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A STRATEGIC REVIEW ON METAL NANOPARTICLES AND ITS THERANOSTICS APPLICATIONS

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ABSTRACT

In the last decade nanotechnology have greatly developed in many research fields such as engineering, electronic, biological and many others. Of which, the majority of its applications are carried out in the medical field, and is constantly looking for new and improved treatments for diseases, which has to be highly efficient and cost-effective. Cancer remains as one of the most deadly diseases worldwide, and the existing anticancer therapies come with several drawbacks. Therefore, there is a need to develop new anticancer strategies. Theranostics is a strategy that is a combination of treatment with diagnosis and monitoring. One important aspect of any treatment is the ability to be able to target only the illness and not cause any harm to another healthy part of the body. For this reason, metal nanoparticles are proposed as one of the most promising theranostic agents for the treatment of cancer. Thus, metallic nanoparticles including iron (Fe), gold (Au), silver (Ag), zinc (Zn), and titanium (Ti), have potential as anticancer agents, either inherently or as a result of surface modifications. As a functional component of theranostic tools, metal nanoparticles have crucial dual roles as a diagnostic and active therapeutic agent for the treatment of cancer. Here we give a brief literature review on various metallic nanoparticles and how they help in diagnosing and the treatment of cancer.

Keywords: Theranostics, Cancer, Metallic Nanoparticles.

INTRODUCTION

Metallic nanoparticles have fascinated scientists for over a century and are now heavily utilized in biomedical sciences and engineering. Metal nanoparticles are of great interest due to their unique physical and chemical properties. Although there is still much to be known about the long-term safety of metal nanoparticlesin medicine, they have already found their place within various biomedical applications such as site-specific imaging in vivo, cancer detection, cancer therapy, neurodegenerative disease therapy, HIV/AIDS therapy, ocular disease therapy , and respiratory disease therapy. Despite the recent advances innanomedicine, there are still many obstacles in the way of nano-therapy, such asit can be hard to achieve a synthesis route which produces easily repeatable results, with many nanoparticle synthesis methods producing a range in both size and shape of nanoparticles and/or do not produce the nonmaterial's in a large enough quantity to make it economically viable. Another key factor is that it is relatively unknown about the long-term toxicity of some nanoparticles over a period of time. Among the many possible uses of metal nanoparticles lies the area of drug delivery. Due to the large surface area that nanoparticles provide, they possess the ability to be able to deliver large quantities of drugs or other medical cargoes. An alternative to single metal nanoparticles is to incorporate a core to the nanoparticle which has alternative properties to the shell material, and one example of this is to incorporate a magnetic core.

Today these materials can be synthesized and modified with various chemical functional groups which allow them to be conjugated with antibodies, ligands, peptides and drugs of interest and thus opening a wide range of potential applications. Moreover, various imaging modalities have been developed over a period of time such as MRI, CT, PET, ultrasound, SERS, and optical imaging as an aid to image various disease states. These imaging modalities differ in both techniques and instrumentation and more importantly require a contrast agent with unique physicochemical properties. This led to the invention of various nanoparticulate contrast agents such as magnetic nanoparticles (Fe3O4), gold, and silver nanoparticles for their application in these imaging modalities.

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BIO-MEDICAL APPLICATIONS OF METALLIC NANOPARTICLES

ANTIMICROBIALAGENTS

Since the discovery of penicillin, bacterial infections were very common. Nan medicine provides us with a new, broad range of possible treatment modalities, with metal nanoparticles being explored for future treatments [Bao *et al.,* 2013]. One material that has been examined for its potential use is silver, which has shown to have a variety of biomedical uses [Rai *et al.,* 2014], for example, Sreekumar et al. utilized silver nanoparticles as part of a network of antimicrobial fibers. The nanoparticles varied in size from 20 to 120 nm, with an antibacterial efficacy against Escherichia coli as high as 94.3% compared to the fibers without silver nanoparticles [Sreekumar *et al.,* 2019]. While it has been shown that an antibiotic such as ampicillin is capable at achieving a kill rate of ≤ 99.9% in E. coli [White et al., 1989], the same study also reported the emergence of resistance to ampicillin in certain strains of E.coli. Also employing silver for its antibacterial properties, Holtz et al. designed a system of 60-nm silver van date nano wires 'decorated' with silver nanoparticles with a diameter of 1–20 nm [Holtz *et al.,* 2010]. This system showed to be promising against three Staphylococcusaureus strains and also interesting lyhada much lower growth inhibiting concentration against methicillin-resistant Staphylococcusaureus (MRSA) than the antibiotic coxacillin. In a similar manner, gold nanoparticles have been reported to have an antimicrobial effect on Corynebacterium pseudo tuberculosis [Mohamed *et al.,* 2017], nanoparticles with an average size of 25 nm, using a dose of 50 µg/ml showed a bacterial growth inhibition of 95% after 20 min of exposure. Similarly, naked gold nanoparticles were shown to have an antimicrobial effect on a variety of gram negative and gram positive bacteria including S. aureus, Klebsiella pneumonia, and Bacillus sub tilis [Shamaila *et al.,* 2016]. A dose of 1.35 µg/ml of AuNPs showed a growth inhibition of

46.4±0.4%, 38.3±0.2%, and 57.8±0.2% for S. aureus, K. pneumonia, and B. sub tilis, respectively.

TYPE OF NANOPARTICLE	SIZE (NM)	ANTIMICROBIAL APPLICATION	MECHANISM OF ACTION
Silver as part of network of fibers	20-120	E.coli	Bacterial growth inhibition
Silver vanadate nanowires	1-20	S.aureus	Bacterial growth inhibition
Naked silver	10-25	C.albicans, P.fluorescens, E.coli	Bacterial growth inhibition
Thioguanine-capped gold	3-4	E.coli, A.fumigatus, P.aeruginosa, and anticancer effect against Hep2	Bacterial growth inhibition, cellular toxicity
Naked gold	25	C.pseudotuberculosis	Vacuole formation in cell wall and agglomeration of NPs within cells
Naked gold	6-40	S.aureus, K.pneumonia, B.subtilis	Bacterial growth inhibition

Table 1: List of antibacterial properties that have been exhibited by some metal nanoparticles and metal nanoparticle conjugates.

ANTIVIRALAGENTS

As with antibacterial applications, metal nanoparticles have shown to be promising in antiviral applications. Both naked and coated silver nanoparticles have been shown to have a range of antiviral applications when in the nano-scale range. Hepatitis B (HBV) is a viral infection that currently affects 257 million people around the world and was responsible for 887,000 deaths in 2015 according to the World Health Organization. Small (10–50 nm) naked silver nanoparticles have been tested as a possible treatment for HBV [8] and were shown to bind efficiently to HBV and further inhibit the production of HBV RNA. The mode of action is hypothesized to be due to the AgNPs binding to the HBV ds DNA (double-stranded DNA). Rogers et al. have demonstrated use for silver nanoparticles, both naked and with a polysaccharide coating as an antiviral agent against monkey pox virus (MPV) [Rogers *et al.,* 2008]. The nanoparticles were tested in vitro against MPV at a range of concentrations between 12.5–100 µg/ml; the results of the study showed that all of the concentrations of polysaccharide-coated silver nanoparticles (Ag-PS-NPs) used were able to reduce MPV-induced plaque formations invitro. Silver nanoparticles may even have a role to play in the treatment of human immunodeficiency virus (HIV) [Lara *et al.,* 2010; Lara *et al.,* 2010]. Lara et al. have demonstrated the effect of silver nanoparticles (30–50 nm) on HIV-1 isolates showing inhibition of all strains of HIV-1 isolates [Lara *et al.,* 2010]. Copper-iodide nanoparticles (CuI-NPs) have been shown to have antiviral properties on several different viruses: feline calicivirus (FCV) [Shionoiri *et al.,* 2012] and more interestingly influenza A virus of swine-origin (H1N1) [Fujimori *et al.,* 2012]. Copper-iodide nanoparticles (CuI-NPs) have been shown to have antiviral properties on several different viruses: feline calicivirus (FCV) [Shionoiri *et al.,* 2012] and more interestingly influenza A virus of swine origin (H1N1) [Fujimori *et al.,* 2012]. One hundred to 400 nm CuI-NPs showed an antiviral property when utilized against FCV, and it was hypothesized that monovalent Cu ions were responsible for the production of are active oxygen species (ROS) that caused subsequent capsid protein oxidation, leading to FCV inactivation. H1N1 virus was also shown to be inhibited by CuI-NPs, in a very similar manner, namely the production of hydroxyl radicals, leading to protein degradation. However, these radicals might also prove to be toxic to non-infected tissues, which would be important to determine before a treatment would be approved for use [Halliwell and Gutteridge, 1984].

TYPE OF NANOPARTICLE	SIZE (NM)	ANTIVIRAL APPLICATION	MECHANISM OF ACTION
AgNPs	10-50	Hpetitis B virus(HBV)	Interaction with DNA and/or binding with virus particles
Ag-PS-NPs	10-50	Monkey pox virus(MPV)	Blocking of virus-host cell binding and penetration
PVP-AgNPs	30-50	Human immunodeficiency virus type 1 (HIV-1)	Prevention of HIV-1 transfection
Au-MES	4	Herpes simplex virus type 1 (HSV-1)	Competition with host cell binding
Gold coated with an amphiphilic sulfate ligand	2	Human immunodeficiency virus type 1 (HIV-1)	Binding to gp 120
Copper iodide (CuI) nanoparticles	100-400	Feline calcivirus (FCV)	ROS generation and subsequent capsid protein oxidation
Copper iodide (CuI) nanoparticles	160	Influenza A of swine origin (H1N1)	Generation of hydroxyl radicals and degradation of viral proteins

Table 2: Some of the metal nanoparticles and metal nanoparticle conjugates that have been demonstrated as having antiviral properties.

IMAGING

Magnetic resonance imaging (MRI) scanning is a very useful tool for medical diagnosis and provides clear anatomical images. Using MRI, one can visualize the blood flow, physicochemical traits, and the states of tissues and organs in the body. Contrast agents are often employed in MRI for improved diagnostic sensitivity. Conventionally used contrast agents are chelate-based, but the major drawbacks of current contrast agents are their biological stability and their toxicity levels when accumulated in cells [Murphy *et al.,* 1996]. Alternatives have been developed to provide an improved scanning efficacy by reducing the negative impact contrast agents can have on the body. Alternatives include metal nanoparticles possibly conjugated with an agent which acts similarly to a contrast agent for MRI scanning[Lee *et al.,* 2005]. Li et al. have demonstrated the use of coated AuNPs as an imaging tool for atherosclerosis; the AuNPs were applied in a type of medical imaging called “single-photon emission computed tomography” (SPECT).The modified nanoparticles specifically targeted atherosclerosis plaques containing apoptotic macrophages, indicating a useful tool for invasively accurate detection of atherosclerosis plaques. AuNPs have previously been demonstrated to be a possible agent for photo acoustic imaging (PA), showing high spatial resolution and sensitivity. AuNPs are potentially better than organic dyes due to the organic dyes’ susceptibility to photo-bleaching and rapid clearing from the blood . AuNPs also have been used in cell imaging for examining the movement of nanoparticles within cells when conjugated with various cargoes.

TYPE OF NANOPARTICLE	SIZE(nm)	SCANNING TYPE
PEG-AuNPs	3-8	CT
Modified AuNPs	17-23	SPEC/CT
AuNPs	130-147	PA
AuNPs with citraconic amide moieties	10	PA
AuNPs in combination with radiotherapy	25	Dual energy/ CT

Table 3: Some examples of metal nanoparticles and metal nanoparticle-conjugates that have been investigated for their use in medical imaging.

BIOMEDICAL CARGO DELIVERY

Nanoparticles make for an ideal molecule for drug delivery due to the huge surface area to the volume ratio they provide when compared to their bulk material [Blasiak *et al.,* 2013]. Also, it is possible to engineer nanoparticles to either avoid or interact with the immune system in specific ways [Buzea *et al.,* 2007; Moyano *et al.,* 2012]. Gold nanoparticles have been extensively studied for their delivery of medical cargo, for example, Bhumkar et al. have explored the application of AuNPs for transmucosal delivery of insulin. Gold nanoparticles were synthesized in the presence of chitosan, which acts as a polymeric stabilizer. These nanoparticles were then loaded with insulin and administered both nasally and orally to diabetic rats. The results showed an overall reduction in the rat's blood glucose levels, an indication of the successful movement of the nanoparticles through the mucosal membranes and into the bloodstream. More recently "smart" AuNPs have been employed in PA. These nanoparticles are roughly 10 nm in diameter and are functionalized with citraconic amide moieties which are susceptible to hydrolysis. The citraconic amides are converted into positively charged primary amino acids at a mildly acidic pH, while the surface molecules adopt negative charges at physiological pH Combined, these two properties cause the "smart" nanoparticles to adopt both positive and negative charges allowing them to aggregate rapidly due to electrostatic attraction. These nanoparticles are referred to as "smart" due to the nanoparticles presenting cancer-specific properties and accumulate rapidly and efficiently in cancer tissues and show a much lower accumulation in normal tissues. Gold nanoparticles can also be used as a delivery system for nucleic acids, including oligonucleotides and small interfering RNA (siRNA). Sandström et al. demonstrated the ability to bind nucleic acids onto gold nanoparticles [Boraschi and, Duschl, 2013], and a similar modification has been done by Rosi et al. where tetrathiol-modified antisense oligonucleotides were bound to 13-nm gold nanoparticles. Being able to conjugate nucleic acids to nanoparticles opens up the possibility of targeted gene delivery, which could, for example, lead to genes coding for a specific protein to be delivered to a cell that was either deficient in that protein or could not produce the protein themselves. It has also been exhibited that gold nanoparticles modified with DNA can transfect cancer cells.

TYPE OF NANOPARTICLE	SIZE (NM)	MEDICAL DELIVERY APPLICATION
Chitosan stabilized AuNPs	10-50	Delivery of insulin across transmucosal membranes
AuNPs conjugated to an oligonucleotide modified with thiol groups	10-20	Delivery of nucleic acids as a potential for gene therapy
AuNPs conjugated to antisense oligonucleotide modified with tetra-thiol groups	13	Delivery of nucleic acids as a potential for gene therapy

Table 4: A range of nanoparticle conjugates that have been examined for medical delivery of cargos.

ANTICANCER DRUG DELIVERY

Cancer is one of the world's leading killers with large areas of scientific research being dedicated to the fight against cancer, and nanoparticles offer a new doorway into methods to target and treat cancer. Paciotti et al. have investigated the application of PEGylated AuNPs as a carrier for tumour necrosis factor (TNF) which is a cell-signaling protein that possesses the ability to induce apoptosis in healthy cells [Sandström *et al.,* 2003]. The Au-PEG-TNF nanoparticles were injected intravenously and agglomerated significantly more in MC-38 colon carcinoma cells compared to other healthy cells/tissues. The TNF not only gave therapeutic action on the MC- 38 cells but also seemed to possess a targeting property, indicated by the lack of agglomeration in healthy cells. Another interesting observation reported was the ability for the Au-PEG-TNF nanoparticles to diminish a tumor mass compared to "free" TNF. Doxorubicin is a widely used cancer therapeutic agent but has dose-limiting associations with cardio toxicity. A gold nanoparticle-doxorubicin conjugate has been developed that demonstrates little no to cardio toxicity to mice while being able to treat cancer [Paciotti *et al.,* 2014]. Dixit et al. demonstrated the selective delivery of folic acid-coated AuNPs into folate receptor (FR) positive cancer cells, whereas when compared with a cell line that did not have folate receptors, uptake was shown to be minimal [Dixit *et al.,* 2006]. These results demonstrated the use of folate to target metal nanoparticles to FR-positive cancer cells for tumor imaging and ablation.

TYPE OF NANOPARTICLE	SIZE (NM)	MEDICAL DELIVERY APPLICATION
PEGylated AuNPs conjugated with TNF	30-34	Delivery of TNF to cancer cells targeted by itself, TNF induces cell apoptosis
AuNPs conjugated with folic acid using a PEG linker	10	Delivery of folic acid (vitamin B9), a precursor for nucleic acid production
AuNPs loaded with doxorubin	30-40	Delivery of doxorubin-loaded gold nanoparticles for tumor targeting /therapy
AuNPs coated with a tumor specific uptake peptide	25-40	Drug delivery of lymphoma cells with gold nanoparticles conjugated with cellular uptake peptides specific to lymphoma cells

Table 5: A range of nanoparticle conjugates that have been examined for anticancer therapy.

Conclusion

The properties which are unique to metallic nanomaterials have been identified and utilized for specific studies that are relevant in the field of nanomedicine. Among the metallic nanomaterials, gold, silver, iron oxide, platinum, gadolinium and palladium nanoparticles have shown the maximum areas of proven anticancer theranostic applications. Some applications are made by combining the metallic nanoparticles in the form of alloys and bimetallic modes. It is essential to test nanoparticle- biological interactions experimentally in a clinical setting and modify the nanoparticles for best biocompatibility with the cell to eliminate any chances of damage to healthy tissue, guarding against alterations in genetic or molecular function while killing the abnormal cells. Thus, this short literature review gives an idea about the applications of bio-metallic nanoparticles.

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