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Molecular Biology and Gene Therapy Fundamentals Using Nanoparticles

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Description

Nanoparticles are spherical, polymeric particles composed of natural or artificial polymers. They range in size between 10 nm and 500 nm. As a consequence of their spherical shape and high surface area to volume ratio, these particles have a wide range of potential applications. Nanoparticle technology is rapidly advancing, providing novel and effective treatments for various diseases including neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases. Nevertheless, effectively and regionally targeting drugs to the brain remain a challenge due to the restrictive properties of the blood brain barrier. This barrier, predominantly formed by endothelial cells that are physically joined by tight junctions in their external membranes, limits the molecular exchange to transcellular transport, thus restricting the passage of molecules across the barrier. The healthy BBB also largely protects the brain from blood-borne nanoparticle exposure; however, a number of pathologies, including hypertension and allergic encephalomyelitis, have been shown to increase BBB permeability to nanoparticles. The likely widespread future applications and impending commercialization of nanoparticles of different composition also pose risks both to humans and to environmental systems. Thus, early evaluations of the health and environmental effects of nanoparticles necessitate careful consideration. These topics are addressed in a number of other chapters of this volume and therefore will not be discussed herein. The focus of this chapter will be complimentary, namely to consider the role of olfactory nanoparticle transport into the central nervous system both as a potential route for effective drug delivery and as a route for the passage of noxious substances into the brain proper to survey the application of nanoparticles as sensors of cell function and toxicity and some adverse effects of nanoparticles on the deregulation of brain redox status.

Nanoparticle Delivery Systems

Solid lipid nanoparticles, in contrast to liposomes, consist of a cationic lipid core and an outer layer of surfactants. Consequently, this construct can be used to co-deliver both hydrophilic and hydrophobic drugs. A nanoparticle containing both paclitaxel and siRNA targeting the antiapoptotic protein Mcl-1 induced greater tumor regression than either paclitaxel or RNA alone in a murine model of human epithelial carcinoma. Polymer-based nanoparticles have also been investigated for the delivery of nanoparticles. Chitosan nanoparticles are highly stable and harbor very low immunogenicity. More recently, the best characteristics of polymer-based and lipid-based nanoparticles have been combined into lipid-polymer hybrid nanoparticles comprising a polymer core and a lipid shell. These hybrid nanoparticles have been tested in a variety of murine tumor models, in which they greatly inhibited tumor growth without activating the immune response.

General Considerations

Nanoparticles have been gaining attention for a transdermal drug delivery carrier. Indomethacin and estradiol permeability through rat skin were enhanced by encapsulating into PLGA nanoparticles. Application of IP to nanoparticle system enhanced accumulation of the nanoparticles into follicles. High charged indomethacin loaded PLGA nanoparticles were prepared by anti-solvent diffusion with preferential solvation method. The nanoparticles showed high electrophoretic mobility. Highly charged indomethacin-loaded PLGA nanoparticles showed greater permeability of indomethacin through rat skin than PVA coated indomethacin loaded PLGA nanoparticles when IP was applied. The highly charged indomethacin-loaded PLGA showed greater accumulation inside skin than PVA-coated indomethacin loaded PLGA nanoparticles because highly charged nanoparticles have higher hydrophobicity than PVA-coated indomethacin loaded PLGA nanoparticles. These results suggested that highly charged nanoparticles have great potential for iontophoretic TDDS.

The majority of micro and nanoparticles used in the eye are based on the degradable polyesters poly (lactic acid) and PLGA. These polymers degrade by hydrolysis and the rate of degradation is controlled by the ratio of lactic acid to glycolic acid subunits, the molecular weight of the polymers, and, in the case of poly (l-lactic acid), and the crystallinity of the polymer. The FDA has approved a number of devices using these materials and there is a wealth of literature looking at these materials for use in the eye. Nanoparticles' based cancer therapeutics is greatly dependent on the development of science and engineering of nanoparticles. In this article, important strategies based on nanoparticles used for cancer treatment are discussed. The inspiration to write this article is not only to review the existing strategies based on nanoparticles but also to highlight the pertinent and possible solutions thereof, especially from the perspective of the properties of nanoparticles. In this review article, the main focus will be on the use of several metal and metal oxide nanoparticles for targeting angiogenesis in cancer and the use of several carbon allotropes (in nanoparticle form) for a variety of cancer treatment strategies as well as antibacterial applications.

NPs charge is another factor that can influence the circulation life and the development of selective accumulation. NPs which have the easiest transition into the cell due to the negatively charged cell membrane have positive charge. It has been reported in the literature that such NPs can disrupt the BBB. Negatively charged NPs also have an effect on the BBB. The important factor in here is the amount of concentration. Compared with negatively charged NPs having low concentration, NPs having high concentration can disrupt the BBB. Neutral and negatively charged NPs provide longer circulation than positive ones and reduce the adsorption of serum proteins. Protein absorption on the NPs surface may cause surface charge to change. In the one of the studies in literature, it has been reported that the conjugation of PEG–PLA NPs with a negatively charged peptide, had

positive effects on BBB penetration and improvement of intracellular transmission to glioma cells. This approach can have complications. Receptor aggregation on the cell surface, for example, can induce unintended events, such as apoptosis. One can engineer the nanoparticle for a particular mode of intracellular entry depending on the choice of nanoparticle targeting molecules, cholesterol favors uptake *via* caveolin mediated endocytosis, and transactivating transcriptional activator peptide favors macro pinocytosis. Nanoparticle surface chemistry also can be manipulated to trigger cargo release under specific circumstances. For example, when exposed to a reducing environment such as is present in the cytosol, reductively labile disulfide based crosslinks between the carrier and cargo are broken. Approaches for targeting nanoparticles to particular subcellular organelles, mitochondria or the nucleus, also have been developed.