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Nanotechnology Based Drug Delivery Systems

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Abstract: ***Nanoparticles hold huge potential as a powerful drug delivery system. In this article we talked about ongoing improvements in nanotechnology for drug delivery. To beat the issues of drug delivery, nanotechnology has picked up enthusiasm for late years. Nanosystems of various structures and organic characterisics have been widely used for drug and quality delivery applications. To accomplish productive drug delivery it is critical to comprehend the cooperations of nanomaterials with the organic condition, focusing on cell-surface receptors, drug release, etc. A several anticancer drugs including paclitaxel, doxorubicin, 5-fluorouracil and dexamethasone have been effectively formulated using nanomaterials . The various nanoparticles used for in vitro RNAi delivery are Quantom Dots, Chitosan, Polylactic/Glycolic Corrosive (PLGA) & PLGA based products. On account of the trouble in getting imaging and therapeutic agents past the blood -brain barrier and into the brain cerebral disease is one of the most troublesome malignancies to distinguish and treat. Anticancer drugs for example, loperamide and doxorubicin bound to nanomaterials have been appeared to cross the unblemished blood -brain barrier and released at remedial focuses in the brain. A recent approach to control disease progression is the utililizaton of nanomaterials as well as peptide based nanotubes to target on vascular endothelial tissue receptorts and cell adheshion molecules like integrins, cadherins& selectins.***

Keywords: Nanotechnology, Doxorubicin, Barrier, Disease, etc.

1. Introduction

Nanoparticles used as drug delivery vehicles are typically < 100 nm, and incorporates biodegradable polymers like natural or artificial polymers, lipids, or metals. Nanoparticles are taken up by cells more productively than bigger macromolecules and hence, likely could be utilized as powerful delivery system. For therapeutic applications, drugs will either be incorporated inside the matrix of the particle or attached to the particle surface. Nanosystems with totally different constitutions and biological characteristics are extensively looked into for drug delivery applications. An approach for achieving efficient drug delivery would be to develop nanosystems based on their interactions with the biological surroundings, target cell population, cell-surface receptors, changes in cell receptors that occur with progression of illness, mechanism and site of drug action, drug retention, multiple drug administration, molecular mechanisms, and pathobiology of the illness taken into account. It is conjointly necessary to know the barriers to drug like stability of therapeutic agents within the living cell surroundings. Reduced drug efficacy may well be because of instability of drug within the cell, unavailability because of multiple targeting or chemical characteristics of delivering molecules, alterations in genetic makeup of cell-surface receptors, over-expression of efflux pumps, changes in signalling pathways with the progression of illness, or drug degradation. As an example, excessive DNA methylation with the progression of neoplasm causes failure of many anti-neoplastic agents like doxorubicin and cisplatin. Higher apprehension of the mechanism of uptake, intracellular trafficking, retention, and protection from degradation within a cell are needed for enhancing effectivity of the encapsulated therapeutic agent.

In this article we tend to discuss the drug delivery aspects of nanomedicine, the molecular mechanisms underlying the interactions of nanoparticles with cell-surface receptors, biological responses and cell signalling, and also the analysis required for the widespread application of nanodelivery systems in medicine.

2. Design of Nanotechnology based Drug Delivery Systems

Nanoparticles will be employed in targeted drug delivery at the site of illness to enhance the uptake of poorly soluble drugs the targeting of drugs to a particular site, and drug bioavailability. A schematic comparison of untargeted and targeted drug delivery systems is shown in Figure 1. Many anti-cancer medication together with paclitaxel, doxorubicin, 5-fluorouracil and dexamethasone are successfully developed using nanomaterials. Polylactic/glycolic acid (PLGA) and polylactic acid (PLA) based nanoparticles are developed to encapsulate dexamethasone, a corticoid with a intracellular site of action. Dexamethasone is a chemotherapeutical agent that has anti-proliferative and anti inflammatory effects. The drug binds to the cytoplasmatic receptors and therefore the consequent drug-receptor complex is transported to the nucleus leading to the expression of certain genes that control cell proliferation.

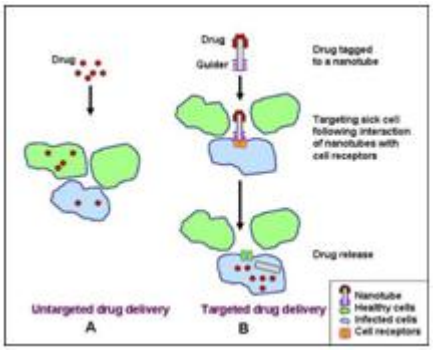

Figure 1

These drug-loaded nanoparticles formulations that release higher doses of drug for prolonged amount of time fully suppressed proliferation of vascular smooth muscle cells.

Colloidal drug delivery modalities like liposomes, micelles or nanoparticles are intensively investigated for their use in cancer therapy. The effectiveness of drug delivery systems

may be attributed to their small size, reduced drug toxicity, controlled time release of the drug and modification of drug pharmacokinetics and biological distribution. Too often, therapy fails to cure cancer because some tumor cells develop resistance to multiple antineoplastic medication. In most cases, resistance develops once cancer cells begin expressing a protein, referred to as p-glycoprotein that's capable of pumping antineoplastic medication out of a cell as quickly as they cross through the cell's outer membrane.

New research shows that nanoparticles could also be able to get antineoplastic medication into cells without triggering the p-glycoprotein pump. The researchers studied in vivo effectiveness of paclitaxel loaded nanoparticles in paclitaxel-resistant human large intestine tumors. Paclitaxel entrapped in emulsifying wax nanoparticles was shown to beat drug resistance in a human colon adenocarcinoma cell line (HCT-15). The insolubility issues encountered with paclitaxel may be overcome by conjugating this drug with simple protein. Paclitaxel bound to bio-compatible proteins like albumin (Abraxane) is an injectable nano-suspension approved for the treatment of breast cancer. The solvent Cremophor-EL employed in previous formulations of paclitaxel causes acute hypersensitivity reactions. to cut back the chance of hypersensitivity once receiving paclitaxel, patients should undergo pre-medication using steroids and anti-histamines and be given the drug using slow infusions lasting some hours. Binding paclitaxel to albumin resulted in delivery of upper dose of drug in brief amount of your time. as a result of it's solvent-free, solvent-related toxicities are eliminated. In phase 3 clinical trial, the response rate of Abraxane was about double than that of the solvent-containing drug Taxol.

3. Nanoparticle-Mediated delivery of siRNA

Short interfering RNA (siRNA) is rising as a robust technique of controlling gene expression with a large variety of applications. Translation of nucleic acid-based therapy to clinical studies would require important advances in the delivery system. Quantum dots (QD) are used to monitor RNAi delivery. PLGA and PLA based nanoparticles have conjointly been used for in vitro RNAi delivery. Although there has been some success in the delivery of siRNA exploitation numerous nanomaterials, following their delivery and observation their transfection potency is troublesome while not an appropriate following agent or marker. Planning an economical and self-tracking transfection agent for RNA interference is a massive challenge. Recently, Tan et al synthesized chitosan nanoparticles encapsulated with quantum dots and used such nanomaterial to deliver human epidermal growth factor receptor-2 (HER2/neu) siRNA. Such a unique nano carrier helped in monitoring the siRNA by the presence of fluorescent QDs in the chitosan nanoparticles. Targeted delivery of HER2 siRNA to HER2 -overexpressing SKBR3 breast cancer cells has been specific with chitosan/quantum dot nanoparticles surface tagged with HER2 antibody targeting the HER2 receptors on SKBR3 cells.

Labeling of nanoparticles with a fluorescent marker, like Cy-5, helps in visualizing uptake and accumulation of nanotubes employing a fluorescent microscope. Recently, Howard et al used such nanoparticles conjugated with siRNA specific to the BCR/ABL-1 junction sequence and located 90th reduced expression of BCR/ABL-1 leukemia fusion protein in K562 (Ph(+)) cells. Effective in vivo RNA interference was additionally achieved in bronchiolar epithelial cells of transgenic EGFP mice after nasal administration of chitosan/siRNA formulations.

4. Targeting Cancer Cells with Nanoparticles

Cancer is one of the most difficult diseases nowadays, and brain cancer is one of the most tough malignancies to detect and treat chiefly as a result of the problem in obtaining imaging and therapeutic agents across the blood-brain barrier and into the brain. several investigators have found that nanoparticles hold promise for ferrying such agents into the brain. Apolipoprotein E was suggested to mediate drug transport across the blood-brain barrier. Loperamide, that doesn't cross the blood-brain barrier however exerts antinociceptive effects when direct injection into the brain, was loaded into human serum albumin nanoparticles and coupled to apolipoprotein E.Mice treated intravenously with this complex induced antinociceptive effects within the tail-flick test. The efficacy of this drug delivery system infact depends upon the recognition of lipoprotein receptors.

Kopelman and colleagues designed Probes Encapsulated by Biologically Localized Embedding (PEBBLE) to carry a range of distinctive agents on their surface and to perform multiple functions. One target molecule immobilized on the surface may guide the stone to a tumour. Another agent might be used to facilitate visualize the target using resonance imaging, whereas a 3rd agent connected to the pebble may delivera harmful dose of drug or toxin to nearby cancer cells.

All 3 functions may be combined in a single small polymer sphere to form a potent weapon against cancer. Another anti-cancer drug, doxorubicin, bound to polysorbate-coated nanoparticles is in a position to cross the intact blood-brain barrier and be discharged at therapeutic concentrations withinthe brain.

Good superparamagnetic iron oxide particle conjugates are often used to target and locate brain tumors earlier and more accurately than reported ways. it's identified that folic acid combined with polyethylene glycol can further enhance the targeting and intracellular uptake of the nanoparticles. Therefore, nanomaterial holds tremendous potential as a carrier for medication to target cancer cells.

5. Targeting Angiogenesis with Nanoparticles

Robust angiogenesis underlies aggressive growth of tumors. Therefore, one amongst the mechanisms to inhibit angiogenesis is to starve tumour cells. angiogenesis is regulated through a complex set of mediators and recent proof shows that integrin αvβ3 and vascular endothelial growth factors (VEGFs) play necessary regulator roles.

Therefore, selective targeting of αvβ3 integrin and VEGFs may be a novel anti-angiogenesis strategy for treating a large variety of solid tumors. One approach is to coat nanoparticles with peptides that bind specifically to the αvβ3

integrin and also the VEGF receptor. The artificial peptide bearing ArgGly-Asp (RGD) sequence is known to specifically bind to the αvβ3 integrin expressed on endothelial cells within the angiogenic blood vessels, which may potentially inhibit the tumour growth and proliferation. Following hydrophobic modifications, glycol chitosan is capable of forming self - aggregated nanotube and has been used as a carrier for the RGD peptide, tagged with fluoreseinisothiocyanate (FITC-GRGDS). These nanotubes loaded with FITC-GRGDS can be helpful for watching or destroying the angiogenic tissue/blood vessels surrounding the tumour tissue. Our analysis group has been learning biological responses of RGDSK self-assembling rosette nanotubes (RGDSK-RNT). These rosette nanotubes are a unique category of nanotubesthat are biologically inspired and naturally water soluble upon synthesis. These nanotubes are formed from guanine-cytosine motif as building blocks. However, one amongst the novel properties of the RNT is that the ability to simply accept a range of functional groups at the G/C motif that imparts functional versatility to the nanotubes for specific medical or biological applications. Therefore, the RNTs are often potentially modified to focus on a range of therapeutic molecules in vivo to treat cancer and inflammatory diseases.

6. Targeting Macrophages to control Inflammation

The potential of macrophages for speedy recognition and clearance of foreign particles has provided a rational approach to macrophage-specific targeting with nanoparticles. Macrophages' ability to secrete a large number of inflammatory mediators permits them to manage inflammation in several diseases. Therefore, macrophages are potential pharmaceutical targets in several human and animal diseases. though macrophages are capable of killing most of the microbes, several microorganisms (Toxoplasma gondii, Leishmaniasp, mycobacteriumtuberculosis and listeria monocytogenes) have developed potential ability to resist phagocytosis activity of macrophages. These pathogens occupy modified lysosomes and degrade macrophage's molecular machinery designed to kill them and therefore, antimicrobial agents are delivered into pathogen-containing intracellular vacuoles in macrophages can be helpful to eliminate cellular reservoirs. This technique can be used to accomplish therapeutic drug concentration within the vacuoles of injected macrophages in reduction in aspects related to the drug administration and therefore the release of proinflammatory cytokines.

Polyalkylcyanoacrylates (PACA) nanoparticles are used as a carrier for targeting antileishmanial medication into macrophages. This nanomaterial didn't induce interleukin-1 release by macrophages. Therefore, equally designed nanosytems can be very helpful in targeting macrophage infections in chronic diseases.

The antifungal and anti-leishmanial agent amphotericin B (AmB) has been complexed with lipids-based nanotubes to develop a less toxic formulation of AmB. Gupta and Viyas developed AmB in trilaurin based nanosize lipid particles (emulsomes) stabilised by soy phosphatidylcholine as a new intravenous drug delivery system for phagocyte targeting. Nanocarrier-mediated delivery of macrophage toxins has established to be a strong approach in getting rid of unwanted macrophages in sequence therapy and different clinically relevant things such as autoimmune blood disorders, T cell-mediated insulin-dependent diabetes mellitus, rheumatism, spinal cord injury, nerve injury, and restenosis after surgical procedure. or else, nanoparticles with macrophage-lethal properties also can be exploited. Exploiting a

range of macrophage cell receptors as therapeutic targets could prove a far better strategy for antigen delivery and targeting with particulate nanocarriers.

7. Conclusion

It seems that nano drug delivery systems hold nice potential to beat a number of the barriers to efficient targeting of cells and molecules in inflammation and cancer. There is also an exciting chance to beat issues of drug resistance in target cells and to facilitating movement of drugs across barriers like those within the brain. The challenge, however, remains the precise characterization of molecular targets and to make sure that these molecules are expressed solely within the targeted organs to prevent effects on healthy tissues. Secondly, it is necessary to know the fate of the drugs once delivered to the nucleus and other sensitive cells organelles. moreover, because nanosystems increase potency of drug delivery, the doses may need recalibration. still, the long run remains exciting and wide open.

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