A STUDY ON NANOTECHNOLOGY FOR CANCER TREATMENT

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Abstract

Nanotechnology has great potential in increasing the approaches towards obtaining cancer cell death while reducing collateral damage to nontoxic cells. Nanoscale materials are progressively targeted on cancer cells with amazing precision through active and passive targeting both. This review summarizes latter-day literature, severing new ground in usage of nanotechnology for cancer treatment with targeted drug delivery being prominent.

Keywords: *NP (nano-particle), PEG (poly ethylene glycol), MPS (macrophage phagocytic system), EPR (enhanced permeability and retention effect), tumor.*

1. Introduction

The increased need for advanced technology playing a crucial role for treatment of cancer is very apparent in statistics specifying that cancer incidences, prevalence and mortality are still at extremely high levels (Ferlay J, Shin HR et al, 2010). One of the most leading causes of deaths worldwide having an estimated 7.6 million deaths each year is cancer. By 2030, cancer related mortality is expected to increase to 13.1 million. Cancer is a multitude of diseases, rather a single disease which targets each organ or system distinctly. Cancer could be avoided, with some estimations showing about 30% of cancer deaths caused by smoking, other lifestyle choices or diet components that could possibly be avoided by behavioral or lifestyle changes (RJ, RS Et. Al, 2004,2007). Be that as it may, simple behavioral changes cannot aid in avoiding the majority of cancers and do necessarily need technological alterations for better outcomes. The modern world has had significant success in reducing cancers caused by viral infections [e.g., human papilloma virus (HPV)] (CF, TC et. Al, 2003). Widespread implementations of existing vaccine technologies could enhance this success and usage of nanotechnology and many other technologies could enhance vaccination efficiency. There is a possibility of increasing the percentage of cancers that could be diagnosed early via nanotechnology. This will lead to improved results for cancer patients in conjugation with more aggressive implementations of existing screening technologies (LE, Lancet, et. Al, 1993). Yet for many cancer types, new approaches for treatment of established disease are needed. To address these

therapeutic requirements, nano-sized molecular tools capable of differentiating between hostile and non-hostile cells and delivering a fatal payload need to be developed. This review shows a summary of many of the innovative techs that have been reported in recent years and holding a promise for improved outcomes for cancer patients.

2. Tumor targeting

Tumor targeting is a potential and basic advantage of nanotechnology for cancer treatment.). Being able to differentiate between hostile and non-hostile cells and selectively removing hostile cells is central to the journey of nanotechnology as it relates to cancer treatment. Passive and active targeting are two fundamental processes involved in differentiating hostile and non-hostile cells. In order to increase the concentration of nanoparticles (NPs) in the tumor, passive targeting takes advantage of the enhanced permeability and retention (EPR) effect (Maeda H, et. Al, 2001, 2014). Active targeting (JD, L, et. Al, 2008) could involve a selective molecular identification of antigens, frequently proteins that are expressed on the surfaces of cancer cells in order to localize NPs to hostile cells or, maybe, exploit biochemical properties associated with hostility such as matrix metalloproteinase secretion (CE, TD, et. Al, 2013). Passive and active targeting can be deployed independently, or can be combined. Both of them can benefit from surface modifications of NPs that minimize uptake by the macrophage phagocytic system (MPS)(Nie S, et. Al, 2010) thus, increasing the time in circulation.

2.1 Passive targeting via EPR (Enhanced permeability and retention effect)

It is a well-known fact that tumor vasculature is leaky relative to the hierarchical structure of normal vasculature because hostile cells are not responsive to cell signaling necessary for orderly vasculogenesis (Evan G, Weis SM, et. Al, 2007, 2011). Macromolecules may enter the tumor through this leaky vasculature and continue because of reduced lymph clearance in tumors by a phenomenon called the enhanced permeability and retention effect (EPR)(Maeda H, et. Al, 2010). Tumor size, tumor type, and tumor heterogeneity, among other factors determine the efficiency of EPR. Its efficiency is also critically dependent on the size of the therapeutic being targeted. Localization of substances through the EPR is operational over the MW range 40 kDa–800 kDa, which for globular proteins corresponds to minimal radii from 2.3 to 6.1 nm (MM, KD, et. Al, 2009). Preferable dimensions for the localization of proteins in tumor tissue through the EPR surprisingly showed a minimum at 25 kDa with enhanced uptake for proteins– albeit smaller peptides required active targeting for retention. Comparatively, liposomes did not benefit from active targeting (MM, KD, et. Al, 2009, 2012). Different kinds of NPs have been shown to confine to tumor tissue via the EPR including multiwalled carbon nanotube (MWNT), single-walled carbon nanotube (SWNT) (Liu Z, Liang Y et. Al, 2008, 2012), and liposomes, as well as viral NPs. NPs could differ significantly in density, and other features from globular proteins and NPs several hundred nanometers in a single dimension have been reported to confine to tumor tissue through the EPR. The relative efficiency of tumor confinement via the EPR for various nanoparticles has not been investigated in any tumor model. Recently, an interesting variant of passive targeting via the EPR was described which had gold nanorods delivered to tumor tissue via the EPR and the tumor was heated upon laser irradiation. This approach was accompanied by delivery of the anticancer agent ADHGM to

cancer cells through recognition of GRP78 that was upregulated in prostate cancer cells in response to the increased temperature (Larson N, Ray A, et. Al, 2012).

2.2 Active targeting

Theoretically, any ligand displaying special binding towards hostile relative to non-hostile cells or that may result in selective activation proximal to hostile cells (Danhier F, Raki M, et. Al, 2012, 2012) can be used to steadily target hostile cells. Regarding this, growth factor receptors like epidermal growth factor receptor (EGFR), transferring (Choi CH, Li JL, et. Al, 2010, 2009), death receptor (DR) complexes (e.g., DR5), and folate ligand (Dixit V, DM, et. Al, 2006) including tumor-specific antigens (e.g., PSMA), have been utilized to localize NPs to hostile cells via active targeting. Nanoparticles have been directed to hostile cells expressing the molecular target receptor including monoclonal antibodies (El-Sayed IH, Huang X, et. Al, 2006), small molecules, and nucleic acid aptamers (Teply BA, Yu C, et. Al, 2006, 2011) using different biological and chemical molecules. Factors contributing to a single type of targeting molecule that is preferentially utilized include molecular weight (MW), targeting affinity, valency, and biocompatibility. Despite active targeting being conceptually straightforward, it does not enhance tumor localization uniformly. A good example would be monoclonal antibody (mAb) targeting which was found to not enhance tumor localization (Singh R, HK, et. Al, 2009). In some cases. Furthermore, this type of targeting could impact other variables like time in circulation, and these effects may confound the effects of direct targeting, indirectly. Using varying amounts of targeting ligands showed that active targeting of NPs may affect cellular uptake in a tumor, rather than targeting the tumor itself (Choi CH, Alabi CA, et. Al, 2010). And hence, active targeting is an important strategy for nanoparticle localization. Caution, however, must be exercised in attributing the biological effects observed to active targeting.

2.3 Minimizing MPS uptake.

Aggregation of nanoparticles in tumor tissues needs extended time in circulation and needs to avoid clearance through uptake by the reticuloendothelial system (RES) (a.k.a. MPS (JV, RN, et. Al, 2011)). Nanoparticles are coated with polyethylene glycol (PEG) or other amphipathic agents to reduce the affinity of proteins involved in the opsonization of Nanoparticles and, hence, reduces MPS uptake. (Romberg B, Hennink WE, et. Al, 2008). MPS uptake of quantum dots (QDs) is reduced up to ninefold with PEGylation, while peptide derivatization had a lesser effect (Lyer G, Koh AL, et. Al, 2009). Using 90 kDa amphiphilic poly (maleic anhydride-alt-1-octadecene)-methoxy poly(ethylene glycol) [C18-PMH-mPEG], it is possible to get 30% of the administered dose of modified SWNT localized in tumor tissue (Liu Z,JT, et. Al, 2008, 2012). The effects of surface modification of gold nanoparticles (GNPs) on interaction with blood components including NP biodistribution were shown in a recent study (Shah NB, White JG, et. Al, 2012). Regardless of surface modification, gold nanoparticles are internalized by monocytes. Whilst correlating with enhanced circulation, enhanced tumor accumulation was also found to be surface-dependent with fresh, rather than lyophilized PEG, enhancing time in circulation. Surface charge effects on cell uptake and biodistribution of PEG- oligocholic acid micelles were systematically evaluated (Xiao K, Li Y, et. Al, 2011). A very minimal negative charge was found to increase the tumor uptake and decrease the uptake by MPS cells of the

liver. Surface modification is a very important strategy to reduce MPS uptake for developing NPs with improved therapeutic activity.

3.0 Nanoparticle- mediated cancer treatment.

Nanoparticles being used for cancer treatment are usually not naturally cytotoxic. Hence, they must alter the chemical and physical environment especially in the regions near the cancer cells to exert cytotoxicity. As mentioned formerly, they are targeted to hostile cells via passive targeting through the EPR or active targeting, frequently based on specific molecular recognition events like the EGF/EGFR interactions. After localization to the tumor, NPs evoke a cytotoxic response in cancer cells usually using one of the three: 1. drug release (Lindner LH, Park JY, et. Al, 2012),2. hyperthermia or thermal ablation (Ghosh S, Dutta S, et. Al, 2009), and (3) reactive oxygen species (ROS)-mediated killing (Love SA, MA, et. Al, 2012). These techniques could be used independently or together in a multimodality approach for treatment of cancer. Advantages related to non-NP-mediated approaches for removal are that NPs could mediate extremely localized effects based on molecular recognition events at a cellular level. And hence by directing NPs to specific cells, we can enhance the elimination of neoplastic tissue while limiting damage to adjacent normal cells. Such an approach is valuable for highly infiltrative hostilities, such as glioblastoma multiforme (GBM), where hostile cells cannot be positionally distinguished from non-hostile cells.

3.1 Nanoparticle- mediated drug release.

This is based on the assumption that it is, for the most part, not more difficult to kill a cancer cell than any other hostile cell. Cytotoxic agents like Doxorubicin (DOX), are highly cytotoxic to cancer cells but unfortunately, are highly cytotoxic to non-hostile cells as well – particularly the rapidly dividing cells in gastrointestinal tract and bone marrow. NP-mediated drug delivery allows a control over drug cytotoxicity based on the bio distribution profile for the NP and not for the free drug (Elias DR, Maeda H, et. Al, 2013). It also reduces the excretion rate of low MW cytotoxic drugs which provide increased opportunities to remain in the circulation and accumulate in the targeted region. A good example would be the liposome-mediated delivery of DOX (e.g., Doxil) (Liu C, Liu F, et. Al, 2013) that has substantially reduced cardio toxicity (Stern ST, SE, et. Al, 2008) relative to free DOX. This platform of nanotechnology has addressed the hydrophobicity-related issue of PTX and has helped to prepare a toxic solvent (cremophor)-free formulation reducing the overall toxicity of the therapeutic. A few recent studies have shown novel approaches for improved drug-delivery using NPs.

3.2 Controlling NP- mediated drug release.

The use of NPs for drug delivery requires release of the drug at the tumor site or into hostile cells upon internalization. Therefore, strategies to enhance the drug release at the tumor site are an important component of NP design strategies for theranostic applications. One of the potential problems with current drug delivery methods is that the drug is only slowly released from the NP following localization to tumor tissue via the EPR. Such a release may result in lower free-drug levels that are not sufficient in exerting a biological response.

3.3 Clinical candidates for NP-mediated drug delivery

Fundamental features which include passive and active targeting and MPS avoidance are important for successful implementation of NPs as therapeutic agents have been developed to such an extent that NP-based therapeutic candidates beyond liposomes have come into clinical trials and showcasing drug release and toxicity profiles showing significant betterments relative to conventional chemotherapy. A particular instance of a NP that combines passive targeting via the EPR with active targeting as well as with evasion of immune cells is BIND-014, which has recently entered the clinical trials. (Hrkach J, Von Hoff D, et. Al, 2012)

BIND-014 uses the RNA aptamer **A10-03** to localize the NP to prostate cancer cells and releases docetaxel chemotherapy. Another significantly promising example are NPs containing magnetic resonance imaging (MRI) contrast agents targeted to the $\alpha_v\beta_3$-intregrin found on the surface of the newly developing blood vessels associated with early tumor development. (Brewer S, Wei B, et. Al, 2010, 2011.) For gene therapy against leukemia, a viral nanoparticle has been developed (Castro JE, Kipps TJ, et. Al, 2012). Cyclodextrin-based nano particle safely encapsulates a small-interfering RNA agent which is capable of eliminating a key enzyme in cancer cells is also under clinical trials (Bartlett DW, Davis ME, Yu Z, et. Al, 2008, 2007).

3.4 Thermal ablative approaches to cancer treatment

Locally ablative approaches (Niibe Y, Hayakawa K, et. Al, 2010) which include, radiofrequency ablation (RFA), laser-induced thermotherapy (LITT), and microwave ablation (Vogl TJ, Naguib NN, et. Al, 2011) are widely used for treatment of metastatic disease (Lo SS, Lu JJ, et. Al, 2011), chiefly to the lung and liver that originate from diverse primary tumors. Thermal ablative approaches which have been currently implemented do not utilize NPs, and thus, implementation of NP's is based on macroscopic detection of metastatic lesions rather than on specific molecular recognition and using NP-mediated ablative approaches is becoming increasingly possible.

It is imperative to note that micro metastatic disease, found particularly at distant sites from the primary tumor, is an extremely poor prognostic indicator. Therefore, the application of nanotechnology approaches for eradicating micro metastatic disease, represents one of the most important objectives for using nanotechnology for cancer treatment. Current thermal-ablative approaches, although not yet specific on a molecular level, do have a high demonstrated success rate with up to 97% positive response using RFA and 98% using LITT for treatment of breast metastases (Vogl TJ, Farshid P, et. Al, 2013) and colorectal cancer metastases (Katz S, Espat NJ, et. Al, 2012). Furthermore, cryoablation alternatively uses localized low temperatures to freeze and kill neoplastic tissue.

Focal ablative therapy is also being explored as an alternative to surgery and radiation therapy for the treatment of localized prostate cancer. In addition to any direct thermal ablative effect mediated by Nanoparticles, ablative therapies also modulate the immune response which will affect the overall antitumor response (Haen SP, Periera PL, et. Al, 2011).

3.5 Nanotechnology and photodynamic therapy

The cytotoxic effects of photosensitizing porphyrins in conjunction with light exposure are precise along with being reliable, and photodynamic therapy (PDT) is widely used for treating bladder cancer (Bader MJ, Stepp H, et. Al, 2013), esophageal cancer (Matzi V, Maier A, et.

Al, 2012), including other hostilities other neoplastic conditions like macular degeneration (Sawa M, Iwata E, et. Al, 2012). Delivery of photosensitizing porphyrins via Nanoparticles is expected to confer many of the same advantages that are related to NP-mediated delivery of cytotoxic drugs also including increased local intratumoral concentrations resulting from enhanced permeability and retention (EPR) effect (Maeda H, et. Al, 2012) and reduced systemic toxicities and, in the case of photoactive compounds, reduced light sensitivity (Chin WW, Heng PW, et. Al, 2008). On the other hand, locally administered Nanoparticles drafted as photosensitizing porphyrins are said to be retained in the targeted tissue which allows multiple exposures to light with a single administered dose.

3.6 Nanoparticle-mediated gene therapy

Although it's been known for decades that DNA is the molecular basis of life that carries information from generation to generation, it was until nanotechnology started using DNA for the detection of macromolecules or to produce biochips, the other potentials of this biomolecule has not been realized yet. The cellular role of DNA is relatively limited, perhaps, because of the restrictions imposed by the structure and bonding between the complementary strands. Other than these roles, nanotechnology is also discovering multiple hidden talents of DNA. By using its amphipathic property, single-stranded DNA sequences could be utilized to solubilize hydrophobic Nanoparticles like carbon nanotubes making it suitable for *in vivo* use. DNA sequences possess the ability to process information in biochemical assays. The structure and self-assembling property made it an ideal scaffolding material to arrange Nanoparticles in biochip and biosensor production.

Antisense gene therapy is a potentially powerful tool for both biomedical research as well as for clinical treatments of various ailments, including cancer. Despite the potential use of antisense gene therapy being recognized decades ago, their development into viable therapeutics faced many challenges regarding low transfection efficiency, DNAse degradation, entry into diverse cell types, and toxicity of the transfecting agents. During the past few years, several researchers showed the potential of augmenting gene therapy using nanotechnology (Castro JE, Barlette DW, Heidal JD, Rosi NL, Wang Z, et. Al, 2012, 2008, 2007, 2006, 2012) addressing a majority of these issues and successfully translated into clinical trials.

3.7 Multimodality NPs for cancer treatment

Tumors square measure heterogeneous in nature, consisting of multiple cell sorts and with advanced interaction between the cellular elements contributory to create treatment difficult. One among the potential benefits of technology is that the role to deliver and/or utilize over one therapeutic modality for treatment. Laboratories square measure investigation a unique multimodality NP that displays sturdy antitumour activity through light-mediated ROS generation with unharness of DNA. Associate in nursing example of a nanomaterial that has been used for multimodality applications, as well as drug-delivery and thermal ablation, are cNTs (Fabbro C, Da Ros T, et. Al, 2012) . Heat alone is unlikely to be a perfect modality for inducement tumor death as heat are often dissipated by blood vessels. Heat also can enhance chemotherapeutical effectualness (hyperthermia), and heat-mediated therapy unharness might augment or enhance direct thermal ablation. Nutritionary deprivation, hypoxia, and acidic pH have all been disputed to sensitize tumor cells to hyperthermy. Chemosensitization ensuing

from hyperthermy will enhance therapeutic effectualness of therapy, and multi-modality NPs are often used for each drug delivery further as stimulation of hyperthermia (Gerweck LE, Dewey WF, et. Al, 1997, 1980).

Hyperthermia is often aroused by NIR irradiation; but, different approaches as well as use of alternating magnetic fields in conjunction with IONPs square measure being evaluated in presymptomatic further as clinical studies, and also the use of high-intensity targeted ultrasound (HIFU) for hyperthermia in conjunction with thermo-sensitive liposomes (TSL) was recently delineated (Grull H, et. Al, 2012). Temperature-triggered unharness of the drug from liposomes is anticipated to boost native drug concentrations within the tumor-enhancing treatment effectualness while not increasing general toxicity. Whereas temperatures higher than 42°C might finish off blood flow, temperatures within the 41–42°C vary will markedly enhance the consequences of therapy and radiation treatment. As an example, or so half-hour less radiation is needed to kill cells heated to 42°C relative to physiological temperature (Krishnan KM, et. Al, 2010), though this can be technically troublesome to keep up tissue temperatures during a controlled fashion higher than physiological temperature. MR is effective in temperature mapping, and MR-HIFU systems are often wont to regionally management temperatures.

4.0 NP-related toxicity

One of the potential risks of victimizing nanomaterials for cancer medical aid further as for human health, in general, is that the potential of toxicity (Yoo D, Love SA, Buzea C, et. Al, 2011, 2012, 2007). Nanomaterials square measure terribly numerous in chemical composition, charge, and even to a point size, and thus, general statements regarding toxicity square measure possible unattainable. A number of the foremost issues square measure that NPs is also cancer by, as an example, inflicting hyperbolic ROS production and resulting in DNA mutations. NP exposure is additionally related to respiratory disease, bronchitis, Alzheimer's disease, and Parkinson's disease. A spread of vascular-related events like blood clots square measure related to NPs that enter the cardiovascular system. Any analysis is needed to delineate real risks related to NP use and determinative to what extent potential edges outweigh these risks.

Conclusion

Nanotechnology has already revolutionized cancer medical aid in several aspects and is radically ever-changing the treatment pattern. It's created a good impact on selective recognizing of the cancerous cells, targeted drug delivery, and overcoming limitations of the traditional chemotherapies. Some technology based mostly formulations have already been launched within the market and lots of square measure undergoing analysis and clinical trials. The facet effects of the standard chemotherapies will greatly be removed by these novel active or passive targeting which might well increase the survival rate. As cancer is one in every of the foremost serious deadly diseases, the contribution of technology in precise treatment avoiding the life-threatening facet effects will doubtless contribute to a positive movement in clinical apply for all times saving approach, at the in the meantime, it is also vital to acknowledge and confirm the potential edges to outweigh the risks of victimizing technology as an area of treatment in cancer.

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