Nanoparticles as Imaging Agents and Delivery Vehicles

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Abstract

For both anatomical and molecular imaging, nanoparticles constitute a novel kind of imaging agent and delivery system. The signal strength, stability, and biodistribution properties of submicron-sized molecular imaging agents are taken advantage of by nanoparticle-based imaging. Quantum dots, an inorganic nanoparticle, are one of the most promising fluorescent markers for cellular imaging. The NIR portion of the spectrum, where tissue autofluorescence is decreased and excitation light penetration is increased, is controlled by the quantum dots to emit light at specified wavelengths. This succinct review included the most current developments in delivery methods and imaging agents based on nanoparticles.

Keywords: Nanoparticles, Imaging Agents, Delivery Vehicles

Introduction

In molecular imaging, NPs have been investigated as fresh labels and contrast agents. Due to the special characteristics of NPs, it is possible to monitor molecular targets, as well as cell responses related to illnesses like cancer and cardiovascular conditions, sensitively and precisely. specialised nanoparticles for imaging For targeted imaging, NPs possess a number of promising qualities. First, because of their enormous surface area, NPs may transport several imaging agents simultaneously, improving sensitivity. Second, NPs may be directed to concentrate in locations where the molecular target is expressed, increasing the local concentration of contrast chemicals, or they may be passively targeted tissues in vivo via the EPR effect. Their employment as in vivo imaging amplifiers is made possible by the large capacity for NP modification. They can also administer a variety of imaging agents to carry out multimodality imaging [1].

Imaging Agents

Monofunctionalized quantum dots (QDs) have been utilised to identify receptors involved in cell migration during development and metastasis as well as to monitor particular proteins in cells. QDs have been employed for imaging certain tumour indicators, such as the targeting of integrin v3 using aginine-glycine-aspartic acid peptide-conjugated near-infrared (NIR) QDS. The ability of targeted QDs to do multiplex imaging, which entails simultaneously imaging several molecular targets utilising various QDs with various emission wavelengths, has also been investigated. QDs have recently been used for multiplex molecular imaging of lymph nodes, embryonic stem cells, tumour cells, and the vascular system [2].

Small organic compounds have been investigated as NIR SERS reporters in gold nanoparticles as a non-invasive technique for in vivo cancer imaging. For the recent identification of HER2-positive tumours in xenograft models, antibody coated gold NPs were combined with a sensitive and reliable cyanine reporter that was created and screened from a combinatorial library of SERS reporters. The use of various targeted SERS gold NPs for multiplexed imaging in mouse models has been the focus of several recent in vivo imaging initiatives. Magnetic NPs are one of the better researched NP systems for molecularly targeted imaging. Real-time visualisation of

biological phenomena, including as cell migration and trafficking, enzyme activity, and other biological interactions at the molecular and cellular level, has showed promise for magnetic NP imaging systems. As contrast agents in magnetic resonance imaging (MRI), a biological approach based on nuclear magnetic resonance of different interacting nuclei, magnetic NPs have also demonstrated promise. SPIONs, a popular MRI contrast agent for cancer imaging, are made from iron oxide crystals coated with dextran or carboxydextrin [3].

When administered intravenously to patients, SPIONs have been found to stay in the tumours for 24 hours as opposed to 1 hour with gadolinium-based MR agents. This discrepancy results from less diffusivity of the NP leaving the tumour and easier NP absorption by tumours. One research showed that tumour cells overexpressing transferrin receptor 1 were the target of a recombinant human heavy-chain ferritin protein shell containing IONPs. In the presence of hydrogen peroxide, iron oxide core also catalysed the oxidation of peroxidase substrates to create a colour reaction that is utilised to see tumour tissues. Glutamic acid residues were added to the protein coat of the bacterial infection virus M13. The electrostatic assembly of NPs along the filamentous structure of the M13 coat was facilitated by the negatively charged residues. Additionally, a peptide that targets the SPARC glycoprotein, which is overexpressed in certain malignancies, was incorporated into the viral coat. This strategy may enhance the contrast while doing MR imaging as compared to conventional methods where NPs are directly functionalized with targeted ligands [4].

Delivery Vehicles

Distributing siRNA for biological research An essential biological technique for usage in living organisms and cell culture is RNA interference (RNAi). Because it permits controlled degradation of mRNA after the introduction of sequence-specific double stranded RNAs into cells, it is typically utilised to examine gene functions. Effective siRNA delivery, however, can necessitate overcoming a number of biological barriers, including: 1) difficulty entering the cell due to high molecular weight and negative charges, 2) degradation by nucleases within the cell, 3) targeting to the right cell compartment, and 4) rapid clearance and instability in vivo. Therefore, effective and biocompatible delivery mechanisms are required to fully exploit the promise of RNAi [5].

NPs provide a potential answer to the problems with siRNA delivery. Due to their capacity to condense a complex with nucleic acids, cationic lipid or polymer NPs have been employed to transport anionic nucleic acids into cells. This keeps them stable and guards against enzymatic deterioration. Additionally, cationic compounds can aid NPs in avoiding lysosome/endosome sequestration. Groups that become protonated in the endosome/lysosome pH milieu, such as the nitrogens in the cationic polymer polyethyleneimine (PEI), can aid endosomal escape by enhancing Cl input in reaction to protonation at acidic pH. Osmotic pressure rises as a consequence, causing swelling and an organelle burst that releases the siRNA NPs. The "proton sponge effect" is the name given to this occurrence. However, a recent study found that siRNA delivery in a cationic lipid NP system was significantly diminished because, as a result of the lipid NPs' egress from late endosomes/lysosomes, almost 70% of the internalised siRNA were recycled to the extracellular medium. Therefore, by creating novel NP carriers that may bypass recycling routes, siRNA distribution may be enhanced. Using fusogenic peptides and cell penetrating peptides, active targeting strategies of non-endocytic uptakes of NP delivery of nucleic acids have also been investigated. SiRNA probes have been utilised to explore intracellular trafficking as well as assembly and disassembly of siRNA NPs in order to better understand how siRNA NPs interact with biological systems [6].

Due to the important functions that immune cells can play in maintaining homeostasis and fighting illness, NPs have recently been employed to transport siRNA to mute genes in these cells. In one work, Cyclin D1 (CyD1), a cell cycle-regulating molecule, was specifically silenced in vivo in leukocytes using NPs to ascertain the precise functions of the protein in gut inflammation. NPs were functionalized using antibodies to β7 integrin and loaded with CyD1 siRNA. A leukocyte's ability to proliferate and the production of the T helper cell 1 cytokine were both suppressed by these targeted NPs, which the study found silenced CyD1 in leukocytes and helped mice recover from experimentally induced colitis.

Another recent study also discussed the use of lipid nanoparticles for the in vivo delivery of siRNA to immune cells in order to silence disease genes. The work validated the viability of targeting numerous gene targets in rodent myeloid cells and showed siRNA-mediated silencing in nonhuman primates' myeloid cell types. Using siRNA that targets tumour necrosis factor (TNFα), the therapeutic potential was verified. In a different investigation, NPs were employed to investigate the immunological triggers of non-alcoholic steatohepatitis (NASH). The researchers discovered that increased production of the chemokines IP-10 and MCP-1 by Kupffer cells caused by TNFα can cause the onset of NASH. Additionally, TNFα silencing in myeloid cells decreased the production of chemokines and stopped the onset of NASH, indicating the potential of TNFα as a fresh therapeutic target in NASH.

In order to examine biological pathways at the single cell level in plant cells, siRNA has also been delivered by NPs. One team transported siRNAs directed at certain genes in the cellulose production pathway using amine-conjugated polymeric NPs. They discovered that NtCesA-1, a substance involved in the creation of cell walls in entire plants, is also crucial for cell wall regeneration in isolated protoplasts. delivering hydrophobic substances devoid of excipients or solvents Numerous chemicals that are physiologically active are hydrophobic and have limited solubility in water. Due to these chemicals' limited solubility in aqueous settings, using them in biological research might be difficult.

The current methods use an excipient like cremophor or a solvent like dimethyl sulfoxide (DMSO). But not all substances can be solubilized using these solvents, and the solvents are usually harmful to living things, which makes the biological experiment more difficult. For instance, wortmannin, a reagent frequently used in biology research and a PI3 kinase inhibitor, needs DMSO for in vitro usage. DMSO is not appropriate for in vivo applications since it is known to have its own effects on cells. Utilising NPs is one way to get around the difficulty of administering these hydrophobic drugs. Numerous NPs, particularly polymeric NPs, have hydrophobic cores and are ideal for delivering hydrophobic drugs because of this [7].

In addition to overcoming the active agent's solubility, using NP delivery vehicles shields the agent from the environment until it is released from NP. By creating an NP formulation of wortmannin, our own team has shown the proof-of-concept for this method. We showed that NP wortmannin enhanced stability and increased solubility. Additionally, we were able to demonstrate that NP wortmannin has the same cell signalling actions as wortmannin. Furthermore, in a mouse model of cancer, NP wortmannin performed as an efficient and powerful therapeutic drug. Injecting substances into subcellular organelles The delivery of different agents to certain organelles is one topic that is being researched. Effective therapeutic and imaging agent delivery depends in part on a target's subcellular accessibility and availability. A number of molecular activities in organelles that are currently

unknown may be revealed by delivering agents to subcellular organelles. Since NPs are simple to manipulate and functionalize, there has recently been interest in employing them as delivery systems for drugs to reach subcellular organelles. Using endocytosis, targeted NPs can attach to targets that are present on the cell surface. However, if the target is intracellular, either intracellular sequestration of the NP or a lack of subcellular targeting skills may prevent NPs and their payload from getting to the desired target.

In instance, for NPs containing oligonucleotides to be targeted, they must first exit the endosome. Tools for precise subcellular distribution to the nucleus, cytosol, mitochondria, endosomes, and lysosomes are developing. Generally speaking, two methods are being researched for designing NPs for subcellular targeting: 1) NPs may be passively targeted to a specific organelle by altering their size, shape, and content. 2) Active targeting of NPs to the target organelle by functionalization of NP surfaces with the organelle-specific targeting ligands. Various degrees of success have been achieved while using these strategies [8]. Biological barriers particular to the target organelle are a barrier to effective sub-cellular targeting. For instance, NPs directed to the nucleus must traverse the nuclear membrane, pass through the cell membrane, avoid endosomal/lysosomal pathways, have a mechanism for interacting with the nuclear pore complex, and be tiny enough to enter the cell. Enhancing nuclear delivery through active transport mechanism has been done by using targeting ligands like the nuclear localization signal (NLS). In one investigation, the DNA of a cancer cell was harmed by the placement of NLS coupled gold NPs at the nucleus. In contrast, in another investigation, NLS attached gold NPs were unable to enter cells or were caught in endosomes, preventing them from targeting cell nuclei from outside the plasma membrane. The nucleus was instead accessed by NPs coupled with both NLS and receptor-mediated endocytosis (RME) peptides. Comparatively to other cellular membranes, the mitochondria have a negative membrane potential, which can result in the buildup of lipophilic cations. Using the anti-cancer drugs ceramide and scarleol to target the mitochondria, stearyl triphenyl phosphonium (STPP) targeted liposomes were created using this theory. Due to its cationic and lipophilic characteristics, STPP was selected. Another team employed a polymeric NP system to deliver medicines with mitochondrial activity. The triphenylphosphonium (TPP) cation, which is known to penetrate into the mitochondrial matrix space, was used to synthesise the NPs. The team discovered an optimised targeted NP by in vitro screening of a library of charge and size variable NPs that outperformed non-targeted NPs or small molecule treatments in terms of efficacy and toxicity for cancer, Alzheimer's disease, and obesity [9, 10].

Conclusions

The visualisation of biological processes has also been investigated using novel NPs with enhanced magnetic characteristics. To tailor certain magnetic characteristics, one such family of materials uses metal-doped ferrite nanoparticles (MFe_2O_4), where M is the $^{+2}$ cation of Mn, Fe, Co, or Ni. Since $MnFe_2O_4$ NPs had the maximum magnetic susceptibility and were determined to be non-toxic in vitro, they could make superior MRI probes. These NPs demonstrated improved MRI sensitivity for the identification of cancer markers when they were coupled with antibodies. The outer and inner mitochondrial membranes, as well as toxicity, are biological obstacles for NPs that are directed towards the mitochondria. For delivery to the mitochondria, the majority of investigations to date have predominantly created metal oxide or liposomal NPs. Electrostatic interactions between the NP and the organelle have furthermore been used to support delivery to the mitochondria.

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