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A Review on Advancement of Cancer Therapy with Metal Based Nanoparticle

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ABSTRACT: *The primary cause of numerous diseases that frequently affect the human body is a compromised immune system. For instance, it can increase the body's susceptibility to infection, which also increases the body's resistance to medicines, by triggering pro-inflammatory reactions and even the loss of good cells and tissues. Metal nanoparticles have the potential to overcome the challenges caused by conventional chemotherapies. Metal nanoparticles play an essential role in the treatment of cancer by targeting, gene suppression, and drug delivery to the targeted area. The best suitable metal nanoparticles better work with targeted ligands to control the energy deposition within the tumors. Other than therapeutic advantages, metal nanoparticles are also helpful as a diagnostic tool for the imaging of cancerous cells. Moreover, metal nanoparticles provide beneficial options in controlled targeted drug delivery, instant diagnosis, and therapeutic methods. Nanoparticles are useful as therapies and diagnostics because cancer cells are heterogeneous. Breast cancer anti-cancer therapy is difficult due to the disease's aggressive spread to the body. Noble metal nanoparticles are used in the treatment of cancer because of their distinctive features, great biocompatibility, surface effects, and tiny size effects. Numerous cancer treatments have been developed thanks to advances in science and technology, but the global mortality rate for cancer patients is still astronomically high, necessitating conventional treatment approaches in order to preserve lives. Scientists are trying to find a cancer cure, working day and night. Due to their effectiveness and promising outcomes, nanoparticles for the treatment of cancer have acquired relevance.*

Keyword: Nanoparticles, Nanomedicine, Noble Metal Nanoparticles, Cancerous Cell

INTRODUCTION

The immune system of humans is a complicated system that is comprised of cells, physical barriers and proteins. All these components work together to prevent diseases in the body and to keep the body fully functional for the healthy survival of the person. If the immune system is working accurately, it has the ability to protect the body from foreign particles with the help of some specific cells and their relevant functions (Tasic et al., 2018).

The underperformance or malfunctioning of immune system is the major reason of different disease that often occurs in human body. For example, if the immune system is working higher than normal, the autoimmunity responses will generate in the body leading to pro-inflammatory responses and even destruction of healthy cells and tissues (Becher et al., 2017). Contrary to this, if the immune system is under active, it can make the body susceptible to infection which also makes the body resistant to antibiotics. Tumorigenesis showed that the immune system is mainly responsible to control the abnormalities related to proliferation of cells by which they become malignant (Huang et al., 2020). This review focuses on the fundamental principles of nanotherapeutics application, current challenges, and future research directions.

Cancerous Cells and their formation

Cancer is the second leading cause of mortality worldwide. The number of annually diagnosed cases of cancer is 18 million. It is stated in the literature that successful growth of tumors included a prolonged journey with various factors which are not clearly known yet (Razak et al., 2021). The growth of the tumor requires a proper mechanism through which immune evasion will be possible (Dhatchinamoorthy et al., 2021). Studies have revealed that the formation of tumors in the human body is only possible when the surrounding environment support its growth by suppressing immune responses. Mainly, cellular signaling, extracellular matrix and secretion of cytokine and growth factor are altered for the formation of cancerous cells (Dhatchinamoorthy et al., 2021)

Immunotherapies

Immunotherapies include all those treatments that make the immune system capable of eliminating malignant cells growth not only protect the other cells but also destroy the further proliferation of cancerous mass of the cells. Immunotherapy has different classes that can target different stages of immune system from initial antigen occurrence to final effector stage. Considering specificity of the cancer and its stages, it has concluded that early immunotherapies give promising results and highly potent in the situations where many different clinical standards failed to provide successful outcomes. One of the effective directions for the treatment of cancer include Nanomedicines that provide prolonged changes in the body to fight against cancer. Drug delivery system by the use of nanoparticles has unique importance in nano-medicines (Huang et al., 2020).

Nanoparticles (NPs) and their synthesis

Nanoparticles are defined as the particles or small bodies whose sizes range within nanometers. Due to their smaller size, these particles cannot view through naked eyes. Nanoparticles have significant properties as they are composed of some specific material that can target the cancerous cells (Tasic et al., 2018).

The formation of organic nanoparticles is based on lipids and polymers along with selective solvents. Nano-participation, emulsion solvent evaporation pathways including nano-gel, liposome and poly-caprolactone are the pathways included in the formation of nanoparticles. Inorganic materials can also be made within nanoparticles that include gold, iron oxides, copper sulphates, silica and silicon. The core of the resulting inorganic nanoparticles has high capacity to move with different optical, magnetic and electrical features. The material selected for the core of nanoparticles depends upon the working, cargo and application of nanoparticles within the human body. It is also known that nanoparticles play a significant role in facilitating the size and shape of cell membrane camouflaged nanoparticles, drug releasing mechanism and pharma-kinetic behaviour (D'Acunto et al., 2021).

Anticancer mechanism of Nano particles

It is stated in different literature that anticancer mechanism of nanoparticles follows different biosynthetic routes and also cause cytotoxicity. The size and the shape of nanoparticle is majorly responsible cytotoxicity, for example, the nanoparticles made by using the material of plants and are spherical in shape plays a significant role against cancerous lines. The process angiogenesis involves the formation of new blood vessels by existing vessels which are helpful in wound healing and in the formation of granulation tissues. Relevant to it, the growth of solid tumor is also occurred due to the formation of new blood vessel as it supplies oxygen and nutrients equally to the cancerous mass. Resultantly, the cancerous cells proliferate and spread in the body. Recent studies have revealed that nanoparticles exhibit a prominent role in the treatment of retinal neovascularization diseases by inhibiting the vascular endothelial growth factor and also block the activation of extracellular signal related kinase by the help of phosphorylation of vascular endothelial growth factor receptor 2. In other words, anti-angiogenesis properties have been used in the treatment of cancer using different approaches related to nano-particles (Ratan et al., 2020).

Nanoparticles and nanomedicine

The field of oncology is strongly focused on nanomedicine due to its remarkable features in the treatment of cancer. The basic outcomes obtained by using nanoparticles for cancer treatment includes their therapeutic nature which results in the structural and chemical modifications according to the requirement of cellular environment. The diagnosis and imaging with the idea of alternation in the vaccine development is also obtained by the nano-medicine treatment (Siegel et al., 2011).

Nano-therapies are competitive in the tumor forming environment that did not improve the circulation of drug but also reduce the toxicity. The results appeared after using the techniques of nanoparticles are outstanding and promising for the clinical development of therapeutic drugs (Hanahan and Weinberg, 2011).

Many therapeutic nanoparticle technologies including polymeric micelles, albumin nanoparticles, liposomes etc. are well known categories for cancer treatment while many other similar technologies including radiation therapy, chemotherapy, immunotherapy, RNA interference therapy, hyperthermia etc. are under clinical trials and investigation (Wicki et al., 2015).

With the advancement in the field of nanomedicine, there are various outstanding outcomes attained but studies have revealed that there are many challenges present yet that need to be resolved in the field of nanotechnology. For example, the chemical modification of tumor with heterogeneity and complexity makes the selection of nanoparticles difficult. Thus, careful selection of the patient is needed to benefit from nano-medicine (Sinha et al., 2006).

Nanoparticles with physico-chemical properties

Nanomedicines have revolutionized the treatments of cancer by offering different health opportunities to the patients. The nanoparticles can easily be modified in shape, size and surface characteristics to treat specific type of tumor. The customization of size is very essential because nanoparticles must travel in the blood stream and deliver the nano-carrier to the targeted tissue. In other words, the optimization of nanoparticle size may help improve the uptake of nanocarrier into the tumor site (Mavaddat et al., 2015).

Solubility and degradation

There are many anti-cancer drugs used for targeting cancer cells but these drugs failed to perform their task because of their poor solubility in water and ultimately eliminated from blood (Wicki et al., 2015). On the other hand, hydrophilic nanoparticles have excellent solubility and allow effective delivery in the tumor environment. The improvement in the development of nanoparticle can make the drug available for longer period of time in the circulation of blood without degradation which can help in suppressing the tumor (Wicki et al., 2015).

Targeting

Nanocarriers can be designed to work as active or passive target tool to reach tumor tissue (Heidel and Davis, 2011). Active targeting involves nano-carrier attachment with ligand that has high specificity for the receptors and target cells. While, passive nano-carrier are designed within the tissues where blood circulation is higher for the supply of drug (Lovrić et al., 2005).

Nanoparticles in combination therapies

Nanomedicine could conduct different therapeutic agents for the purpose of treatment. Loading different siRNA could increase the rate of sensitivity in the treatment. These features of nanoparticles make them extraordinary unique for the treatment of cancer (Wang et al., 2013).

Cancer cell treatment Methodology

Nanoparticles are useful as therapies and diagnostics because cancer cells are heterogeneous. Breast anti-cancer therapy is difficult due to the disease's aggressive spread to the brain, bone, lung, and liver. For the diagnosis and defense against metastatic breast cancer, magnetic nanoparticles are essential (Subhan et al., 2022). Metal based nanoparticles are undoubtedly versatile molecules that can be used in different biomedical treatments as they possess high diagnostic characteristics like sensitive assays, radiotherapy based enhanced treatments, thermal ablation, targeted gene as well as drug delivery etc. It has also been studied that nonmetal-based nanoparticles offered as nontoxic carriers for the purpose of gene and drug delivery (Johnson et al., 2010). Nanoparticles with noble metal-based nanoparticles can help providing simultaneous diagnostic options and therapeutic benefits. These nanoparticles can penetrate in better way and track the targeted area for drug delivery that ultimately decreased the risk as possible in conventional therapies (Thornburg et al., 2008).

Noble metal nanoparticles, such as gold, silver, platinum, and palladium nanoparticles, are frequently utilized in the treatment of cancer because of their distinctive optical features, great biocompatibility, surface effects, and tiny size effects (Zhao et al., 2022).

Metal nanoparticles-based therapies

Tumor Targeting

Metal based nanoparticles provided two types of tumors targeting strategies that are known as active and passive targeting. In passive targeting, metal nanoparticles faced the tumor based defective vasculature and failed lymphatic drainage due to instant proliferation of solid tumors. Thus, metal nanoparticles entered the tumor environment through angiogenic vasculature that enhanced the targeted permeation and retention of the drug as shown in fig 1. In case of active targeting, the metal-based nanoparticles function to perform various task in the form of different biological moieties including peptides, antibodies, RNA or DNA cellular receptors. The monoclonal antibodies based on metal nanoparticles successfully target cancerous cells or surface proteins and initiate the anticancer process and decrease the risk of damaging healthy cells (Vogelstein and Kinzler, 2004).

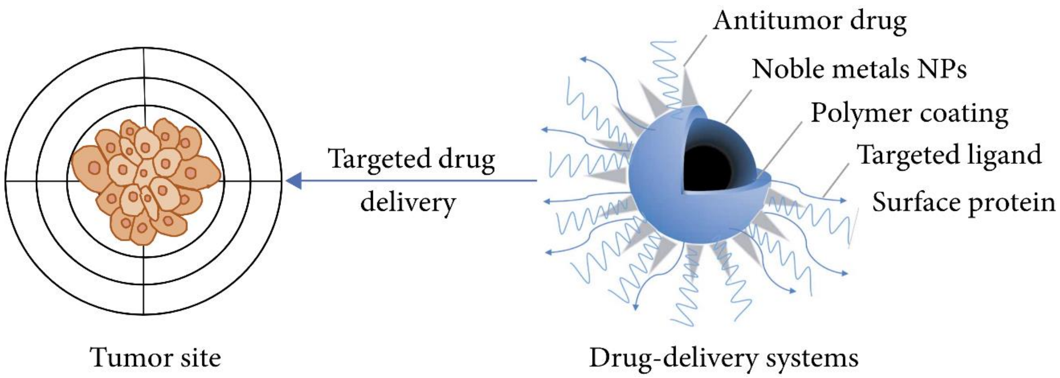

Fig. 1. Brief schematic of drug delivery systems (Ding et al., 2013)

Gene Silencing

The studies have revealed that gold nanoparticles have effective intracellular drug delivery option that can work as antisense vehicle for oligonucleotides and for siRNA and protect it against RNA's and promote selective targeting. The gold nanoparticles attached with single stranded oligodeoxy nucleotides have powerful ability to work in gene therapy as efficient gene regulator. These molecules provide high loading capacity of antisense DNA without causing toxicity which is ultimately a beneficial property in anticancer treatment (Ferrari, 2005).

Hyperthermia

Hyperthermia therapy in cancer has been widely accepted both by direct irradiation and by customizing temperature vector which are metal nanoparticles. These nanoparticles increase the temperature of the cancerous cells beyond their tolerance ability but lower than the temperature of normal tissues by failed blood circulation and selectively kill them. This technique is used by exposing the patient or the targeted area to the magnetic field or intense light range that cause the nanoparticles to increase the temperature and cause thermal ablation of the cancerous cells (Meyer et al., 2015).

Drug Delivery

The studies have revealed that metal-based nanoparticles have potential to work as vector for targeting cancer cells and help optimizing the distribution of drugs. Gold nanoparticles have been used as tool for the anticancer drug delivery including platinum-based drugs i.e., oxaliplatin, cisplatinetc (Sperling et al., 2008).

Radiotherapy

The technique is widely used for the treatment of cancer by the use of radiation on the proliferating cells. This treatment has a major challenge of damaging healthy tissues located near the cancerous environment that uptake intense radiations. Radiotherapy has been modified by the introduction of noble metal nanoparticles that act as antennas to target the radiations on the specific cancerous environment and protect the healthy tissues. The radiations are also targeted in a control manner to avoid the risk of healthy cells damage (Hainfeld et al., 2004).

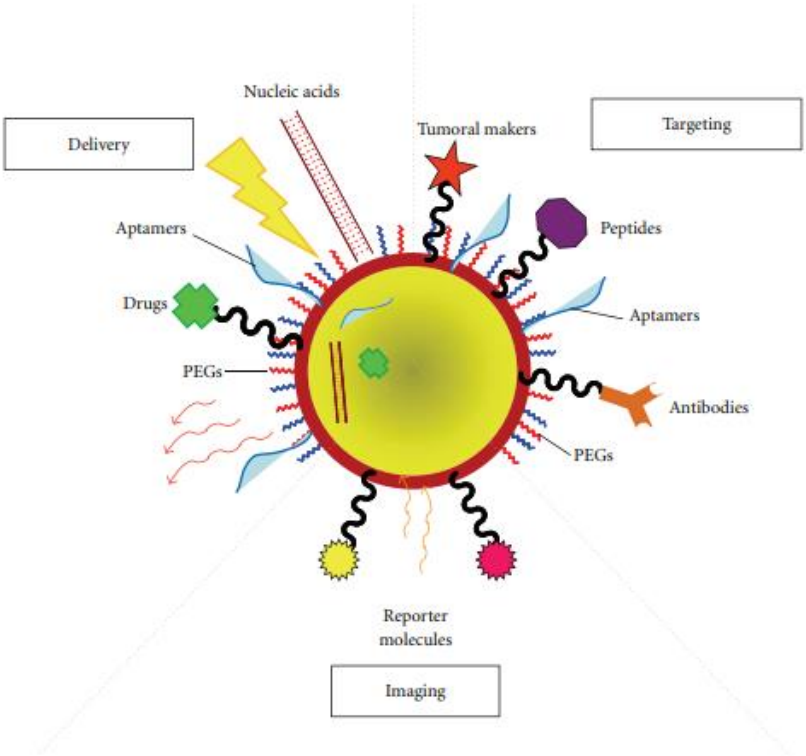

Fig. 2. Multifunctional Metal based nanoparticle system for tumor targeting, delivery and imaging (Van Vlerken et al., 2006)

Table 1: Nanoparticles applications in different types of cancer recognition

	Platform	Application	Indication	Reference
1	Silica Nanoparticles	Lymph node imaging	Head and neck melanoma	(Maggiorella et al., 2012)
2	Hafnium oxide nanoparticles	Radiotherapy	Solid tumor, head and neck cancer, lymph node cancer	(Diaz-Gil et al., 2016)
3	Iron oxide nanoparticles	Magnetic resonance imaging	Prostate cancer	(Fortuin et al., 2013)
4	Gold coated silica nanoparticles	Photo-thermal ablation	Head and neck cancer	(Gupta et al., 2013)
5	Colloidal gold nanoparticle	Tumor necrosis factor delivery	Solid tumors	(Libutti et al., 2010)

Table 2: Use of nanoparticles in different cancer therapies

Nanoparticle	Drug	Cancer type	Approval
Albumin bound nanoparticle	Pacilitaxel	Breast cancer, pancreatic cancer, lung cancer	2005
Liposome based nanoparticle	Doxorubicin	Ovarian cancer, Breast cancer, Lung cancer, ovarian cancer	1996
Liposome based nanoparticle	Paclitaxel	Breast cancer, ovarian cancer	1999
PEG polymeric nanoparticle	L-asparaginase Styrene maleic anhydride neocarzinostatin (SMANCS)	Liver cancer, Renal cancer	2007
Iron oxide nanoparticle	Doxorubicin	Thermal ablation glioblastoma	2010
Polymeric protein nanoparticle	Vincristine	Leukemia	2006

Tissue compatibility and inflammation of nanoparticles

Nanoparticles are made using different natural and artificial polymers, dendrimers, ceramics, lipids and metals. Nanoparticles has the ability to deliver therapeutics in a reliable manner and can access intracellular components by different biological processes i.e., phagocytosis and endocytosis. The decrease in the size of particles assists material to penetrate biological barriers of the cells and ultimately cause inflammation. It has been known that nanoparticles can trigger the inflammatory responses as they enhance the production of reactive oxygen species in lung epithelial cells and macrophages that resultantly cause lung infections and even injury (Table 1). Thus, it is important to consider nanoparticles inflammatory response when designing a drug to cure a specific organ of the body (Powell et al., 2010).

(i) Generally, biomaterials are considered as the foreign molecules and bodies that are responsible to start inflammatory responses in the body. Inflammatory reactions that occur during the implantation of nanoparticles are mainly caused by the interaction of proteins with the surface of reactive site (Xie, 2013).

(ii) The level of inflammation varied from the type of proteins which is to be implanted along with nano-particles. Commonly, albumin, fibrinogen, vitronectin and fibronectin are responsible for the inflammatory reactions of implanted nanoparticles (Table 2). Inflammatory reactions also depend upon other factors including surface charge and chemical composition of the material. It has been studied that the topography is also responsible for the adsorption of plasma proteins within extracellular matrix(Eniu et al., 2008).

(iii) The acute inflammatory responses are generated in different conditions. For example, any injury that includes the implantation of biomaterials resultantly introduced neutrophils that ultimately activate the mast cells. The absorption of proteins on the surface of cells also leads to acute inflammatory response. The cells resultantly release reactive oxygen species (ROS) and cytokines for example, interleukin 3 and interleukin 4 that cause oxidative stress and joining of monocytes in the blood. Moreover, addition of biomaterial enhances the production of inflammasomes. Inflammasomes are the intracellular multi-protein bodies that involved in the activation of pro-inflammatory cytokines for example, Interleukin-18 and interleukin 1-β. The phagosome rupture after the uptake of material through phagocytosis and their interaction with plasma membrane also resulted in the production of inflammasomes (Ferraz da Costa et al., 2012).

(iv) The use of nanoparticles in tissue engineering creates the same inflammatory scenario as created by other biomaterials, i.e., cytokines, inflammatory cells and enzymes etc. but their response is quite different from these biomaterials. Nanoparticles possess different features like surface nano-topography and inflammatory cell response. For example, surface architecture of nano-porous scaffolds influenced the production of cytokines in macrophages (Gupta et al., 2014).

It is worthy to mention that the nanoparticles and carbon nanotubes are utilized as individual entities instead as a component of bulk biomaterials. It means that two classes of nanomaterials are different from each other even at nano-scale features. That is why they are taken up by cells through phagocytosis or by other means. The specificity in the responses of the cells with the interaction of nano-particles explains the activation of inflammatory cells (Haynes et al., 2006). On the other hand, the cells in contact with nano-scale surface features are activated via adsorbed protein-receptor interaction. Nanoparticles geometry including size, shape, structure and reactive capacity is responsible for inflammatory responses (Wang et al., 2011). The inflammatory responses of nanoparticles are regulated by shape and size and their characterized features are associated with the level of inflammation. The inflammatory responses of nanoparticles can be optimized by addition of material that shows necessary biocompatibility, anti-inflammatory molecules association with nanoparticles and chemical modifications when the drug is introduced in the body (Chapekar, 2000). The chemical composition of nanoparticles also involved in eliciting inflammatory responses. Nanoparticles with non-biodegradable composition and cationic polymers have greater chance to induce more inflammatory responses compared with biodegradable composition with anionic behaviour (Harrison and Atala, 2007).

CONCLUSION

With the advancement in medicines and technology, there are many cancer treatments have been introduced but still the death rate of cancer patients in the world is exponentially high which requires conventional treatment strategies to save lives. The technique of radiotherapy is widely used for the treatment of cancer, but this is challenging due to highest rate of damaging healthy tissues. The studies have revealed that metal-based nanoparticles have potential to work as vector for targeting cancer cells and help optimizing the distribution of drugs. Recent studies based on nanoparticles for the cancer treatment gained importance because of efficiency and promising results. The formation of nanoparticles using green chemistry is environment friendly, cheap to afford and nontoxic in nature. These nanoparticles increase the temperature of the cancerous cells beyond their tolerance ability but lower than the temperature of normal tissues by failed blood circulation and selectively kill them. The process of delivering nanoparticles in the cancerous patients is quite simple and cause less side effects compared with radiotherapy and chemotherapy.

CONFLICT OF INTEREST

Authors declare there is no conflict of interest.

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