RESEARCH ARTICLE

The potential role of nanomedicine in lung diseases

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Abstract:

Nanomedicine is a rapidly emerging interdisciplinary field in which medicine is coupled with nanotechnology tools and techniques for advanced therapy with the aid of molecular knowledge. Nanoscale drug delivery systems provide a platform to improve the pharmacokinetics and increase the bio-distribution of therapeutic agents to target organs, thereby resulting in improved efficacy while limiting drug toxicity. These systems have revolutionized drug delivery approaches and are exploited for therapeutic purposes to carry the drug in the body in a controlled manner from the site of administration to the therapeutic target. Several promising molecular targets that have been identified as potential therapies for acute and chronic respiratory conditions have been limited because of difficulty with delivery systems. In particular, delivery of peptides, proteins, miRNAs to the lung is an ongoing challenge. Hence, it is an attractive strategy to test potential targets by employing a nanotechnology approach. Nanobiotechnology and nanoscience can provide innovative techniques to deliver drugs targeted to the site of inflamed organs. Here we review some of the nanomedicine approaches that have been proposed and studied over the last decade to facilitate the delivery of therapeutic agents specifically for acute and chronic lung diseases. Development of nano-sized carriers including nanoparticles, or liposomes holds great potential for diagnosis and advanced delivery systems for immunomodulation in respiratory diseases; however translational studies are urgently needed to validate the use of nanotechnology for clinical applications.

Introduction:

The global burden of respiratory illnesses continues to be on the rise. The morbidity and mortality from acute and chronic respiratory conditions such as Acute Respiratory Distress Syndrome (ARDS), pneumonia, Chronic Obstructive Pulmonary Diseases (COPD), asthma, Idiopathic Pulmonary Fibrosis continues to remain high (Villar 2014; Boyle 2013; Boyle 2014; Barrecheguren et al 2018). In the past few decades although our understanding of molecular pathogenesis of acute and chronic respiratory conditions has increased exponentially there has been a major lag in

terms of development of new therapies in particular RNA and gene based approaches. Based on the molecular understanding of these diseases several promising targets have been identified as potential candidates for treatment, however, in many cases the translation to human therapies has been limited because of delivery systems. In particular proteins and peptides, are susceptible to degradation in the gastrointestinal tract and the first-pass metabolism after oral administration (Sadikot 2004; Sadikot et al 2014). The desired oral dosages should protect the drugs under unstable biological environments including drug degradation induced by the gastrointestinal tract and first-pass liver effects after oral administration before reaching the targeted sites, and to maximize the drug uptake and absorption in the cellular regions. The use of nanoparticles may allow the development of a broad armamentarium of targeted drugs against specific immune cells (da Silva 2017; Sadikot et al. 2014).

Nanoscience is the study of nanoscale materials, processes and devices. Nanotechnology involves the design, synthesis and characterization of materials that have a functional organization in at least one dimension on the nanometer scale. Nanoparticles, defined by the US National Nanotechnology Initiative as materials having at least one diameter measuring 100 nm or less, are increasingly utilized in consumer products. Nanotechnology is a powerful tool to design nanotherapeutics for different therapeutic and diagnostic purposes (Sadikot 2009; Koo et al 2005). Recent advances in nanotechnology have provided novel opportunities which have made it possible to develop a variety of nanoparticles (NPs) with diverse applications. These different types of nanoparticles include polymer, metal, dendrimer, liposome, micelles, nanocrystals, and nanotubes (Thorley 2013; van Rijt et al 2014). These nanoparticles provide several advantages over conventional drugs especially for pulmonary drug delivery to treat acute conditions such as Acute Respiratory Distress Syndrome (ARDS) or Pneumonia and chronic lung diseases such as Chronic Obstructive Pulmonary Disease (COPD), asthma, Idiopathic Pulmonary Fibrosis (IPF), and cystic fibrosis (Merchant 2016; Ratemi 2016; Willis et al. 2012**)**. The main advantages include local delivery to the zones to be treated, limiting systemic side effects and allowing for a reduction in the doses administered to the patient.

Nanomedicine approach for Acute Respiratory Conditions:

Acute respiratory distress syndrome (ARDS) develops secondary to a variety of causes and is characterized by severe hypoxemia and pulmonary edema secondary to increased permeability of the alveolocapillary membranes. Despite recent advances in diagnostic and therapeutic modalities Acute Respiratory Distress Syndrome (ARDS) still represents an unmet medical need because it is associated with significantly high morbidity and mortality (30–40%) with increased health care cost (Villar 2014). Hence, it represents and unmet medical need and novel strategies to treat this devastating disorder are much needed. Unfortunately, contemporary drug development approaches to address this challenge that center on single pathway inhibitors have shown to be insufficient

because diverse mechanisms are responsible for complex pathogenesis of ARDS.

We have developed nano-formulations to deliver anti-inflammatory agents and tested these in murine models of lung injury and inflammation. These approaches harness unique attributes of novel, biocompatible and biodegradable long acting peptides which are covalently linked to polyethylene glycol of molecular weight 2000 (DSPE-PEG2000). These are sterically stabilized phospholipid nanomicelles (SSM) in aqueous milieu (size, ~ 15 nm; that encompass amphipathic peptide drugs, human glucagon-like peptide-1 (GLP-1) (Lim 2011), triggering receptor expressed on myeloid cells (TREM-1) peptide (Yuan 2016) and 17-allylamino-17-demethoxygeldanamycin (17-AAG), a water-insoluble cytotoxic drug (Sadikot 2009). The lipid based formulations have shown to enhance neutrophilc lung injury. Our studies have also demonstrated that administration of nanoformulations is much more efficient than administering naked peptides.

Other strategies to deliver nanomedicine to the lungs have been investigated. In a murine model of acid induced lung injury Kaviratna et al used nanovesicles of 300 ± 50 nm composed of nonlamellar phospholipids as pulmonary surfactant aerosols for therapy. In this study a combination of dipalmitoyl phosphatidylcholine and dioleoyl phosphatidylethanolamine and optimized the nanovesicles was used. Nanovesicle aerosols reduced pulmonary edema and interestingly this study showed that that the nanovesicle aerosols of nonlamellar lipids improved the resistance of pulmonary surfactants to disintegration. This approach could be promising as a non-invasive aerosol therapy in acute lung injury (Kaviratna 2012). Nanovesicle surfactants used in their study can also act as suitable platforms for noninvasive delivery of agents to the alveoli.

Lin et al investigated Polyethyleneimine (PEI) and DNA nanoparticles-based gene therapy in a mouse model of acute lung injury (Lin 2013). This study showed that nanoparticles formed by PEI/DNA can deliver genes in mouse lung even in the presence of pre-existing ALI suggesting that PEI/DNA nanoparticle-based gene therapy could have potential in future clinical applications for inflammatory diseases such as ARDS (Lin 2013) .Together these studies highlight the potential of nanomedicine approach to administer targeted therapies for lung inflammatory diseases such as ARDS. This strategy amplifies drug delivery to the lung thereby maximizing efficacy and enhancing resolution of inflammation while reducing collateral damage to innocent bystander organs as can occur in patients with ALI and ARDS.

Ventilator associated pneumonia (VAP) is the second most common hospital-acquired infection in the intensive care units and results in increased mortality, morbidity, and medical costs (Barbier 2013; Kollef et al 2013). One of the main sources of bacterial colonization within the airway is the endotracheal tube (ETT) which can provide a direct conduit from the outside environment to the lungs allowing migration of bacteria to the alveoli. Many of the bacteria exude biomolecules such as exopolysaccharides, which allows the adherence of bacteria together forming biofilms while shielding them from antibiotics. In this type of extracellular matrix or biofilms bac-

teria become especially resistant to both antibiotics and the immune system of the patient (Maurice et al 2018). Reducing bacterial adhesion and biofilm formation on the surface of an ETT could potentially reduce further colonization of the ETT. Recent studies have investigated the use of coating endotracheal tubes with nanomaterials to inhibit the adhesion and growth of bacteria (Puckett 2010; Tran 2010; Tran et al 2011). There has also been an interest in using metal oxides, such as Zinc, iron and Magnesium oxide to reduce infections especially because many of these have inherent antimicrobial properties (Taylor 2011; Geilich 2013; Verrisimo et al 2015). These properties are enhanced when the particles are on the nanoscale rather than the microscale (Taylor et al 2011). Geilich et al used polyvinyl chloride (PVC) from conventional endotracheal tube and embedded them with varying concentrations of zinc oxide (ZnO) nanoparticles (Geilich 2013) and tested them for growth of S. aureus biofilms on these nanocomposite surfaces. They showed that the samples embedded with the highest concentration of ZnO nanoparticles had a significant reduction in bacterial colony counts compared to the controls. , Thus nanoparticle antioxidants may provide unique opportunities to counteract the pathogenicity of microorganisms and formation of biofilms.

Collectively, these studies suggest that surface engineering of biomaterials using a nanotechnology approach can minimize infections, and may thus decrease antibiotic usage; all of which can decrease the presence of antibiotic resistant bacteria in the clinical setting. Studies to investigate the potential of these nanomodified endotracheal tubes in the critical care setting are needed to establish the role of these novel approaches for prevention of VAP.

Nanomedicine Approaches for Chronic Respiratory Diseases:

Chronic respiratory diseases contribute to significant mortality and morbidity and recent data suggest that chronic lung diseases including COPD, asthma and interstitial lung fibrosis are on the rise. Pulmonary drug delivery compared to systemic drug administration presents a number of advantages to treat chronic lung diseases. Most of the chronic respiratory diseases are associated with inflammation. Structural changes and inflammatory response contribute to bronchial hyper-responsiveness and overall reduced lung function in patients with chronic asthma and COPD. Experimental studies using animal models have tested the efficacy of nanoformulations and have shown promising results.

Xiao et al investigated the immunotherapeutic effects of recombinant Caryota mitis profilin (rCmP)-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles in a murine model of allergenic asthma. By regulating Th1/Th2 equilibrium rCmP-loaded PLGA nanoparticles were able to prevent and show therapeutic benefit in this mouse model of asthma (Xiao 2013). In a murine model of ovalbumin induced asthma Park et al investigated the effects of silver nanoparticles on bronchial inflammation and hyperresponsiveness. They showed that silver nanoparticles exhibit anti-oxidant effects and attenuate antigen-

induced airway inflammation and hyperresponsivity (Park 2010). Wang et al investigated if curcumin nanoparticles can attenuate hyperresponsiveness in an ovalbumin rat model of asthma. They compared curcumin-solid lipid nanoparticles (curcumin-SLNs) and curcumin alone. They found that curcumin concentrations in plasma suspension were significantly higher in mice who received curcumin-SLN compared to curcumin alone. Following administration of the curcumin-SLNs, all the tissue concentrations of curcumin increased, especially in lung and liver. In the animal model of asthma, curcumin-SLNs effectively suppressed airway hyperresponsiveness and inflammatory cell infiltration and found that curcumin SLN were much more efficacious at attenuating inflammation in ovalbumin (OVA)-induced allergic rat model of asthma (Wang 2012).

Recently, we have reviewed the delivery of nanoparticles in lung inflammation and have examined total as well as regional particle depositions in the whole-lung airway model (WLAM), as inhaled from a dry powder inhaler (DPI). The validated modeling methodology has been employed to study the delivery of curcumin aerosols into lung airways using a commercial DPI (Kolanjiyil 2017). Chen et al used an aerosolized liposome formulation for inhalational delivery of Salbutamol sulfate (SBS) in rat and guinea pig model of asthma. Pulmonary delivery of liposomes in their rat model showed that the liposomes were effectively distributed in the airways and lungs, and that the release of SBS from liposomes was sustained for at least 48 hours. The pharmacodynamics were different in the guinea pig model which showed that the anti-asthmatic effect of SBS liposomes persisted for up to 18 hours, whereas that of free SBS solution was less than 8 hours (Chen 2012). These data suggest that the pharmacodynamics and pharmacokinetics may also depend on the size of the lungs.

Although angiogenesis has shown to contribute and is a feature of asthmatic inflammatory responses, specific therapeutic anti-angiogenesis interventions have not been investigated. A study by lanza et al investigated anti-angiogenic prodrug therapy delivered by a micelle therapy in a house dust mite allergic asthma model. They showed a significantly reduced microvascularity, bronchial remodeling, and airway hyper-responsiveness in a rat model of allergic asthma. Their study suggests that direct anti-neovascular therapy can contribute significantly to asthma management (Lanza 2017).

In a recent study by Amore et al two solid lipid microparticles (SLMs) using chitosan (a natural linear bio poly amino saccharide) and alginate such as mucoadhesive polymers were tested for their biocompatibility and effectiveness. The study compared SLMs with the free drug in controlling senescence and inflammatory processes in cigarette smoke extracts in an experimental model. Their data showed that fluticasone propionate (FP)-loaded SLMs were more effective than FP alone in controlling oxidative stress thus suggesting that FP-loaded microparticles could be a promising strategy for the treatment of the chronic inflammatory pulmonary diseases (Amore 2017). The utility of chitosan in pulmonary drug delivery systems was recently reviewed by Dua et al (Dua 2017). The review high-

lights that currently there is a lack of clinical data and approaches for the use of chitosan and further studies are needed before they can be tested in clinical studies. In a recent study Vij et al studied the efficacy of a PEGylated immuno-conjugated PLGA-nanoparticle (PINP) to selectively deliver ibuprofen specifically to neutrophils which are often the most abundant in refractory inflammatory conditions. In a murine model of obstructive lung disease they show that they were able to efficiently target the drug to neutrophils allowing for an enhanced resolution of inflammation (Vij 2016).

The use of nanoparticles in measuring lung morphology and to assess their applicability was assessed and reviewed by Londahl et al. Their study suggests that the recovery of inhaled airborne nanoparticles may be more useful for diagnosis of airways and may offer several advantages (Londahl 2016). Although many of the above studies demonstrate efficacy of nanoformulations administration of nanoparticles to the lungs may also pose the risk of developing allergic inflammation and asthma and will need careful evaluation.

Summary and Conclusions:

Development of nano-sized carriers including nanoparticles, or liposomes holds great potential for diagnosis and advanced delivery systems for immunomodulation in respiratory diseases. Nanoparticles can be used to more effectively manipulate or deliver immunologically active components for acute or chronic lung diseases. The ability to target specific cells in tissue without causing damage to distant organs to detrimental actions of drugs is an exciting avenue to explore although still needs to be established at a clinical level. The use of nanomedicine may also play a role in controlling conditions such as ventilator associated pneumonia by using nanoparticle coated endotracheal tubes which demonstrate antimicrobial properties. The application of nanotechnology to drug delivery has the potential to have an impact in many areas of medicine particularly so for lung diseases. Nanomedicine offers several advantages including increased bioavailability, with controlled release and targeted delivery with reduced toxicity. However the safety, large scale production and cost effectiveness will need to be established as these have not been studied in clinical settings. Translational studies with different nanotechnology platforms will need to demonstrate safety, efficacy, and clear therapeutic advantage over existing treatments for respiratory condition in addition to cost-effectiveness in production. Rigorous clinical testing will be needed to define the side of effects of nanoparticles when administered to the lungs. There is an urgent need to pursue translational studies using nanomedicine approach to develop novel tangible therapies.

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