ROLE OF NANOTECHNOLOGY IN CANCER

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1. Background of Nanotechnology

Nanotechnology is a technology that deals with dimensions and tolerances of less than 100 nanometres, especially the manipulation of individual atoms and molecules. The word Nano came from the Latin word “dwarf” which means small. Basically, nanoparticles are used in drug delivery with the size of 100-200nm (Poon, Kingston, Ouyang, Ngo, & Chan, 2020). It is also important to know that the nanoparticle behaves as a chemical as well as the physical agent that effects on the target tissue or organs of the body (Zolnik & Sadrieh, 2009).

2. Nanoparticles

Nanoparticles are belonged to nanoscience that deals with the chemistry, biology, medicine, engineering, and chemistry etc. So, it is the swift advancing discipline and continuously attracting interest from the researchers across the world. Furthermore, they are being used in various industries such as environmental remediation, textile, catalysis, cosmetics, and pharmaceuticals (Emerich & Thanos, 2003).

3. Synthesis Approaches of Nanoparticles

Nanofabrication employs both top-down and bottom-up methodologies **(Figure 1).** The bottom-up strategy is preferable to the top-down strategy because it has a higher likelihood of developing nanostructures with fewer flaws, a more homogeneous chemical composition, and better short- and long-range ordering. According to a bottom-up synthesis process, crystal planes are formed by stacking atoms on top of one another, and these crystal planes are then stacked on top of one another to form the nanostructures on the substrate. Thus, the building blocks are added to the substrate to create the nanostructures in a bottom-up fashion, which can be thought of as a synthesis method (Ariga, Hill, & Ji, 2007). According to a top-down synthesis process, crystal planes that are already existent on the substrate are removed in order to create the nanostructures. Thus, a top-down technique can be thought of as a method where the components of the nanostructure are taken out of the substrate (Biswas et al., 2012).

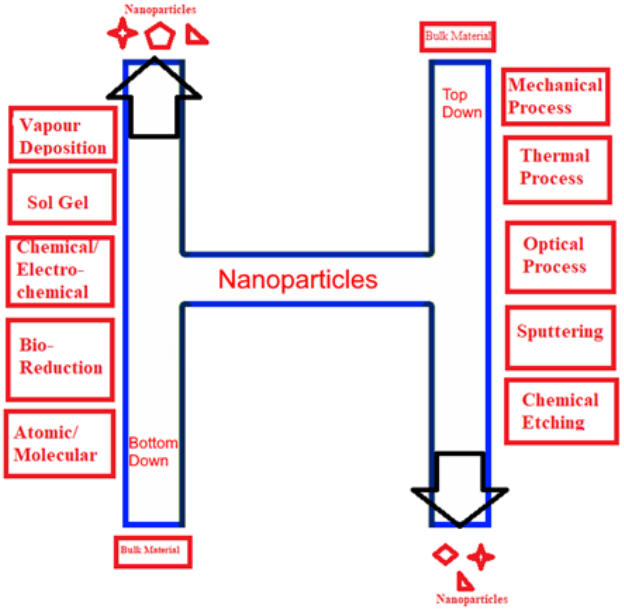

Figure 1. Top-down and bottom-up methods for nanofabrication (Bayda, Adeel, Tuccinardi, Cordani, & Rizzolio, 2019)

4. Types of Nanoparticles

There are many types of nanoparticles (Sircar, Rayavarapu, Bist, Yadav, & Singh, 2021) that have role to treat different cancers via various mechanisms. The classification of nanoparticles has been discussed in the **Figure 2** (Sircar et al., 2021).

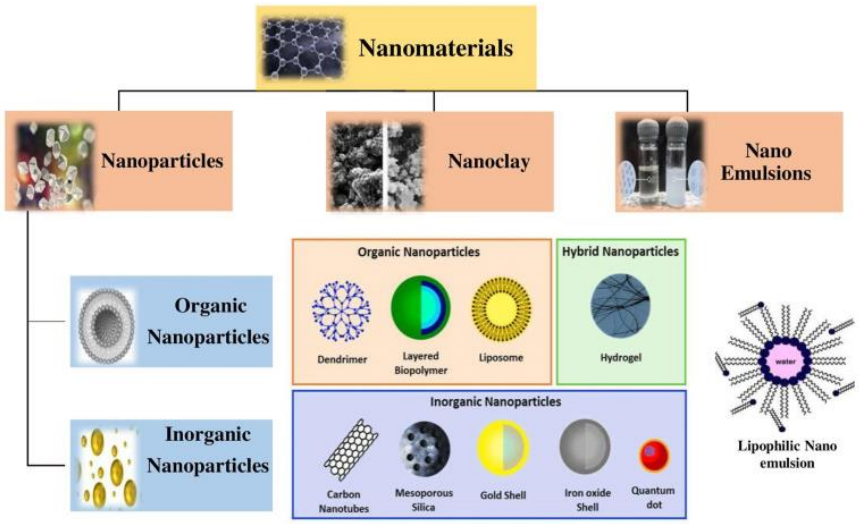

Figure 2. Classification of various nanoparticles (Mageswari, Srinivasan, Subramanian, Ramesh, & Gothandam, 2016; Sircar et al., 2021)

4.1. Carbon Nanotubes

Carbon nanotubes are the third allotropic crystalline form of the carbon sheet. These crystals have electrical properties. The diameter typically varies in the range 0.4-40 nm, but the length can be from 0.14 nm to 55.5 cm. They enhance the solubility and increase the penetration to

the nucleus as the carrier for the gene and peptide delivery. They have been widely used in the cancer diagnosis and therapeutics due to its physiochemical properties (Ji et al., 2010).

4.2. Nanocrystals Quantum Dots

Nanocrystals Quantum dots, a semiconducting material have been synthesized by II-VI and III-V column. They occupy the small space that is closely related to atoms due to their small size (2-9.5 nm). They have also been used in the (Tang, Huang, He, Ma, & Wang, 2020).

4.3. Solid Lipid Nanoparticles

Solid lipid nanoparticles vary in size, made up of spherical solid and lipid particles; dispersed in the aqueous solution. These nanoparticles have been used in a wide range of diagnostic and therapeutic implications. Tumor targeting has been achieved with the combination of solid nanoparticles with other drugs such as methotrexate, camptothecin, and tamoxifen (Hashem, Nasr, Khairy, & technology, 2014).

4.4. Polymeric Nanoparticles

These nanoparticles are made up of solid particles, which can be present as synthetic or semi-synthetic polymers. They are 10-1000 nm in size. They have been used in the food industry as well as in the treatment of cancer (Begines et al., 2020).

4.5. Functional Nanocarriers

Functional nanocarriers are made up of protein, enzymes, and peptides. These nanocarriers are the backbone of medical fields as it has a significant role in drug delivery system. These nanocarriers could be delivered the drug to the specific point thus enhancing its specificity and efficiency (Mejía, Sánchez, Vásquez, & Orozco, 2021). Therapeutic agents or drugs are loaded into the matrix (linked to the core surface) of functional nanocarriers either during or after synthesis of such nanocarriers which increases the efficiency of drug delivery to the targeted organs (Zhang, Jin, & Stenzel, 2021).

4.6. Magnetic Nanoparticles

Magnetic nanoparticles have a small size, large surface area and strong magnetic response towards therapeutic agents (Li, Li, Wang, & Liao, 2021). These nanoparticles have been used in the oncology field as the drug carrier by binding with other antibodies, chemotherapeutic medicines and drugs (Khizar et al., 2021). These nanoparticles have also been used in the photothermal therapy (PTT) (Wang & Hou, 2021) and photodynamic therapy (PDT) (M.-H. Lee et al., 2021).

4.7. Silver Nanoparticles

Silver nanoparticles are widely used in the paints, clothing and medical devices due to their specific antimicrobial activities (Safdar et al., 2019). These nanoparticles have also been used in DNA sequencing and surface-enhanced Raman scattering (Vo-Dinh, Yan, Wabuyele, Brillouin, & Scattering, 2005).

4.8. Gold Nanoparticles

Gold has 79 atomic number and its symbol is Au. The synthesized gold nanoparticles (AuNPs)

are present from vibrant red to pale blue in color due to different size and resonance of light. They are divided into various types on the basis of their size and shape. They range in size from 0.02 nm to 100 nm that have a high surface to volume ratio. These nanoparticles have been designed to treat many harmful diseases such as cancer. The conventional therapies such as chemotherapy not only destroy the cancer cells but also affects the other cells or tissues of the body such as liver, kidney, and spleen (Arshad et al., 2019). Conversely, these nanoparticles may only kill the cancer cells and do not have any significant adverse effect on other tissues of the body (Safdar, Ozaslan, Junejo, Channa, & Sciences, 2021).

For instance, the newly developed AuNPs injected into the patient and after injection, these nanoparticles selectively infiltrated cancerous cells as they are very small in size so that they could easily enter inside the cell where the cancer transcripts are present. When the patient with AuNPs was treated with the short laser pulses, nanoparticles heated up and evaporated the water inside the cancer cell which created very small water bubbles inside the cancer cells. These small bubbles expanded rapidly and burst and ripped cancer cell apart. Because the gold did not react with the oxygen and it moved via the bloodstream and the blood enter into the kidney where it filtered and, in the heart, where it carried out oxygen and sent it to the major organs such as liver and muscles (Arshad et al., 2019).

These AuNPs have widely been used in the medicine and industries, but the safety of the NPs exposure remains unclear. They are used in the laboratory for the purpose of the tracer in the process of DNA fingerprinting for the detection of the DNA sequence in the sample. In a study, it was evaluated that the liver, brain, heart and kidney and other tissues. They were examined for the effects and unclear mechanism of AuNPs using mice models (Arshad et al., 2019). Their results showed that the NPs distributed via blood and accumulated in the major organs such as heart, kidney, and other tissues. Additionally, it depicted that the excess dose of the NPs was damaged the functions of kidney and liver. After further analysis, they showed the irregular function of mitochondria that led to necrosis and apoptosis of the hepatocytes due to production of the reactive oxygen species and the disorder of the expression of the genes (p53, caspases 2, 3, 8, 9,) in the various organs of mice such as liver and kidney (Arshad et al., 2019). The scientists believe that the size of the AuNPs play important role in the toxicity of the NPs. The large size of the nanoparticles accumulates in the membrane and do not cross the membrane and so they showed hepatotoxicity. Actually, they have particular physicochemical properties including the surface Plasmon resonance and could form the bond with the thiol groups allowing surface modification and use in the many other applications especially biomedical applications (Arshad et al., 2019; Safdar et al., 2021; M. SAFDAR & M. J. Z. B. S. ÖZASLAN).

In a study, the AuNPs demonstrated a successful treatment of various deadly disease (Arshad et al., 2019; Safdar et al., 2021; M. SAFDAR & M. J. Z. B. S. ÖZASLAN) and showed the ability to combine with the other proteins and peptides. Actually, these nanoparticles attached with the specific ligands that interact with other compounds to treat such diseases (McNeil, 2005).

In addition, the AuNPs play a vital role to stop the false DNA replication and these particles intercalate in the groove of DNA and induced cell death in the cancer cell. They also produce the change in the membrane of the cell and cause the cell death or the apoptosis. It is classified

into two pathways; extrinsic and intrinsic and, both are caspase-dependent. In this process, three signaling cascades are reported and these signaling pathways activate the caspases. They trigger the extrinsic and intrinsic pathways so the oxidative stress paradox of the nanoparticle induces cell death. Due to high potency of the AuNPs, they induce lysosomal membrane destabilization and destroy the cancer cells. Another way of killing cancer cells is autophagy. In this process they produce oxidative stress that is caused by the accumulation of the damaged proteins and mitochondrial stress (Safdar et al., 2021).

5. Functional AuNPs

Surface properties of the AuNPs play a vital to identify their bonding with the biological system and these bonding indicate the toxicity of the AuNPs (Carnovale, Bryant, Shukla, & Bansal, 2019). Some scientists investigated that the toxic effect of the AuNPs associated with the anionic and cationic side chain in the kidney of monkey. They evaluated the properties of cationic and anionic nanoparticles and found that they are equally toxic (Mironava, Hadjiargyrou, Simon, Jurukovski, & Rafailovich, 2010). Another parameter is the surface hydrophobicity. It is examined by Chompoosor and their colleagues. They investigated the toxicity of the gold nanoparticle with the hydrophobicity of the surface ligands that induced higher cytotoxicity in the cells (Srijampa et al., 2020).

6. Biomedical Applications of the AuNPs

Due to the biological modification and optical properties, AuNPs are being used for the biomedical applications. The SPR effect is sensitive to the dielectric environment so any change in the environment (aggregation and refracting index of the medium) leads the shift of SPR band and such property is used for the huge range of the biomedical applications (K.-S. Lee & El-Sayed, 2006).

7. Cancer

It is a group of diseases that are characterized by the invasive abnormal growth of the cell. The origin of the cancer word was described by the Greek physician Hippocrates and he described a tumor as a karkinos and karkinona. Galen described that a tumor was similar to the legs of a crab and that was the reason the name of the disease karkinos (cancer) which meant crab in Greek (Iavazzo, Trompoukis, Siempos, & Falagas, 2009).

In 2008 about 12.7 million cancer cases were diagnosed with the deaths of 7.6 million globally. In the UK 325,000 people were found with cancer in 2010. Many women feel that stress and anxiety caused them to be diagnosed with breast cancer. Because there has been no clear proof of a link between stress and a higher risk of breast cancer, researchers in the United Kingdom conducted a large prospective study on the issue and they are trying to find the exact link of the cause.

8. Cancer and Nanotechnology

Cancer and nanotechnology are one of the newest fields on which researchers are keeping work on the treatment of cancer that involve primarily its detection, diagnosis, and treatment of cancer. This technology is intersected with the chemistry, biology medicine and the engineering (Roco, 2003). In cancer, nanotechnology-based fluorescence is used to detect the tumor cells.

The quantum dots named semiconductors are also developed that regulate the limitations of organic dyes and also improve optical qualities which were important for the applications of biological methods and decrease the limitations of the organic dyes.

9. Nanomedicine

Recently, some nanomedicine products are available in the market which is used to optimize the nano-sized devices that have been used to deliver drugs. This industry is flourishing from the past few decades. These nano size devices having a high demand in the clinical trials (Safdar et al., 2021). These nano-resonance imaging and tracking of the cell are exploited by the magnetic nanoparticles (Khizar et al., 2021). It showed metastasis in the tumor cells. Therefore, the fluorescence probes in the biomolecular and cellular imaging are the significant use of the nanomaterials for the imaging applications regarding the labeling of cells.

10. Role of Mitochondria and Nanomedicine

The role of the mitochondria is a vital role in the cell life. It controls cellular parameters such as the modulation of the redox status, maintenance of the calcium homeostasis and energy production. The effects of nanoparticles may improve the dysfunctional of mitochondria that cause many chronic diseases such as multifactorial cancer. It may be a great opportunity in the field of biomedicine in the next few years.

11. Mitochondria Role and Cell Death

The pro-apoptotic factors such as cytochrome c and caspases are located in the mitochondrial intermembrane space. In the apoptotic stimuli, pores are formed in the outer membrane of the mitochondrial membrane and it gets permeabilization in the outer membrane of the mitochondria. This event is known as the “point of no return” cell death. It releases particular proteins from the cytosol. These proteins such as cytochrome c and second mitochondria-derived activators of the caspase inhibitor of the apoptotic–binding protein starts the cell death through the activation of the caspases.

Caspases play a vital role in the apoptotic responses to cell death. There are 11 human caspases that are identified till now and only 7 caspases are responsible for the apoptotic process. There are four caspases (2, 8, 9, 10) that are initiators caspases while others (caspase 3, 8, 7) are effectors.

In the normal cells (non-tumor), caspases are zymogens or catalytically inactive. For the activation of the caspases, the proteolytic activity is important. In the apoptosis, stimuli activates the auto-activated initiator caspases which further activates the effector caspases through the breakage or the cleavage at the aspartate residues between the large (p20) and small (p10) subunits and these two subunits are attached by forming the caspase monomers (Riedl & Shi, 2004).

For the activation of caspase, multi-component complex is required. A particular protein such as cytochrome c releases into the cytosol and forms this complex called apoptosome with the dATP, APAF1, and initiator caspase 9 that activates caspase 9 (Riedl & Shi, 2004). After the activation of the initiator caspases, the effector caspases proteolytically cleaved and following factors has developed such as blabbing of the membrane, phosphatidylserine, and condensation

of chromatin happens (Riedl & Shi, 2004).

12. Anti-Apoptotic Family

Anti-apoptotic family include Bcl-2, Bcl-w, Bcl-x that are responsible for the inhibition of the multi-component complex (MOMP) and release the cytochrome c for apoptosis and cell death (Suk, 2005).

13. Pro-Apoptotic Family

Pro-apoptotic family include Bax and Bax that are responsible for the initiating of the mitochondrial apoptotic pathway. These proteins are found in the cytosol (Suk, 2005).

Apoptotic molecules such as Smac/DIABLO, apoptosis-inducing factors (AIF) and endonuclease G (EndoG) are released from the intermembrane of the mitochondria and cause the cell death through the various ways. The release of the cytochrome c activates the caspase cascade and as result apoptosis occurs. Htra2/Omi and Smac/DIABLO stop the inhibitors of the apoptosis and EndoG and AIF enters into the nucleus and damages the nuclear DNA (Suk, 2005).

14. Advantages of Nanoparticles

Nanoparticles have various advantages such as followings

(a) They can only bind to the specific ligand and target specific cells.
(b) To improve the stability and therapeutic index.
(c) To minimize the toxic effects.
(d) They can be administered by the nasal, oral and ocular routes.
(e) They have active and passive drug targeting pathways.
(f) Their pathways can be done by the manipulating after changing their particle size and the surface characteristics.

15. Disadvantages of the Nanoparticles

Despite of many advantages, these nanoparticles have few drawbacks such as followings.

(a) Limited drug loading
(b) Small size
(c) Large surface area led to the aggregation of the particle

In addition, drawing conclusions from tests on healthy animal models may be unsuitable as some of the effects of nanoparticles may only be a risk for susceptible organisms and predisposed individuals, but not to healthy people. For instance, age, respiratory tract problems and other pollutants can modify the pulmonary inflammation and oxidative stress induced by nanoparticles.

16. Green and Non-Toxic Nanoparticles

Green synthesis of nanoparticles involves the use of non-toxic chemicals for the bio-reduction of metal ions into their elemental form in the size range 1-100 nm. They are required to avoid the production of unwanted or harmful by-products through the build-up of reliable, sustainable, and eco-friendly synthesis procedures. The use of ideal solvent systems and natural resources

(such as organic systems) is essential to achieve this goal (Arshad et al., 2019; Hashem et al., 2014; Safdar et al., 2021; M. SAFDAR & M. J. Z. B. S. ÖZASLAN; Safdar et al., 2019). The pathways and mechanisms of AuNPs has explained in **Figure 3** to inhibit breast cancer cells via green gold nanoparticles.

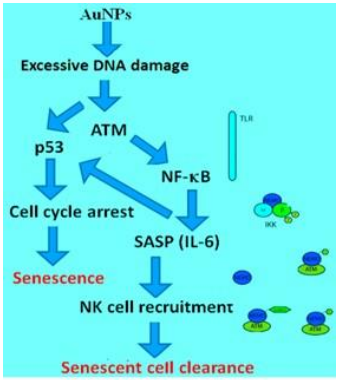

Figure 3. Pathways and mechanisms to inhibit breast cancer cells via AuNPs (M. Safdar & M. ÖZASLAN).

17. Limitations of Nanotechnology

Nanotechnology has a lot of potential to make new products and processes in the various fields, but there are a lot of problems. The main challenge is to make edible delivery systems in food and medicine that are cheap to make and that are safe for people to their health. It is very important to keep people safe by making green nanoparticles from packaging materials, it means they don't get into products. The nanomaterials that are added either directly or indirectly are sometimes left alone because they moved from other places. There is still a lot we don't know about how to analyse materials at the nanoscale, and the materials behave in completely different ways. The more we know about nanoscale functions and toxicities of nanomaterials, the more useful and safer they will be in the real world and in safety rules. The effects of nanoparticles, the risk they pose, and the toxicity issues and environmental concerns that come with them must be looked at. Nanoparticles have been reported to be able to get through the body's natural defences and into cells and organs. Synthesis of nanoparticles using different chemical methods can also have negative effects and produce harmful, non-ecofriendly byproducts that cause a lot of pollution in the environment. Because nano-based marketable products are becoming more popular and people want to eat them, they need to be processed, packaged, and eaten by humans in a way that takes into account safety, regulatory policy, biosafety, and public concerns. In addition, nanoparticle interactions with living things need to be studied in vitro and in vivo before they can be used in commercial products and for the production of antibacterial nanoparticles that are safe for the environment.

18. Future Prospective, and Recommendations of Nanotechnology

Nanotechnology helps with the detection of toxins, pathogens, and pesticides, as well as tracking–tracing–monitoring that can help keep body safe. Nanotechnology is not hampered by things like the lack of skilled workers, the high cost of analysis, or the need to buy high-tech equipment. However, some nanosystems are still in the early stages of development or are being

worked on to become powerful nanocomponents. Research can be done in the following areas for a wide range of applications. Safety and challenges can be taken into account at the same time.

Smart packaging is a new idea that can make antigen-specific biomarkers, and putting together nanoparticles to make nanocomposite polymer films that can slow the processes of breakdown of products, but extensive research is needed to fulfill this area.

Nanocomposites are biodegradable molecule, therefore, in the near future, they could be used to make food packaging material. In the meanwhile, Nanosilica could be used for commercial purposes in medical kits as it has better barrier properties.

Antigen-specific biomarkers can be used to detect pathogens, such as bacteria, viruses, and mycotoxins, quickly and accurately.

Use of nano-sensors in film packaging to detect gases that are released when our medicine or products are spoiled. This would benefit for producers, retailers, as well as consumers.

Nanomaterial based sensors can be used to cut the mechanisms of pathogens to overcome the drug resistance in various diseases.

Carbon nanotubes are also being used to make the sensors into packaging materials that are being used to detect microorganisms, toxic substances, and food spoilage but, extensive research is still needed.

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