pharmaceutics

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Article

Nanotoxicologic Effects of PLGA Nanoparticles Formulated with a Cell-Penetrating Peptide: Searching for a Safe pDNA Delivery System for the Lungs

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Received: 24 October 2018; Accepted: 27 December 2018; Published: 3 January 2019

Abstract: The use of cell-penetrating peptides (CPPs) in combination with nanoparticles (NPs) shows great potential for intracellular delivery of DNA. Currently, its application is limited due to the potential toxicity and unknown long-term side effects. In this study NPs prepared using a biodegradable polymer, poly(lactic–*co*–glycolic acid (PLGA) in association with a CPP, was assessed on two lung epithelial cell lines (adenocarcinomic human alveolar basal epithelial cells (A549) and normal bronchial epithelial cells (Beas-2B cells)). Addition of CPP was essential for intracellular internalization. No effects were observed on the mitochondrial activity and membrane integrity. Cells exposed to the NPs–DNA–CPP showed low inflammatory response, low levels of apoptosis and no activation of caspase-3. Increase in necrotic cells (between 10%–15%) after 24 h of incubation and increase in autophagy, induced by NPs–DNA–CPP, are likely to be related to the lysosomal escape mechanism. Although oxidative stress is one of the main toxic mechanisms of NPs, NPs–DNA–CPP showed decreased reactive oxygen species (ROS) production on Beas-2B cells, with potential antioxidant effect of CPP and no effect on A549 cells. This NP system appears to be safe for intracellular delivery of plasmid DNA to the lung epithelial cells. Further investigations should be conducted in other lung-related systems to better understand its potential effects on the lungs.

Keywords: alveolar; bronchial; apoptosis; autophagy; gene delivery

1. Introduction

Gene therapy has been rapidly advancing in recent years, and the commercial use of nanotechnology is increasing. Among the several uses of nanotechnology, nanomedicine has the potential of treating several diseases including cystic fibrosis, cancer, and other gene-related diseases [1]. The decrease in size into the nano-scale range provides novel physical and chemical properties to well-known materials. Although these unique properties offer a great potential for entering and transporting different materials into cells, its application has been limited due to the potential toxicity and unknown long-term side effects [2]. Careful measures need to be taken to ensure that no cellular dysfunction or harm has taken place following the administration of these nanoparticles (NPs).