like alyl isothiocyanate at higher doses by avoiding the lower dose stimulation effect of ayly isothiocyanate on DNA damage and cell migration. Alyl-isothiocyanate coupled silicon quantum dots outlined biphasic anticancer properties in human hepatoma HepG2 cells [27].

Solid Lipid Nanoparticles

These are the colloidal nanocarriers which are composed of phospholipid monolayer coating a solid hydrophobic core and encasing a drug in a high melting point like waxes or glycerides [90]. Anticancer drug mitoxantrone encased in SLN has reported improved bioavailability, drug safety, reduced toxicity. Increased efficacy of doxorubicin and idarubicin being incorporated in SLN's demonstrated better results to treat leukemia cells and murine leukemia in mice models[28,29].

Liposomes

Liposomes are made up of natural phospholipids. Thus, they are biologically inert, elicit low intrinsic toxicity and weak immunogenicity. They are spherical-shaped nanoparticles consisting of the lipid bilayer to encase therapeutic drugs[30]. The presence of lipid bilayer made them prodigious candidates to deliver hydrophilic and hydrophobic drugs. Myocet®, Doxil®, DuanoXomer® are globally approved liposome-based nanoparticles which contain Duanorobucin as an anticancer drug for metastatic breast cancer treatment. MCC-465 (PEG-immunoliposome-doxorubicin) is going through clinical trials for the treatment of stomach cancer, similarly, SPI-077 (Liposomal cisplatin) is also undergoing clinical trials for the treatment of various cancers, OSI-211 (liposomal lurtotecan), Aroplati, (liposomal oxaliplatin), OSI-7904L (liposomal thymidylate synthase inhibitor), LEP ETU (liposomal paclitaxel), LE-SN38 (liposomal SN38 or liposomal irinotecan metabolite) are the products for liposomal-based nanoparticles which are

going through clinical trials phase 2 for the treatment of various cancers. A group of scientists has reported the production of the first C60 based slow-release liposomal aerosol to deliver paclitaxel for treating lungs cancer and this product marked a big achievement with promising outcomes [31].

Gold Nanoparticles

Gold nanoparticles are the intracellular drug delivery agents and possess unique properties, like; their size can be controlled very easily, their surface properties can be modified accordingly, their visible light extinction behavior makes them feasible to encounter nanoparticle trajectories in the cells. To target HER2 positive breast carcinoma, AntiHER2 functionalized gold-on-silica nano-shells have been prepared, to wipe out the problem of the presence of salt in gold Sodium bromohydride is used[32]. However, sodium bromohydride is unsuitable for target-specific peptides because it lessens the chemical composition of peptides[33]. Hydrazine, dimethyl formamide, sodium bromohydride are the limitations in the therapeutic use of gold nanoparticles [34].

Conclusion And Future Perspectives

Nanotechnology applied to cancer therapy has led to a new era of cancer treatment. Various types of NPs, including organic and inorganic NPs, have already been widely used in the clinical treatment of several cancer types. Compared to traditional drugs, NP-based drug delivery systems are associated with improved pharmacokinetics, biocompatibility, tumor targeting, and stability, while simultaneously playing a significant role in reducing systemic toxicity and overcoming drug resistance. These advantages enable NP-based drugs to be widely applied to chemotherapy, targeted therapy, radiotherapy, hyperthermia, and gene therapy. Moreover, nanocarrier delivery systems provide improved platforms for combination therapy, which helps overcome mechanisms of drug resistance, including efflux transporter overexpression, defective apoptotic pathway, and hypoxia tumor microenvironment. According to different mechanisms of MDR, NPs that are loaded with varieties of targeting agents combined with cytotoxic agents can achieve the reversal of drug resistance. With increasing research, various types of hybrid NPs have shown improved properties for delivery and aroused more attention. Further studies on the biological characteristics of individual cancers will lead to more precise research directions for these drugs. Furthermore, designing hybrid NPs that are more suitable for cancer therapy and engineering NPs that target cancer cells more specifically using targeting moieties merits further exploration. Notably, the interactions between NPs and the immune system are complex (Najafi-Hajivar et al., 2016). The NP size, shape, composition, and surface are all the factors that affect the interactions of NPs with the immune system. Although nano vaccines and artificial APCs have demonstrated increased efficacy compared to traditional immunotherapy, the clinical efficacy of this treatment remains unsatisfactory, and the safety and tolerance of these new approaches need to be further investigated. Moreover, developing immunomodulatory factor-loaded NPs may improve the effectiveness of vaccines for immunotherapy. Accordingly, a better understanding of the TME and a further investigation of the crosstalk between NP-based drug delivery systems and tumor immunity are warranted for drug design and exploitation.

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