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Review Article

Nanoparticles and Tumor Hypoxia: A Review

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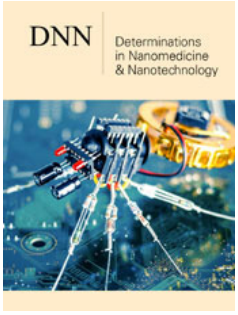
Abstract

Nanoparticles are microscopic particles with particle size less than 100nm and characterized by unique physical and chemical characters which allow it to have good biological activities and among these biological activities is their use in modulating the tumor hypoxia to enhance the radiotherapy and chemotherapy treatment outcome. Tumor hypoxia is one of the major characteristics of solid tumors and it arises from the inadequate blood supply for the rapidly proliferating cancer cells. Tumor hypoxia is a bad prognosis factor as it increases the aggressiveness of the tumor and increases it is resistance to the treatment that's why overcoming tumor hypoxia provide a great therapeutic benefits for the cancer patients. Hypoxia mediates it is effect mainly through hypoxia inducible factor 1 which causes drug resistance, metastasis, angiogenesis, metabolic shifting, radiotherapy resistance and overall tumor aggressiveness and poor prognosis. There is keen research working on the tumor hypoxia and trying to discover new drugs and approaches to correct the tumor hypoxia like manganese dioxide nanoparticles, sliver nanoparticles, other metal nanoparticles, prodrugs activated by hypoxia, hyperbaric oxygen, oral oxygen therapy and finally hypoxia inducible factors inhibitors like for example benzopyranyl 1,2,3-triazole, glyceollins and vorinostat.

Keywords: Nanoparticles; Nanomedicine; Tumor; Tumor hypoxia; Tumor microenvironment

Abbreviations: NPs: Nanoparticles; HIFs: Hypoxia Inducible Factors; VEGF: Vascular Endothelial Growth Factor; TCA: Tricarboxylic Acid; IGF-2: Insulin-Like Growth Factor 2; IL-6: Interleukin-6; MIF: Macrophage Migration Inhibitory Factor; EGFR: Epidermal Growth Factor Receptor; MMP1: Matrix Metalloprotease-1; OER: Oxygen Enhancement Ratio; IR: Ionizing Radiation; DSBs: Double-Strand Breaks; SSBs: Single-Strand Breaks; MDR: Multidrug Resistance; ABC: ATP-Binding Cassette; ROS: Reactive Oxygen Species; TME: Tumor Microenvironment; OsSx: Osmium nanoparticles; PEG: Poly Ethylene Glycol; MNPs: Metallic nanoparticles; HAPs: Hypoxia Activated Prodrugs; HBO: Hyperbaric Oxygen Treatment



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Introduction

Nanoparticles

Nanoparticles definition: Nanoparticles (NPs) is considered as a microscopic particle with a particle size range from 1-100nm and these particles have special and specific physical characters like optical activity and conductivity which allow them to play important role in biology and medicine [1]. Nanoparticles can be classified into different categories depending on size, morphology and chemical properties like carbon-based NPs, metal NPs, ceramics NPs, semiconductor NPs, polymeric NPs and lipid-based NPs [2].

Nanoparticles physical and chemical characters: Nanoparticles have unique characteristic physiochemical properties compared to the bulk materials and it is described as follow:

i. Size and surface area of the particles as the decreasing of the size of the particles increase it is surface area exponentially relative to the volume [3].

ii. Effect of particle shape and aspect ratio as different particle shapes have different aspect ratio and mor the aspect ratio the more the toxicity of the nanoparticles [4].

iii. Effect of the surface charge as surface charge paly major role in determining the particles toxicity as it determine it is action with the biological molecules like for example the plasma protein binding and hence the toxicity [5].

iv. Effect of composition and crystalline structure as the crystalline structure of the particles along with it is size determine the toxicity of the particles in the biological system [6].

v. Effect of aggregation and concentration, the aggregation of the particles depends mainly on the size and surface charge which will eventually affect the particle toxicity too [7].

vi. Effect of surface coating and surface roughness as particle surface play important role in determining the fate of the particle- cell interaction and hence the toxicity [8,9].

Tumor hypoxia

Hypoxia is very common in many of the solid tumors and the hypoxic tumor microenvironment is characterized by the increased level of Hypoxia Inducible Factors (HIFs) which are responsible for the tumor progression, chemotherapy and radiotherapy resistance, stimulated cell proliferation and the survival of cancer cells [10]. The uncontrolled tumor cell proliferation will cause the depletion of oxygen and nutrients from the normal vasculature surrounding the tumor cells and will eventually cause the cells to be hypoxic and starved. Finally, this hypoxic harsh condition will lead to the massive overproduction of the angiogenesis mediated factors from the hypoxic tumor sites, which in the end will cause the vascularization of the tumor mass [11]. Overall, tumor hypoxia will increase the cell proliferation, genetic instability, disease progression, cancer invasiveness and hinder the tumor response to cytotoxic and targeted therapies [12].

Effect of tumor hypoxia in disease prognosis

Tumor hypoxia and angiogenesis: Angiogenesis is a growth factor dependent process which is stimulated by hypoxia where new blood vessels are formed from the preexisting ones also angiogenesis is critical for tissue repair [13]. HIF-1 is one of the well-studied stimuli for inducing angiogenesis and the expression of several genes, including Vascular Endothelial Growth Factor (VEGF), in a variety of tissues [14]. VEGF is mostly associated with angiogenesis and vascular permeability [15]. HIF-1 stimulates VEGF and its receptor VEGF-R_2 expression in the endothelium, regulating an autocrine VEGF signaling loop that is critical for endothelial cell survival, proliferation, migration, and tube formation [16].

Tumor hypoxia and metabolism: Under hypoxic settings, HIF-1 has been found to directly regulate the genes of numerous enzymes involved in the cellular import and conversion of glucose, resulting in an increase in the cell's glycolytic activity (anaerobic glycolysis) [17]. This distinct metabolic profile confers numerous selective advantages to cancer cells, including adaptation to hypoxia, resistance to mitochondria-mediated apoptosis, and acidification of the tumor microenvironment, which leads to increased tumor invasion and metastasis [18]. HIF-1 stabilization has long been known to induce transcription of the pyruvate dehydrogenase kinase genes 1 and 3 and these kinases phosphorylate and inactivate the E1 subunit of pyruvate dehydrogenase, preventing pyruvate from entering the Tricarboxylic Acid (TCA) cycle and reducing mitochondrial oxygen consumption while increasing cellular pyruvate levels [19]. The stabilization of HIF-1 has been shown to cause a generic increase in transcript and protein levels for glycolytic enzymes to ensure adequate flux through the pathway, and it has been demonstrated that most glycolytic enzymes are inherently over-expressed in 70% of human cancers, with the most prevalent glucose transporter isoforms GLUT1 and GLUT3 expressed under hypoxic conditions [20].

Tumor hypoxia and acidosis: The glycolytic pathway implies excessive proton production, which, if retained within the cells, would result in fatal intracellular acidosis; however, malignant cells solve this problem by increasing proton transport mechanisms, which expel the excess acidity and this mechanism allows cancer cells to maintain a normal intracellular pH or even overshoot this mechanism, allowing for a slightly alkaline intracellular tensile strength. [21]. Clinical studies have revealed that tumors in an acidic environment have a worse prognosis and a higher metastatic incidence, as well as increased mutation rates and resistance to chemotherapy and radiotherapy [22].

Tumor hypoxia and cell proliferation: HIF-1 has been shown to stimulate the production of growth factors such as transforming growth factor (TGF-β), Insulin-Like Growth Factor 2 (IGF-2), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Macrophage Migration Inhibitory Factor (MIF), and growth factor receptors such as the Epidermal Growth Factor Receptor (EGFR), resulting in continuous proliferative signaling [23]. C-Myc is a cell cycle regulator and oncogene, and HIF-2 can increase c-Myc activity and promote cell cycle progression [24].

Tumor hypoxia and metastasis: It has previously been demonstrated that hypoxic cells are more aggressive and invasive, with a greater ability to metastasize [25]. Hypoxia facilitated HCC cell migration, invasion, and distant pulmonary metastasis [26]. Hypoxia/HIF-1 has previously been shown to regulate the expression of metalloproteases such as Matrix Metalloprotease-1 (MMP1) and MMP3 in order to promote metastasis [27]. Cancer cells could continue to redesign the vessels to gain access by secreting the HIF-1-regulated metalloproteinases MMP1 and MMP2 [28].

Tumor hypoxia and radio resistance: Cancerous cells can stay alive in hypoxic environments and play an essential part in cancer cell radioresistance [29]. Radioresistance manifests in oxygen <10mmHg and becomes maximal around 0.5mmHg [30]. The o_2 impact is frequently measured using the Oxygen Enhancement Ratio (OER), which is the ratio of dosage necessary to attain the very same biological effect under hypoxic and oxic circumstances [31]. Ionizing Radiation (IR) causes DNA Double-Strand Breaks (DSBs), DNA Single-Strand Breaks (SSBs), DNA base damage, and DNA–DNA and DNA–protein crosslinks under normoxic conditions (DPCs) [32] while inadequate amount of O_2 in the tumor cells environment may result in ionizing radiation–induced harm that can be fixed and normal cellular function regained [33].

Tumor hypoxia and chemotherapy resistance: Multidrug Resistance (MDR) is a primary cause of chemotherapy-based

therapeutic failure [34]. In response to hypoxia, HIF-1 can trigger the multidrug resistance 1 (MDR1) gene, which encodes for the membrane-resident P-glycoprotein (P-gp), which belongs to a group of ATP-Binding Cassette (ABC) transporters that can reduce the intracellular levels of a variety of chemotherapeutic agents [35]. Hypoxia can also produce chemoresistance by regulating the ATP-Binding Cassette subfamily G member 2 (ABCG2), which is one of the key multidrug-resistance transporters [36].

Tumor hypoxia as a therapy target

Nanoparticles: As previously discussed, we can conclude that tumor hypoxia is responsible for the bad prognosis of the tumors and responsible for therapy failure so correcting it by using nanoparticles could be considered as a successful strategy for fighting cancers so here in this section I'm going to list the nanoparticles used in correcting the tumor hypoxia.

a. **Manganese dioxide nanoparticles:** Hypoxia and high cancer cell proliferation generate an excess of Reactive Oxygen Species (ROS), such as hydrogen peroxide (H_2O_2), which increases mutagenesis, spread of cancer cells, angiogenesis, and resistance to treatments, all of which contribute to therapeutic failure [37]. The high reactivity of manganese dioxide nanoparticles (MnO_2 NPs) toward H_2O_2 allows for constant synthesis of O_2, pH modulation, and efficient cancer hypoxia reduction by targeted administration of MnO_2NPs to hypoxia [38]. MnO_2 nanoparticles are used for continuous and localized synthesis of molecular O_2 in cancers to alter the Tumor Microenvironment (TME) and improve radiation effectiveness, since the efficacy of radiation is significantly dependent on the relative level of oxygen in the cancer at the time of irradiation [39].

b. **Sliver nanoparticles:** Sliver nanoparticles (AgNPs) which has been used before as broad-spectrum antimicrobial agent and was found to act as anticancer agent as AgNPs act by inhibiting the function of HIF-1α in cells under hypoxic conditions, leading to the downregulation of VEGF-A and GLUT1 and inhibition of angiogenesis impaired glucose metabolism and thus cannot meet the energy demand of the tumor cells and eventually cause tumor cell death [40].

c. **Osmium-based nanoparticles:** Osmium Nanoparticles (OsSx) are considered as a new kind of nanomaterials with numerous applications. OsSx-PEG (PEG=Poly (Ethylene Glycol)) NPs a highly efficient catalytic was constructed from the osmium nanoparticles as a tool to modulate the tumor hypoxia by catalyzing the decomposition of the intratumor hydrogen peroxide (H_2O_2) into oxygen which will then sensitize the tumor cells to radiotherapy [41].

d. **Metallic nanoparticles:** Metallic nanoparticles (MNPs) like calcium, iron, cerium and copper nanoparticles can be used to alleviate the tumor hypoxia by generating intracellular oxygen be decomposing intracellular peroxides through catalytic reaction also these metallic nanoparticles are used to selectively delivering therapeutic loads into the tumor cells [42] (Figure 1).

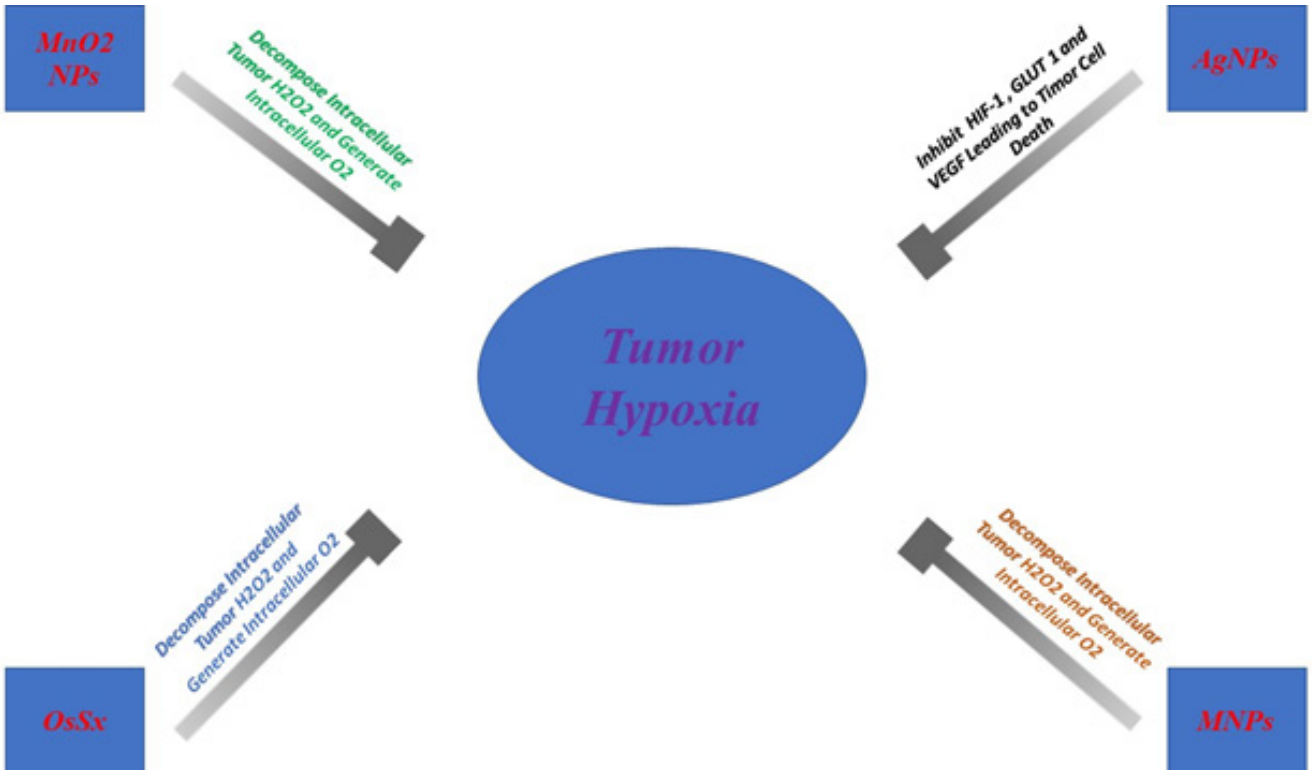

Figure 1: Role of nanoparticles in correction of tumor hypoxia.

Prodrugs activated by hypoxia: Cancer cell hypoxia is a primary cause of therapy failure in a wide range of cancers. Hypoxia, on the other hand, provides therapy prospects, as evidenced by the development of new drugs that address hypoxic areas within tumors [43]. The production of Hypoxia Activated Prodrugs (HAPs), which include chemical constituents that are metabolized by enzymatic reduction, is a potential technique for targeting hypoxic malignancies [44]. Hypoxia-activated prodrugs are deactivated or disguised cytotoxins that undergo biotransformation after reductive metabolism by intrinsic human cellular oxidoreductases, a mechanism that is normally blocked by O_2, hence conferring selectivity for the hypoxic tumor environment [45].

Hyperbaric oxygen: The use of oxygen under increased atmospheric pressure, that is, at a pressure greater than the pressure found on the earth's surface at sea level, which is defined as 1 atm, is known as Hyperbaric Oxygen Treatment (HBO) [46]. HBO therapy has been used for millennia to treat or alleviate illnesses involving hypoxia and ischemia by increasing the quantity of dissolved oxygen in the plasma and hence improving O_2 delivery to the cells [47]. HBO can raise the concentrations and pressure of oxygen in the blood, as well as the pace and distance of oxygen diffusion in tissues, reducing hypoxia and boosting oxygen levels in the cancer cells, resulting in improved susceptibility to chemo- and radiotherapy [48]. HBO coupled with sorafenib causes synergistic inhibitory effect on cell growth and death in hepatoma cells, indicating that HBO coupled with sorafenib might be used to treat HCC patients [48].

Oral oxygen therapy: Eble M [49] outlined the idea of oral oxygen treatment, indicating that oral administration of oxygen-enriched water enhanced the dissolved quantity of oxygen in blood in patients with head and neck carcinomas [49]. It was also reported by El-Boreay M [50] that administration of oxygenated water which is freshly prepared water rich with oxygen increased the efficacy of the anticancer drug doxorubicin against hepatocellular carcinoma compared to the efficacy of doxorubicin alone [50].

HIF-1α/HIF-2α inhibitors: It's now widely recognized that most solid tumors contain significant portion of hypoxic area, and it is also well known that hypoxia render the tumor more aggressive, metastatic and resistant to both chemotherapy and radiotherapy, but it also exploits the hypoxic tumor microenvironment to develop targeted therapy for cancers like HIF-1α/HIF-2α inhibitors [51] and here we are going to list several of them in the following lines.

a. **Benzopyranyl 1,2,3-triazole:** It is a brand-new chemotherapeutic agent which is reported to cause HIF-1 inhibition through increasing it is hydroxylation and proteasomal degradation and it is also decrease the expression of the VEGF and angiogenesis in a dose dependent way [52].

b. **BIX-01294 (diazepin-quinazolin-amine derivative):** BiIX-01294 has been shown to reduce HIF-1 expression in $HepG_2$ hepatocellular carcinoma cells by boosting PHD_2 and pVHL expression, hence decreasing HIF-1 stability [53].

c. **Glyceollins:** They are members of the phytoalexins group which are de novo synthesized in the soybean in response to microbial invasion and chemical stressing [51]. Glyceollins reported to cause inhibition of the VEGF expression through regulating the HIF-1α and this is done through two pathways either through blocking HIF-1α translation via blocking the PI3K/AKT/mTOR pathway under hypoxic conditions or through decreasing the Hsp90 binding activity and therefore decreasing the HIF-1α stability [54,55].

d. **IDF-11774**: Is an aryloxy acetyl aminobenzoic acid analogue it exhibits it is anticancer activity through increasing the expression of VHL which will result in the inhibition of the HIF-1α accumulation and through inhibiting the expression of the mRNA of the hypoxia targeted genes like VEFGF and EOP [56,57].

e. **Vorinostat:** It is known as suberoylanilide hydroxamic acid and it has dual action as anti HIF-1/HIF-2 activity, and it is shown anti-tumor action against HCC in both *in vivo* and *in vitro* [58]. It is exhibits it is action through inhibiting the HIF-1/2 stabilization by direct acetylation of heat shock protein 90 and by increasing the HIF-1/2 degradation through a ubiquitin-based mechanism [59].

f. **PT2385 and PT2399:** They are selectively HIF-2α inhibitors through inhibiting it is dimerization with HIF-1β and it showed to be effective in renal cell carcinoma with good safety profile [60].

Conclusion

Nanoparticles are considered a microscopic particle with size range from 1-100nm, these particles have specific physical and chemical characters that allow it to do specific functions which bulk materials cannot do and due to these specific characters, it has been widely used in healthcare and in drug delivery to enhance the therapeutic outcome and reduce the drug toxicities. Among their use in healthcare is their use in modulating the tumor hypoxia as it is well known that most of the solid tumor contain substantial area of hypoxia due to the rapid proliferation rate of the cancer cells and the inadequate blood supply which don't match this proliferation rate that lead to the deficiency of oxygen and nutrition and finally hypoxia and it is considered as a poor prognostic factor of cancer which means that the severe the hypoxia the more aggressive the cancer and finally the low survival rate.

Hypoxia mediate it is effect through the HIF-1α, HIF-2α and HIF-3α but the most prominent one is the HIF-1α as it is the responsible one for the deleterious effect of the hypoxia as it causes the stimulation of the angiogenesis, glycolysis, metastasis and treatment resistance. As being explained earlier hypoxia causes the cancer to be more aggressive and more resistance to therapy but it on the other hand offers a great opportunity as a therapy target with great specificity to the cancer cell only without harming the normal one and this is a great advantage as many anticancer drugs has low safety profile and the patient may suffer more from the side effects of the drug than the disease itself. One of the methods to

target cancer hypoxia is using nanoparticles like manganese dioxide nanoparticles, sliver nanoparticles, osmium-based nanoparticles and other metallic nanoparticles which will generate intracellular oxygen by decomposing the intracellular H_2O_2 trough a catalytic reaction leading to the reoxygenation of the hypoxic tumor cells and sensitize it to chemo and radio therapy.

Also, there are other methods used to correct the tumor hypoxia through increasing the blood oxygenation either by hyperbaric oxygen or by oral oxygen therapy which depends on the administration of water highly saturated with oxygen and it can be used either alone or along with other anti-cancer drugs to increase their efficacy as correction of the hypoxia increase the activity of the chemotherapeutic agents. Finally, HIF-1α/HIF-2α inhibitors are small molecules designed to block the effect of the HIF-1α/HIF-2α and as a result will block the deleterious effect of the cancer hypoxia and enhancing both the chemotherapy and radiotherapy activity. Those inhibitors can work by increasing the degradation of the HIF-1, decrease the expression of HIF-1, interfering with the Hsp90 binding activity, the expression of the mRNA of the hypoxia targeted genes like VEFGF and EOP and by inhibiting it is dimerization with HIF-1β which in the end will lead to better prognosis and better treatment outcome.

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