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GOLD NANOPARTICLE IN CANCER TREATMENT

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INTRODUCTION

The nanotechnology is the technology of creating, manipulating and using the structure in nanometer size range. The origin of nanotechnology lies in the convergence and growth of many scientific branches. The goal of nanotechnology is to create effective, economic and highly specific nanomedicine and nanodevices that can help human being to fight against deadly diseases. The nanoparticles have a wide range of applications in medical field and the results are quite helpful to patients, scientists and physicians.

The gold Nanoparticles have most promising range of applications in cancer treatments as compared to newly evolved nanodevices like nanorods, nanowires, quantum dots. The gold nanoparticles possess superior physiochemical properties, unique optical properties that can be used for early detection and treatment of cancer through photothermal and radiotherapy. Cancer is the major cause of death from past three decades and remains one of the biggest biomedical challenge. The advanced research has been conducted and new innovative and promising methods like Molecular targeted therapy, virus therapy, Tumor targeting fields, hyperthermia therapy have been discovered to fight against the cancer.

Previously gold nanoparticles are used to detect the cancer however in the current study heating the gold nanoparticles are used to kill the cancer cells. Because of their good biocompatibility and controllable biodistribution pattern gold nanoparticles are the ideal candidates for innovative therapies.

BACKGROUND

With about 7 million new death per year cancer is remain concerning cause of death. The treatment of cancer involves surgery, chemotherapy and radiation therapy but due to increase in complexity of disease, genetic and various environmental factors leads to birth of new advanced treatment. Understanding the advantages of gold nanoparticles can leads to the successful treatment of cancer. The gold nanoparticles have low atomic mass by which they can absorb radiation and increases the radiation dose in the tumor causes collapse which results in damaging cancer cells without affecting the healthy cells.

In order to treat the specific types of cells, specific antibodies can be joined with gold nanoparticles. The successful impact of radiations caused by gold nanoparticles helps to used particles more effectively. Recently gold

nanoparticles are used as anticancer drug carrier and as an enhancer for radiation doses. The anticancer bleomycin can easily go into the gold nanoparticles through gold -thiol bond.

The main focus is to reduce the time, effort and expenses in cancer detection and treatment. The gold nanoparticles help to fight against the oral, stomach, colon and skin cancer. The gold nanoparticles are promising contrast agent, drug delivery vehicle and radiosensitizers and very helpful to improve cancer detection and therapy treatment. The traditional way of administered the anticancer drug have lot of drawback like unwanted biodistribution of drugs in patient body, stability in blood and accumulation of blood in organs gold nanoparticles can overcome these problems as they have amazing plasmonic properties.

MAJOR MILESTONE

In the recent years the development of various reliable methods leads to produce gold nanoparticles in desired shape and size to use in medical field. Gold nanoparticles are used in the development of new generation of antiviral drugs that can attack virus and destroy it. They are used in early diagnosis of heart attack.

The gold nano rode is used in vaccine development that are used in treatment of schistosomiasis. Crosslinking gold nanoparticles with collagen gels are used in ageing or treatment of damaged skin. The nano vaccines are also designed on basis of gold nanoparticles their surface carries high density of tumor peptide antigens when deliver to specific cells helps to trigger the antitumor immune response. Over 160 years old Michael Faraday developed the pure sample of colloidal gold in lab in London that experiment is actual becomes the base for future experiments for the nanotechnology and nanomedicine.

The innovative applications of gold nanoparticles involve the gene therapy, tumor detection, radiotherapy, drug delivery and dose enhancement. The multiple entities, multiple receptor targeting, and multimodality imaging are the multifunctional of gold nanoparticles that serves as major milestone to fight against the cancer. The earliest gold nanoparticles are gold nanosphere then there are nano-rode, nano-shell, nanocages comes into existence. It is a major milestone that the gold nanoparticles can destroy the cancer by negative the side effects of chemotherapy and radiations like erectile dysfunction, tissue toxicity without affecting the healthy tissues.

The patients who are treated in clinical trial shows no signs of cancer return after one year from the treatment while the chemotherapy and radiation therapy increase the risk of developing different types of cancer in life. In some patients the development of second cancer linked to affect of past cancer treatment.

METHODS

Gold nanoparticles proved as a milestone in local enhancement of radiation dose and targeted delivery of anticancer drugs. For experiment bleomycin has chosen as anticancer drug. BLM binds with DNA causing unwinding double helix and thus producing the reactive oxygen species cause the DNA strands breaks down. The sulphate ending of BLM gets attached to gold nanoparticles makes it an ideal drug. Gold nanoparticles of size 10nm derived with the citrate reduction method then penta-peptide is used to stabilized it. RGD domain of peptide added to stabilize the gold nanoparticles.

This modified gold nanoparticles are called as GNP-RGD and then bleomycin is added using the gold-thiol bond onto the surface of gold nanoparticle then it is called GNP-RGD-BLM. When the cells are treated with GNP-RGD-BLM decreases in tumor cell survival. The experiment shows at low concentration one conjunction of anticancer drug gold nanoparticles leads to effectively drug delivery. For GNP mediated combined therapy cells were treated with GNP-RGD-BLM.

This GNP mediated chemotherapy and radiation when tested in vitro cell using the concentration of cells in nanomolar and then very small radiation were used that leads to decrease in cell survival as compared to cell treated with bleomycin and radiation, GNP-RGD-BLM causes increase in rate of cell death. When Gold nanoparticles used as drug carrier and radiation sensitizer with chemo and radiation therapy causes significantly improve the results of combination therapy.

PROTEIN PLAYER

Tumor protein p53 acts as tumor suppression as it regulates the cell division and growth either in a fast or uncontrolled way. One of the important features of p53 protein is it helps in reducing serine acid that help the cancer cells to grow. P53 do not forms the orderly crystals making it a flexible molecule which are difficult to study x-ray crystallography. It consists of four similar protein chains which are tied by a tetramerization domain at the center. P53 structure is studied by removing the flexible regions while the stable structures are formed due to solving structure of pieces. It also consists of a large DNA binding domain which is enriched in arginine residue interact with DNA. The domain found the specific regulatory site on the DNA.

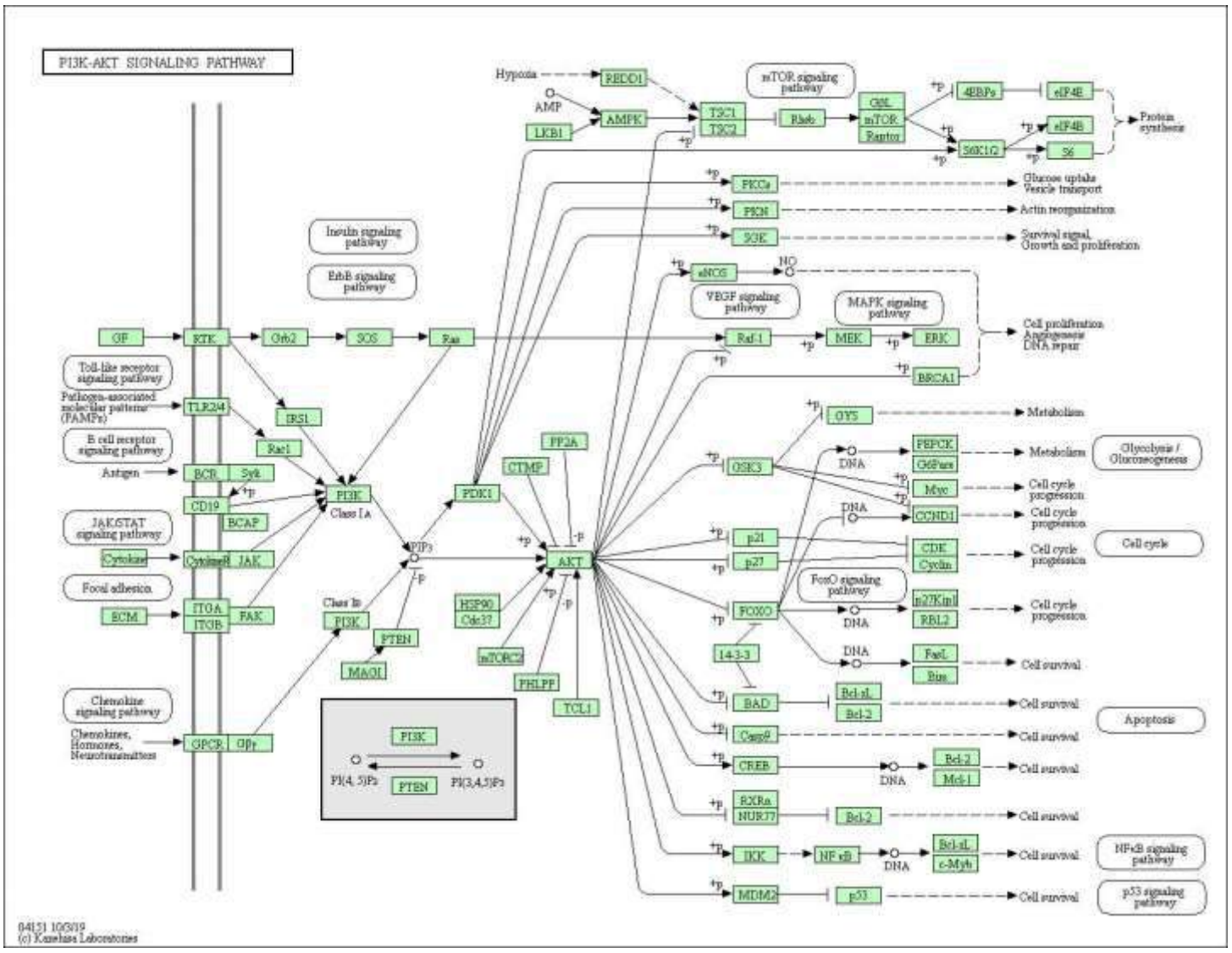
The third domain of transactivation domain attached to near the end of each arm that activated DNA reading. The four arms of DNA are binds with the p53. The binding site consists of three parts two p53 domain for a specific binding site a variable stretch of 0 to 13 base pair and the second binding for other two p53 domain. The two p53 are bound to top and other two p53 are bound at bottom of identical sites. The tetramerization domain lies behind the helix where all the four chains are bound together. The four transactivation can activate the other protein involves in reading the DNA while these extends to DNA helix.

The flexible chains help p53 to binds to variants of the binding sites that allows to regulate transcription in the genome. Cancer cells have two mutations causes uncontrolled growth and other is block normal defense that control the uncontrolled or multiplication of cells. P53 mutation changes information at one position of DNA. And makes cell to produce p53 with defect by exchange an incorrect amino acid in protein chain. Due to this normal function of p53 is affected causing it unable to stop cell multiplication, when cells have mutation causes uncontrolled growth as a result cell will develop into a tumor.

By studying the structure it was found that DNA binding domain contains the mutation of P53 that causes cancer The mutations are formed around and inside the DNA binding face of protein. Arginine 248 are common mutation that forms strong stabilizing interaction with DNA by snaking into it. Other mutations are 175,273,249,282,245 some are connected directly while other are attached position other than the DNA binding amino acid.

SIGNALING PATHWAY

The gold nanoparticles have low cytotoxicity and high biocompatibility made them ideal for drug delivery on nano scale. P13K-AKT regulates the cell growth, proliferation, apoptosis and other important cellular functions. The divergent P13K-AKT results in survival and proliferation of cancer cells, while increase activity pathway leads to resistance to cancer therapy. The PKB or protein kinase are the serine kinase AKT. The kinase, B and T cell receptor, tyrosine, integrins, cytokine, g protein coupled receptors help to activate the AKT signaling. P13K has three classes while class I is implicated in cancer, primary role is to convert (P14,5P2) TO (P1P3). In cancer there are two mutation identified that increases activity of P13K. The phosphatidylinositol 3-kinase and AKT/protein kinase B are the major proteins involved. The AKT is central node of pathway activated by P1P3 acted downstream of P13K to regulate cellular processes. mTOR is major protein acting upstream and downstream of AKT and regulates protein synthesis for cell growth and cellular endpoints. Three homologous AKT(AKT1,2,3) are coded by separate genes. The elevation in AKT activity due to angiogenic, genetic alteration and oncogenic growth factor that causes cancer. Due to the downstream effects the P13K-AKT should be carefully regulated. Loss of PTEN (phosphatase and tensin homolog causes overactivation of AKT. The P13K-AKT pathway is regulated by PTEN as it affects the activity of the pathway.



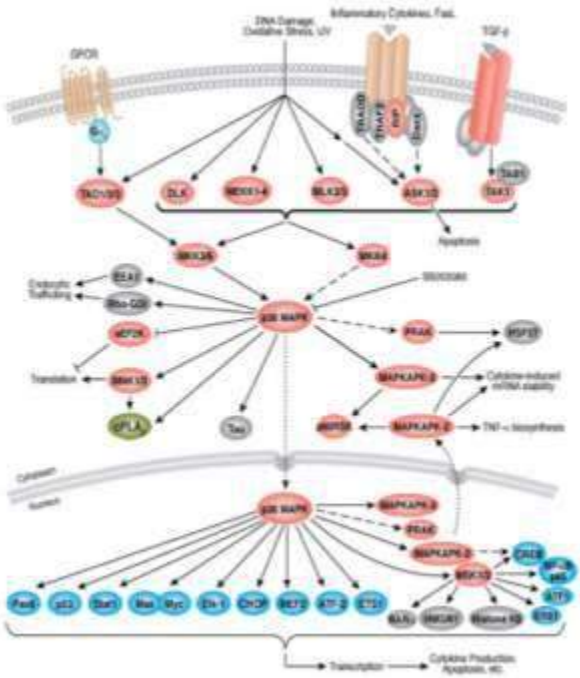
CELLULAR INTERACTIONS

The gold nanoparticles can be administrated in patients either through oral, injection or inhalation it starts interacting with proteins lipids and nuclei acid. The gold nanoparticles help to monitor the development of immune response by combining their photothermal properties with therapeutics. Gold nanoparticles are promising materials to deliver antigens and adjuvants enables the immune system to fight against tumor by inducing T cell lymphocytes. The protein corona forms as a result of interaction between protein and gold nanoparticles which might influence distribution of gold nanoparticles in varied tissues.

The most cluster area unit ERK1/2(protein kinases, p38 MAP kinase and c-junNH-2 terminal kinase concerned in MAPK signaling. The factors that are responsible for activating the pathway are cell stimuli, cellular stress and various growth factors. These are the factors responsible for the sequence of signaling events. The ERK is responsible for growth, development and differentiation where as JNK MAPK are responsible for the apoptosis, growth, inflammation and differentiation. The results of a recent study done on mice within which the disruption of genes that encoded the p38 kinase shows the potential role of this pathway in tumor suppression through enhancing

the transformation of fibroblasts. The p38 further activated p53 that has a lead role in suppression tumor proliferation. Researchers are incessantly engaged on discovering innovative drugs that could effectively target the MAPK signaling. BRAF mutation for melanoma in 2002 and followed by BRAF inhibitor vemurafenib for melanoma treatment in 2011. A lot of advanced and specific studies are done to search out new treatment to focus on the molecule of MAPK pathway. Gold nanoparticles interacts with receptor protein that causes the activation p-38 mitogen activated protein kinase (MAPK) changes the expression of differentiation relevant genes that are responsible for promoting osteoblast differentiation from MSCs and then inhibit their differentiation into adipocytes.

The gold nanoparticles interact with cytoplasmic protein and cell membranes during cellular uptake and this process activates p-38 MAPK signaling inflicting differentiation into osteoblasts. The gold nanoparticles created by pre-osteoblasts promotes them to differentiation into osteoblasts. The expression of BMP-2, RUNX-2, OCN and COL-I are up- regulated and MAPK pathway was activated thanks to exposure to AUNPs. A recent analysis showed that the NF-KB signaling pathway in murine B-lymphocyte cell line (CH12.LX) can be activated by 10nm gold nanoparticles. This leads a way for AUNPs to mediate inflammatory responses of lymphocytes NF-KB is to keep up drug resistance using victimization expression of pump protein and sensitivity to therapy medication. The gold nanoparticles additionally have an effect on the cell spreading and adhesion on a culture substrate and reduces cell viability.



(Niu et al., 2019; Ortiz et al., 2019; Palussiere et al., 2019)

BIOCOMPATIBILITY

The gold nanoparticles utilized in cancer treatment helps to eliminate tumor and mitigating the damage to healthy cells by enhancing targeted therapy that convert infrared light to heat. The therapy involves the accumulation of

cluster of gold nanoparticles in cancer cells and the heated up by infrared light as a result the fluid around the cluster reaches at a high causes vaporization of fluid and finally it breaks up that ultimately kill the cancer cells and mitigating harm to the healthy cells. This treatment includes the risk of cell damage from the intense laser impulses and attachment of gold nanoparticles to the cell surface, however there are various strategies like using immobilized gold nanostars on activated bottom microplates and2-D plasmonic nano lithographic structures are proved to be effective than laser transfection with gold nanoparticles.

Gold nanoparticles are injected and accumulated thanks to their sensible biocompatibility. They can deliver drugs effectively to a specific location and interact with immune system and larger cells like macrophages is safe and biocompatible. The interaction with B-cells chiefly depends on the surface and shape of nanoparticles. Spherical gold particles polymer coated are stable and do not interact with B-cells while rod shaped are not stable because they are heavy and interact with immune system. The uncoated spherical gold nanoparticles can form clumps. B-cells used as target for drugs to treat cancer they are additionally utilized in treatment of brain cancer due to their smaller size. The gold nanoparticles are injected into the body and moved towards the tumor. B cells plays a vital role in control inflammation and cancer cells.

Due to their great biocompatibility, non-cytotoxic and controlled biodistribution patterns gold nanoparticles are ideal candidates for various innovative therapies. Their configuration plays a critical role in the interaction with immune system. The gold nanoparticles have varied blessings like anti oxidative, anticorrosive, bacteriostatic properties proved necessary in medical treatments and innovative therapies. Patients has booming cancer treatment and are cancer free after one year from the treatment by victimization gold nanoparticles because it has negative aspect result, safe and nontoxic.

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