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REVIEW ON NANOPARTICLES AS DRUG DELIVERY SYSTEM CONTAINING ANTICANCER DRUGS

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ABSTRACT: -

Now a day in medical science and research, cancer is one of the most life-threatening diseases but unfortunately still now we have no medical treatment for procurement of this disease. The pathology is not totally clear but according to medical evidence if we consider genes then we must agree that oncogene and tumor suppressor genes are mainly responsible. There are some risk factors also consider which may leads to cancer. The conventional treatments are surgery, Radiotherapy, and chemotherapy but the real fact is none of the above-mentioned treatment is enough for procurement of cancer and that's why now scientist and researchers are thinking about nanoparticles. NCI has identified that nanoparticles have the potential to make paradigm changing impacts on the detection, treatment, and prevention of cancer. There are different strategies for cancer therapy using nanoparticles like targeted and non-targeted nano-articles.

Key words: Nano particles, Radiotherapy, Chemotherapy, Targeted.

INTRODUCTION

Cancer is the third leading cause of death (after heart disease and stroke) in developed countries and the second leading cause of death (after heart disease) in the United States. Studies have shown that there were 10 million new cases, 6 million deaths, and 22 million people living with cancer worldwide in the year 2000. These numbers represent an increase of about 22% in incidence and mortality from that of the year 1990. It is projected that the number of new cases of all cancers worldwide will be 12.3 and 15.4 million in the year 2010 and 2020, respectively. In 2008, a total of 1,437,180 new cancer cases and 565,650 cancer deaths were estimated to occur only in the United States [1]. Nanoparticles, an interdisciplinary research field involving chemistry, engineering, biology, and medicine, has great potential for early detection, accurate diagnosis, and personalized treatment of cancer. Nanoparticles are typically smaller than several hundred nanometers in size (generally <1000 nm), comparable to large biological molecules such as enzymes, receptors, and antibodies. With the size of about one hundred to ten thousand times smaller than human cells, these nanoparticles can offer unprecedented interactions with biomolecules both on the surface of and inside the cells, which may revolutionize cancer diagnosis and treatment. The most well-studied nanoparticles include quantum dot, carbon nanotubes, paramagnetic nanoparticles, liposomes, gold nanoparticles, and many others [2].

Pathophysiology:

Cancer is fundamentally a disease of failure of regulation of tissue growth. In order for a normal cell to transform into a cancer cell, the genes which regulate cell growth and differentiation must be altered. The affected genes are divided into two broad categories. Oncogenes are genes which promote cell growth and reproduction. Tumor suppressor genes are genes which inhibit cell division and survival. Malignant transformation can occur through the formation of novel oncogenes, the inappropriate over-expression of oncogenes, or by the under-expression or disabling of tumor suppressor genes. Typically changes in many genes are required to transform a normal cell into a cancer cell. Small-scale

mutations include point mutations, deletions, and insertions which may occur in the promoter region of a gene and affect its expression or may occur in the gene's coding sequence and alter the function or stability of its protein product. Disruption of a single gene may also result from integration of genomic material from a DNA virus or retrovirus and resulting in the expression of viral oncogenes in the affected cell and its descendants. Replications of the enormous amount of data contained within the DNA of living cells will probabilistically resulting in some errors (mutations). Complex error correction and prevention is built into the process and safeguards the cell against cancer. If significant error occurs, the damaged cell can "self-destruct" through programmed cell death, termed apoptosis. If the error control processes fail, then the mutations will survive and be passed along to daughter cell [3].

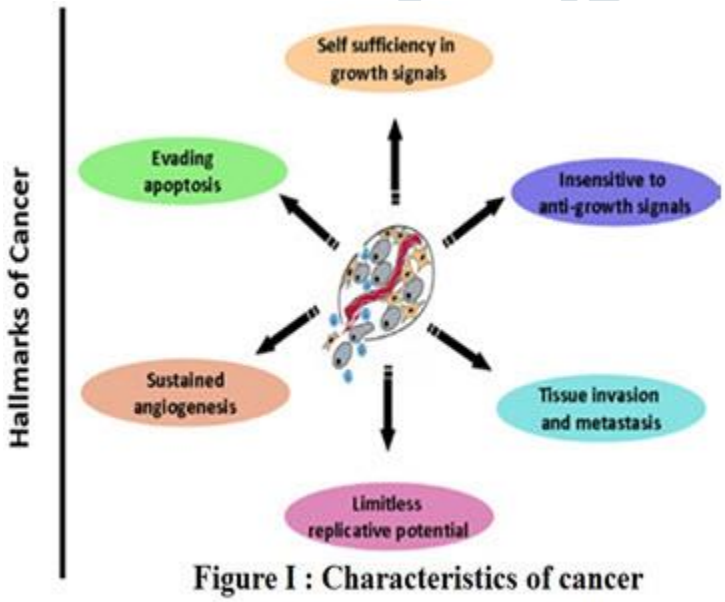

Figure I : Characteristics of cancer

CHARACTERISTICS OF CANCER: -

Six characteristics alterations in cell physiology are associated with malignant growth includes self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of programmed cell death (Apoptosis), (Figure: I) limitless replication potential, sustained angiogenesis, and tissue invasion and metastasis. Each of these physiological changes acquired during tumor

development leads to the successful violation of an anti-cancer defense mechanism by the cell and tissues. Six acquired capabilities of cancer. Most of the cancers have acquired these functional capabilities during tumor development [4].

Prevention:

Cancer prevention is defined as active measures to decrease the risk of cancer. Thus, cancer is considered a largely preventable disease. Risk factors including tobacco, overweight / obesity, an insufficient diet, physical inactivity, alcohol, sexually transmitted infections, and air pollution [5].

CONVENTIONAL TREATMENT METHODS

1. Surgery:

Surgery, often the first line of treatment for cancer, is used to remove solid tumors (benign tumor as well as in early stage of cancer). But Surgery has no great effect if the tumor is already spread to other organs.

2. Radiation therapy:

High energy radiation kills cancer cells by either directly damaging DNA or by generating reactive oxygen species (ROS) preventing cellular division. It is of two forms: a) Brachytherapy- where the radioactive source (in pellets) is placed close to the tumor, eg: uterine cancer and b) Teletherapy- where the patient is irradiated from a source place some distance away from the body. eg, skeletal tumors.

3. Chemotherapy:

Chemotherapy is the most widely used therapy method where chemotherapeutic agents (chemicals) are injected or orally delivered to kill rapidly growing malignant cells (Normal cells also killed). Most of these chemicals interfere with normal DNA replication primarily blocking the cells to complete the S phase of cell cycle. In addition, there are chemotherapeutic agents cause extensive DNA damage as well as spindle fiber inhibitors [5].

MECHANISMS OF TARGETING: -

Targeting of cancer cells specifically is a vital characteristic of nano-carriers for drug delivery, as it enhances the therapeutic efficacy while protecting normal cells from cytotoxicity. Numerous studies have been carried out to explore the targeting design of NP-based drugs. In order to better address the challenges of tumor targeting and the nano-carrier system design, it is crucial to first understand tumor biology and the interaction between nano-carriers and tumor cells. The targeting mechanisms can be broadly divided into two categories, passive targeting and active targeting (Figure 2).

FIGURE 2

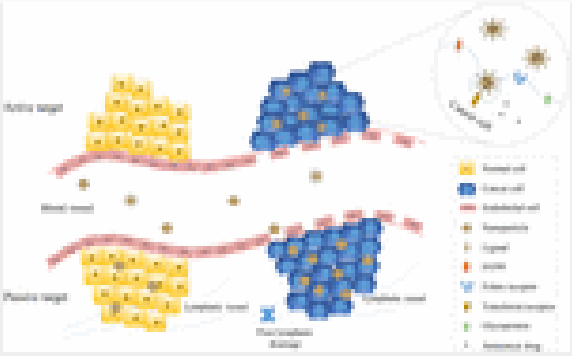

Figure 2.

Passive and active targeting of Nanoparticles to cancer cells. Targeting of Nanoparticles enhance therapeutic efficiency and reduce systemic toxicity. Passive targeting of Nanoparticles is mainly achieved by the enhanced permeability and retention (EPR) effect, which exploits the increased vascular permeability and weakened lymphatic drainage of cancer cells and enables

Nanoparticles to target cancer cells passively. Active targeting is achieved by the interaction between ligands and receptors. The receptors on cancer cells include transferrin receptors, folate receptors, glycoprotein (such as lectin), and epidermal growth factor receptor (EGFR).

PASSIVE TARGETING: -

Passive targeting is designed to utilize the different characteristics of tumor and normal tissue. In passive targeting, the drugs are successfully delivered to the target site in order to play a therapeutic role. High proliferation of cancer cells induces neovascularization, and large pores in the vascular wall lead to a worsening perm selectivity of tumor vessels compared to normal vessels (Carmeliet and Jain, 2000). The rapid and defective angiogenesis enables macromolecules, including Nanoparticles, to leak from blood vessels that supply the tumor and accumulate within tumor tissue. Meanwhile, the poor lymphatic drainage associated with cancer increases the retention of Nanoparticles, allowing the nano-carriers to release their contents to tumor cells. These processes cause the EPR effect, one of the driving forces of passive targeting (Maeda, 2001). The EPR effect is influenced by the size of Nanoparticles, as many studies have demonstrated that smaller Nanoparticles have better penetrability but do not leak into normal vessels (Torchilin, 2005; Carita et al., 2018). On the other hand, larger particles are more likely to be cleared by the immune system (Sykes et al., 2014). In addition to the EPR effect, the tumor microenvironment is also an important factor in the passive delivery of nanomedicines. Glycolysis is one of the metabolic characteristics of cancer cells and is the main source of energy for cancer cell proliferation (Pelicano et al., 2006). Glycolysis yields an acidic environment and reduces the pH of the tumor microenvironment. Subsequently, some pH-sensitive Nanoparticles are triggered by the low pH level and are able to release drugs within the vicinity of cancer cells (Lim et al., 2018).

However, there are some limitations with regards to passive targeting, including non-specific drug distribution, non-universal existence of the EPR effect and different permeability of blood vessels across various tumors (Jain, 1994).

ACTIVE TARGETING: -

Active targeting specifically targets cancer cells through direct interactions between ligands and receptors. The ligands on the surface of Nanoparticles are selected to target the molecules that are overexpressed on the surface of cancer cells, which allows them to distinguish targeted cells from healthy cells (Shi et al., 2011; Kamaly et al., 2012). The interaction between ligands on Nanoparticles and the receptors on the surface of cancer cells induces receptor-mediated endocytosis, which allows internalized Nanoparticles to successfully release therapeutic drugs (Farokhzad and Langer, 2009). Therefore, active targeting is particularly suitable for macromolecular drug delivery, such as proteins and siRNAs. The types of targeting moieties include monoclonal antibodies, peptides, amino acids, vitamins, and carbohydrates (Danhier et al., 2010). These ligands specifically bind to receptors on targeted cells, and the widely investigated receptors include transferrin receptor, folate receptor, glycoproteins, and the epidermal growth factor receptor (EGFR).

TARGETING TO CANCER CELLS: -

Transferrin, a type of serum glycoprotein, functions to transport iron into cells. Transferrin receptors are overexpressed in most solid tumor cells and are expressed at low levels in normal cells. Thus, transferrin-conjugated Nanoparticles are used as an active targeting method to deliver drugs for cancer treatment (Amreddy et al., 2015; Liu et al., 2015; Santi et al., 2017). Compared to unmodified Nanoparticles, transferrin-modified Nanoparticles have been shown to exhibit higher cellular uptake efficiency and enhanced intracellular delivery of drugs (Cui et al., 2017). Moreover, evidence indicates that transferrin-conjugated polymeric Nanoparticles play a significant role in overcoming drug-resistant chemotherapy (Soe et al., 2019).

Folic acid, a type of vitamin, is essential in nucleotide synthesis. It is internalized by a folate receptor that is expressed on few normal cell types. However, the alpha isoform of folate receptor (FR-α) is overexpressed in approximately 40% of human cancers, while FR-β is expressed on the surface of hematopoietic cancers

(Low and Kularatne, 2009). Thus, the folate receptor-targeting strategy by folate-conjugated nanomaterials has been widely used for cancer treatments (Muralidharan et al., 2016; Samadian et al., 2016).

In addition, cancer cells usually express various types of glycoproteins, including lectins, which are non-immunological proteins that recognize and specifically bind to certain carbohydrates (Minko, 2004). Targeting cancer cell-surface carbohydrates by lectins conjugated to Nanoparticles constitutes the direct lectin targeting pathway, while inversely targeting lectins on cancer cells using carbohydrates moieties that are incorporated into Nanoparticles is referred to as the reverse lectin targeting pathway (Minko, 2004; Obaid et al., 2015).

Epidermal growth factor receptor is a member of the ErbB family of tyrosine kinase receptors. EGFR, which is overexpressed in varieties of cancers, is involved in several processes of tumor growth and progression and has already been utilized as a target for cancer treatment (Nicholson et al., 2001; Sigismund et al., 2018). For example, targeting human epidermal receptor-2 (HER-2) is a common therapy for HER-2 positive breast and gastric cancer. Hence, Nanoparticles that have been designed to incorporate modified ligands that bind to EGFR in order to target EGFR-overexpressed cancer cells is a promising method of drug delivery (Alexis et al., 2008). Furthermore, conjugating two cancer-specific ligands into a single NP is another way of active targeting, as it can help improve target specificity (Balasubramanian et al., 2014).

TARGETING TO ENDOTHELIUM: -

Some Nanoparticles do not directly target cancer cells but instead have an effect on angiogenesis, which is another method of cancer treatment. The interaction between vascular endothelial growth factor (VEGF) and VEGF receptors (VEGFRs) plays an essential role in vascularization (Apte et al., 2019). Additionally, targeting VEGFR-2 and VEGFR-3, two major VEGF receptors, simultaneously by liposomes has been shown to enhance therapeutic efficacy (Orleth et al., 2016).

Integrins are cell surface receptors for extracellular matrix proteins that play an important role in tumor cell migration and invasion (Desgrosellier and Cheresh, 2010). The αvβ3 integrin is highly expressed in tumor neovascular endothelial

cells, rather than the resting endothelial and normal cells, and is important in the calcium-dependent pathway that induces endothelial cell migration (Nisato et al., 2003). Hood et al. have reported the favorable treatment efficacy of cationic Nanoparticles coupled with an αvβ3 integrin-targeting ligand for gene delivery into tumor-bearing mice (Hood et al., 2002). In addition, αvβ3 integrin is associated with VEGFR-2 signaling (Ruoslahti, 2002), and blocking αvβ3 integrin-binding can lead to a reduction in VEGF signaling, indicating that targeting αvβ3 integrin can enhance the effectiveness of anti-VEGFR treatment.

Vascular cell adhesion molecule-1 (VCAM-1) is an immunoglobulin-like glycoprotein that is also expressed on the surface of the tumor endothelium and is involved in angiogenesis by interacting with vascular endothelial cells. Overexpression of VCAM-1 can be observed in various cancers (Dienst et al., 2005), indicating its potential role in the active targeting of Nanoparticles for drug delivery. A study by Pan et al. (2013) have reported the high efficiency of VCAM-1 targeted Nanoparticles in a breast cancer model.

Moreover, matrix metalloproteinase (MMP), a component of the tumor microenvironment, is engaged in extracellular matrix remodeling and tumor neovascularization (Lia et al., 2009). MMP-sensitive Nanoparticles have been reported to play a potential antitumor effect in several types of cancers, including breast cancer, pancreatic cancer, and melanoma (Mansour et al., 2003; Xiao et al., 2018; Cun et al., 2019).

Figure II : Advancement of Nano Technology

NANOPARTICLES:

Nanoparticles is a multidisciplinary field that uses principles from chemistry, biology, physics, and engineering to design and fabricate Nano scale devices. In its strictest definition, nanoparticles refer to structures with a size range of 1–100 nm in at least one dimension that are developed using top-down or bottom-up engineering. The resulting nano-material demonstrate unique capabilities based on intrinsic properties such as shape and size as well as functional properties conferred through surface modifications as shown in (figure: II) Cancer Institute (NCI) has identified nanoparticles (Figure: III) as having the potential to make paradigm-changing impacts on the detection, treatment, and prevention of cancer.

Strategies for Cancer Therapy Using Nanoparticles:

Treatment of cancer therapy acts on three strategies. They are 1. Metastatic Cancer: Spread of cancer cells from the primary tumor site to distant organs, establishing secondary tumor sites is known as metastatic Cancer. Detachment of cancer cells from the primary tumor site and circulation in the blood allows the cells to arrest in organs such as the lungs, liver, lymph nodes, skin, kidneys, brain, colon, and bones, where they can proliferate. Despite significant increases in the understanding of metastatic cancer pathogenesis, early diagnosis, surgical methods, and irradiation treatment, most cancer deaths are due to metastases that are not curable. Reasons for this include resistance to treatments, difficulty accessing the tumor sites and removing all cancer cells during surgery.

Figure III : Strategies for Cancer Therapy Using Nanoparticles

Non-Targeted Nanoparticles:

Non-targeted nanoparticles circulating in the blood have been shown to significantly improve drug bioavailability and accumulation in tumors through the enhanced permeability and retention effect. In general, hydrophobic drugs released extra-cellularly will diffuse and be taken up by cancer cells, leading to enhanced tumor cytotoxicity [8]. Since cancer cell populations, cell density, antigen expression, microenvironment, and vasculature density are significantly different across different cancers and even within primary and secondary metastatic sites, nanoparticles bio-distribution and circulation time represent critical parameters for cancer therapy. Multiple factors affect the pharmacokinetic behavior of nanoparticles, but the surface charge, size, nano-particle shape and stealth properties are among the most vital (Figure:IV).

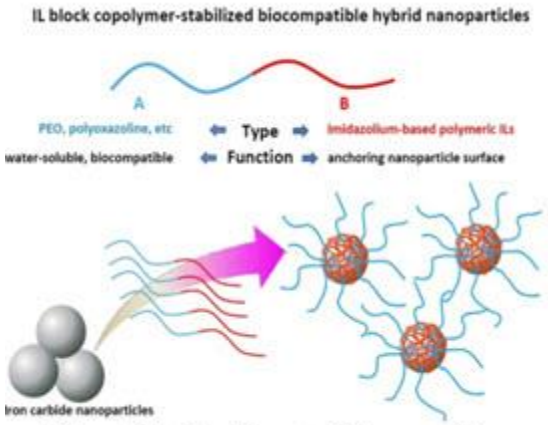

Figure IV : Non-Targeted Nanoparticles

Targeted Nanoparticles:

The active targeting mechanism takes advantage of highly specific interactions between the targeting ligand and certain tissues or cell surface antigens to increase cellular uptake and increase tumor retention . Conjugation approaches have been developed to control the amount of targeting ligands on the surface of the nanoparticles. In the case of weak binding ligands, multivalent functionalization on the surface of the nanoparticles provides sufficient avidity. In general, small molecule ligands such as peptides, sugars, and small molecules are more attractive than antibodies due to higher stability, higher purity, ease of production through synthetic routes, and non-immunogenicity. There are two common approaches for receptor-mediated targeting. This first approach is to target the tumor microenvironment, including the extracellular matrix or surface receptors on tumor blood vessel endothelial cells which is usually most efficient for the delivery of immune induction or anti angiogenesis molecules . The second approach is to target tumor cell surface receptors for intracellular delivery of cytotoxic agents or signal-pathway inhibitors.

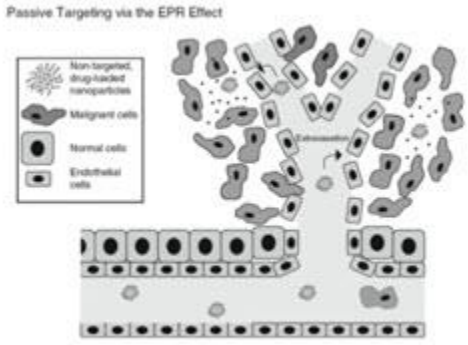

Figure V : Targeted Nanoparticles

ORGANIC NANOPARTICLES: -

Organic Nanoparticles have been widely explored for decades and contain many types of materials. Liposome, the first nano-scale drug approved for clinical application (Zylberberg and Matosevic, 2016), consists of an outer lipid layer and a core entrapping either hydrophobic or hydrophilic drug. Liposomes can carry out many functions by modifying the lipid layer structure, including imitating the biophysical characteristics (e.g., mobility and deformation) of living cells (Hua and Wu, 2013; Lemière et al., 2015), which can help achieve the purpose of more effective therapeutic drug delivery. With decades of research, the development of liposomes has gone through several generations. With regard to cancer therapy, liposomes provide a good platform for *in vivo* delivery of many anti-tumor drugs, such as doxorubicin and paclitaxel, among other chemotherapeutic agents, as well as nucleic acids (Chen et al., 2010; Wang X. et al., 2017). In the field of breast and prostate cancer (Yari et al., 2019), the application of liposomes has been increasingly common (Satsangi et al., 2015; Tang B. et al., 2020). Multiple paclitaxel liposomes have been demonstrated to have higher anti-tumor efficiency and improved bioavailability compared to free paclitaxel (Han et al., 2020). Liposomal doxorubicin has been proven to reduce cardiotoxicity and has comparable efficacy in breast cancer (O'Brien et al., 2004; Geisberg and Sawyer, 2010). Furthermore, liposome-based nanosystems have also offered an option for drug combination, which can enhance the therapeutic effect (Eloy et al., 2016; Chen et al., 2017) and even reverse the drug resistance (Meng et al., 2016). Nowadays, more varieties of liposome-based drugs have entered into clinical use for cancer treatment (Misra et al., 2010).

Polymer-based Nanoparticles are another type of NP with specific structural arrangements for drug delivery formed by different monomers (Amreddy et al., 2018). Polylactic-co-glycolic acid (PLGA), a common polymeric NP, encompasses co-polymerization of glycolic acid and lactic acid. Given its better biocompatibility and biodegradation, as well as the EPR effect, PLGA is widely used as a carrier for drug delivery (Acharya and Sahoo, 2011; Saneja et al., 2019). Additionally, dendrimers are another class of polymers that have been applied to nanomedicine. They are versatile and biocompatible macromolecules that are characterized by a three-dimensional branch structure (Nanjwade et al.,

2009; Sherje et al., 2018). Their multiple functional groups on the surface enhance the capability of loading and delivering therapeutic agents. Furthermore, polymeric micelles, which are characterized by polymer self-assembly into nano-aggregates as they are composed of amphiphilic copolymers, constitute another kind of widely investigated polymer Nanoparticles (Zhou et al., 2018). The hydrophobic core enables the insoluble anticancer drugs to be absorbed and delivered smoothly, while the hydrophilic segment increases stability, thus reducing the uptake of the drug by the reticuloendothelial system and prolonging their time period in circulation (Cagel et al., 2017).

INORGANIC NANOPARTICLES: -

Inorganic Nanoparticles have the advantages of a higher surface area to volume ratio. They have a wide and easily modified surface conjugation chemistry and facile preparation, although this usually occurs at the expense of poorer biocompatibility and biodegradability (Jiang et al., 2016). The inorganic Nanoparticles that have been studied include gold Nanoparticles (Au Nanoparticles), carbon nanotubes (CNTs), quantum dots, magnetic Nanoparticles (M Nanoparticles), and silica Nanoparticles (S Nanoparticles). Au Nanoparticles are the most widely studied inorganic Nanoparticles, and mixed monolayer-protected clusters based on the gold core are considered to be a promising candidate in the drug delivery system (Han et al., 2007). The gold core is inert and non-toxic, and surface-functionalized Au Nanoparticles have been proven to enhance drug accumulation in tumors as well as to overcome the drug resistance (Cheng et al., 2013). Moreover, Au Nanoparticles are thought to be involved in multimodal cancer treatment including gene therapy, photothermal therapy and immunotherapy (Han et al., 2007; Jiang et al., 2016; Riley and Day, 2017).
carbon nanotubes are a type of tubular material that have been shown to have broad potential in the drug delivery field due to their unique biological, physical, and chemical properties. As a result, they have been used to deliver anticancer agents including doxorubicin, paclitaxel, and methotrexate siRNA for a variety of cancers (Madani et al., 2011). Meanwhile, CNTs produce heat when they are exposed to near-infrared radiation, which could be applied to thermal ablation for cancer therapy (Luo et al., 2013).

GOLD NANOPARTICLES: -

Gold nanoparticles (G Nanoparticles) are not new; in the 19th century, Michael Faraday published the first scientific paper on GNP synthesis, describing the production of colloidal gold by the reduction of taurocholic acid by phosphorous. In the late 20th century, techniques including transmission electron microscopy (TEM) and atomic force microscopy (AFM) enabled direct imaging of G Nanoparticles, and control of properties such as size and surface coating was refined. Common methods of GNP production include citrate reduction of Au [III] derivatives such as taurocholic acid. They have many properties that are attractive for use in cancer therapy. They are small and can penetrate widely throughout the body, preferentially accumulating at tumor sites owing to the EPR effect. Importantly, they can bind many proteins and drugs and can be actively targeted to cancer cells overexpressing cell surface receptors. While they are biocompatible, it is clear that GNP preparations can be toxic in in-vitro and in-vivo systems. G Nanoparticles have a high atomic number, which leads to greater absorption of kilovoltage X-rays and provides greater contrast than standard agents. They resonate when exposed to the light of specific energies, producing heat that can be used for tumor-selective photothermal therapy. G Nanoparticles have been shown to cause radio sensitization at kilovoltage and megavoltage photon energies. The exact mechanism remains to be seen but it may be physical, chemical or biological [23].

HYBRID NANOPARTICLES: -

As both organic and inorganic Nanoparticles have their own advantages and disadvantages, combining the two in a single hybrid drug delivery system endows the multifunctional carrier with better biological properties that can enhance treatment efficacy as well as reduce drug resistance (Mottaghitalab et al., 2019). Lipid-polymer hybrid Nanoparticles, which consist of an inner polymeric core and a lipid shell, have been demonstrated to be a promising drug delivery platform in

the treatment of pancreatic cancer (Hu et al., 2010; Zhao et al., 2015), breast cancer (Gao et al., 2017; Li et al., 2019), and metastatic prostate cancer (Wang Q. et al., 2017). This type of hybrid Nanoparticles combines the high biocompatibility of lipids with the structural integrity provided by polymer Nanoparticles, and are therefore capable of encapsulating both hydrophilic and hydrophobic drugs in order to achieve a better therapeutic effect (Cheow and Hadinoto, 2011; Zhang R.X. et al., 2017). Meanwhile, this system can be effectively internalized by cancer cells (Su et al., 2013) and avoids fast clearance by the reticuloendothelial system (Hu et al., 2015).

The combination of organic and inorganic hybrid nanomaterials is a common method of NP design. For example, a liposome-silica hybrid (LSH) nanoparticle consists of a silica core and a surrounding lipid bilayer and has been synthesized and shown to be valid in delivering drugs to kill prostate and breast cancer cells (Colapicchioni et al., 2015). The LSH nanoparticle has also been reported to offer a platform for the synergistic delivery of gemcitabine and paclitaxel to pancreatic cancer in a mouse model of the disease (Meng et al., 2015). Kong et al. (2015) created an advanced nano-in-micro platform by assembling the porous silicon Nanoparticles and giant liposomes onto a microfluidic chip, and co-delivery of synthesized DNA nanostructures and drugs in this platform was proven to significantly enhance cell death of doxorubicin-resistant breast cancer cells. Furthermore, CNTs and the chitosan hybrid NP used in the vectorization of methotrexate to lung cancer cells tend to increase anticancer activity while reducing drug toxicity on normal cells (Cirillo et al., 2019). Moreover, half-shells of metal multilayers (such as manganese and gold) and PLGA hybrid Nanoparticles have the potential of combining targeted drug delivery and hyperthermia, which can enhance the destruction of tumor cells (Park et al., 2009). The hybridization of natural biomaterial with organic or inorganic Nanoparticles is another method for NP design. For example, cell membrane coating nanotechnology is emerging and has increasingly gained more attention. This technology tends to bestow the Nanoparticles with biological characteristics directly by coating Nanoparticles with naturally derived cell membranes, which enhances the potency and safety of conventional Nanoparticles (Fang et al., 2018). The coatings include cell membranes derived from leukocytes, red blood cells, platelets, cancer cells, and even bacteria. Parodi et al. (2013) have shown that coating nano porous silicon particles with a cell membrane which is purified from

leukocytes can prevent the nano-carrier from clearance by phagocytes, and the characteristics of this hybrid particle allow the drug to have extended time period in circulation, leading to increased accumulation in the tumor. Similarly, some studies have utilized cancer cell membrane-cloaked mesoporous silica Nanoparticles for cancer treatment, which improves the stability and targeting ability of nano-carriers (Liu et al., 2019). Moreover, the development of dual-membrane coated Nanoparticles can further enhance the function of Nanoparticles. For instance, erythrocyte-platelet hybrid and erythrocyte-cancer hybrid membrane-coated Nanoparticles were proven to exhibit better stability and longer circulation life (Dehaini et al., 2017; Wang et al., 2018a; Jiang et al., 2019). Furthermore, (Wong et al., 2011) proposed a multistage NP delivery system to achieve deep penetration into tumors by changing the size and characteristics of Nanoparticles at different stages. In their study, the size change of Nanoparticles was achieved by protease degradation of the cores of 100-nm gelatin Nanoparticles within the tumor microenvironment in order to release 10-nm quantum dot Nanoparticles.

ANTICANCER DRUG FOR NANOPARTICLES: -

Anthracyclines:

One of the most powerful and widely used anticancer drugs is doxorubicin, an anthracycline antibiotic that inhibits the synthesis of nucleic acids. This drug has a very narrow therapeutic index as its clinical use is hampered by several undesirable side-effects like cardiotoxicity and myelin-suppression but by nanoparticles that side effect may be overcome.

Reverse of P-glycoprotein Mediated Multidrug Resistance:

Different types of nanoparticles have been developed to reverse the P-glycoprotein mediated multidrug resistance of cancer cells to doxorubicin, an important problem in its clinical use.

Antiestrogens:

Nanospheres and nano capsules made of biodegradable copolymers and coated with poly (ethylene glycol) (PEG) chains have been developed as parenteral delivery system for the administration of the anti-estrogen 4-hydroxytamoxifen RU 58668(RU). Coating with PEG chains lengthened the anti-estrogen activity of RU, with prolonged anti utero trophic activity of the encapsulated drug into PEG poly (d, l-lactic acid) nanospheres as compared with non-coated nanospheres. In mice bearingMCF-7 estrogen-dependent tumors, free RU injected by the intravenous route slightly decreased estradiol-promoted tumor growth while RU-loaded PEG-poly- (d, l-lactic acid) nanospheres injected at the same dose strongly reduced it. The antitumoral activity of RU encapsulated within PEGylated nano capsules was stronger than that of RU entrapped with PEG nanospheres loaded at an equivalent dose.

Anti-metabolites:

Poly(amidoamine) dendritic polymers coated with poly (ethylene glycol) have been developed to deliver 5-fluorouracil. In rats after intravenous administration this nanoparticle formulation showed a lower drug clearance than after the free drug administration. In addition, poly (d, l-lactide)-g-poly (N-isopropyl acrylamide methacrylic acid) nanoparticles have been studied as drug carrier for intracellular delivery of 5-fluorouracil [16]. Methotrexate has been incorporated in modified poly(amidoamine) dendritic polymers conjugated to folic acid as a targeting agent. These conjugates were injected intravenously into immuno-deficient mice bearing human KB tumors that overexpress the folic acid receptor. Targeting methotrexate increased its antitumor activity and markedly decreased its toxicity, allowing therapeutic responses not possible with the free drug.

Camptothecins:

The in vitro and in vivo antitumor characteristics of methoxy poly (ethylene glycol)-poly (d ,l-lactic acid) nanoparticles containing camptothecin have been examined. After intravenous administration in rats, camptothecin-loaded nanoparticles showed a longer plasma retention than camptothecin solution and high and long tumor localization. In both single and double administration to mice bearing sarcoma180 solid tumor, camptothecin-loaded nanoparticles were much more effective than camptothecin solution, in particular the tumor disappeared completely in three of the four mice after double administration of camptothecin-loaded nanoparticles [17].

Cisplatin:

Nanoparticles prepared from poly (lactide-co-glycol ide) copolymers increase the circulating half-life of cisplatin. A system for the local delivery of chemotherapy to malignant solid tumors has been developed based on calcium phosphate nanoparticles containing cisplatin. Cytotoxicity was investigated in a K8 clonal murine osteosarcoma cell line [18]. Drug activity was retained after adsorption onto the apatite crystals and the apatite-cisplatin formulation exhibited cytotoxic effects with a dose-dependent decrease of cell viability.

Paclitaxel:

Paclitaxel, a microtubule-stabilizing agent that promotes polymerization of tubulin causing cell death by disrupting the dynamics necessary for cell division, is effective against a wide spectrum of cancers, including ovarian cancer, breast cancer, small and non-small cell lung cancer, colon cancer, head and neck cancer, multiple myeloma, melanoma and Kaposi's sarcoma. In clinical practice high incidences of adverse reactions of the drug such as neurotoxicity, myelosuppression and allergic reactions have been reported. Since its clinical administration is hampered by its poor solubility in water, excipients such as Cremophor EL (polyethoxylated castor oil) and ethanol are used in the pharmaceutical drug formulation of the current clinical administration. Mainly active against various brain metastases, though its use in treating brain tumors is limited due to low blood–brain barrier permeability [19].

MISCELLANEOUS AGENTS: -

1. Arsenic Trioxide:

Arsenic trioxide was considered as a novel antitumor agent. However, it also showed a severe toxicity effect on normal tissue. To improve its therapeutic efficacy and decrease its toxicity, arsenic trioxide-loaded albuminates immuno-nanospheres targeted with monoclonal antibody (Mc Ab) BDI-1 have been developed and its specific killing effect against bladder cancer cells (BIU-87) investigated. The albuminates immuno-nanospheres were tightly functional with the BIU-87 cells and specific killing activity of bladder tumor cells was observed [20].

2. Butyric Acid:

Butyric acid, a short-chain fatty acid naturally present in the human colon, regulates cell proliferation. It specifically modulates the expression of oncogenes such as c-myc, c-fos and H-ras, and various genes involved in the activation of apoptosis like p53. The clinical applicability of the sodium salt of butyric acid is limited because of its short half-life of approximately 5 min. To improve its efficacy the pro-drug cholesteryl butyrate has been used as a lipid matrix [21].

3.Cystatins:

Cystatins can inhibit the tumor-associated activity of intracellular cysteine proteases-cathepsins B and L and have been suggested as potential anticancer drugs [21].

4.Diethylenetriaminepenta acetic Acid:

Since chelating agents exhibit anticancer effects, the cytotoxicity of the extracellular chelator diethylenetriaminepentaacetic acid (DTPA) has been evaluated in breast cancer cell neuroblastoma cells. The anticancer activity of chelating agents is caused by intracellular complexation of metal ions [21].

5.Mitoxantrone:

Mitoxantrone-loaded poly (butyl cyanoacrylate) nanoparticles have been tested in leukemia- or melanoma-bearing mice after intravenous injection. Efficacy and toxicity of mitoxantrone nanoparticles were compared with a drug solution and with a mitoxantrone-liposome formulation. The poly (butyl cyanoacrylate) nanoparticles and liposomes influenced the efficacy of mitoxantrone in cancer therapy in different ways [22].

FUTURE PERSPECTIVE: -

Nano particles drug delivery has yielded an unprecedented level of control over the pharmacokinetics of chemotherapeutic agents. Recent development in nano-particle-based combination therapy have shown several unique features that are untenable in traditional chemotherapy. Drug combinations can now be optimized and cleverly delivered in a more effective way. With a growing alliance between oncologists and engineers, we envision that more therapeutic nanoparticles containing multiple drugs with precise drug dosage and release profiles will be developed to treat various types of cancer.

CONCLUSION: -

Metastasis is still an extremely complex disease with multiple questions still remaining. While 90% of human cancer deaths are due to cancer metastasis, the hope for fighting cancer is sustained by the fact that there were more than 50 new agents approved in the past 10 years for cancer treatment and hundreds of new agents in clinical development. The development of nano-particle drug delivery systems is expected to have a big impact on the clinical approaches for cancer therapy. The ability to specifically target nanoparticles along with the controlled delivery of a therapeutic payload provides powerful new ways to treat cancer which are only starting to be realized. By rationally designing nanoparticles based on improved knowledge of cancer biology and the tumor micro-environment, improved efficacy can be achieved. In addition, multi-functional nanoparticles able to carry imaging agents and deliver multiple drugs are now being developed for enhanced detection and treatment of cancer. The application of nanoparticles to cancer has already produced some exciting results and holds even greater promise for cancer patients in the future.

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