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The potential role of nano- and micro-technology in the management of critical illnesses ☆

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ABSTRACT

In recent years nanomedicine has become an attractive concept for the targeted delivery of therapeutic and diagnostic compounds to injured or inflamed organs. Nanoscale drug delivery systems have the ability to improve the pharmacokinetics and increase the biodistribution of therapeutic agents to target organs, thereby resulting in improved efficacy and reduced drug toxicity. These systems 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. The mortality in many of the critical illnesses such as sepsis and acute respiratory distress syndrome continues to remain high despite of an increased understanding of the molecular pathogenesis of these diseases. Several promising targets that have been identified as potential therapies for these devastating diseases have been limited because of difficulty with delivery systems. In particular, delivery of peptides, proteins, and miRNAs to the lung is an ongoing challenge. Hence, it is an attractive strategy to test potential targets by employing nanotechnology. Here some of the novel nanomedicine approaches that have been proposed and studied in recent years to facilitate the delivery of therapeutic agents in the setting of critical illnesses such as acute respiratory distress syndrome, sepsis and ventilator associated pneumonia are reviewed.

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Contents

1. Introduction

The global burden of critical care illnesses continues to be on the rise. The morbidity and mortality from critical illnesses such as sepsis and acute respiratory distress syndrome continues to remain in the range of 40–60% despite of improved supportive care [1–4]. Sepsis, multi-organ failure and acute respiratory distress syndrome represent an unmet medical need and there is an urgent need to develop new therapies to treat patients with this condition. Despite of timely administration of antibiotics exuberant host inflammatory response can be overwhelming in sepsis which can emanate into multi-organ failure. In the past two decades our understanding of molecular pathogenesis of sepsis and ARDS has increased exponentially however there has been a major lag in terms of development of new therapies for these devastating illnesses [5–7]. Based on the molecular understanding several promising targets have been identified as potential candidates for treatment for multi-organ inflammatory diseases however they have not been translated to human therapies because of the limitation with delivery systems. In particular proteins and peptides are susceptible to the gastrointestinal tract and the first-pass metabolism after oral administration. 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

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administration before reaching the targeted sites, and 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.

Nanoscience is the study of nanoscale materials, processes and devices. The concept of nanotechnology was introduced by Feynman while describing molecular machines building with atomic precision [8]. The term nanotechnology was introduced by Taniguchi in 1974 to describe the precise machining and finishing of materials, progressing from larger to smaller scales and ultimately to nanoscale [9]. Nanotechnology involves the design, synthesis and characterization of materials that have a functional organization in at least one dimension on the nanometer scale [10–13]. 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. Nanomaterials are being used in the production of consumer products such as sunscreens, cosmetics and food products such as is bottles made with nanocomposites that minimize the leakage of carbon dioxide out of the bottle thus increasing the shelf life of carbonated beverages without having to use heavier glass bottles or more expensive cans. Another example is food storage bins with silver nanoparticles embedded in the plastic. The silver nanoparticles kill bacteria from any food previously stored in the bins, minimizing harmful bacteria [14].

In 1977 Drexler introduced the application of nanotechnology to molecular biology and medicine [15]. Since then the medical community has vested in investigating the unique properties of nanomaterials for various applications. 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 and its associated treatment tools. Nanobiotechnology and nanoscience can provide innovative techniques to deliver drugs targeted to the site of inflamed organs.

Nanoparticle drug-delivery systems can be used to provide delivery of drugs, improve bioavailability and sustain release of drugs for systemic delivery. These systems have the ability to improve the pharmacokinetics and pharmacodynamics of agents allowing an increase in the biodistribution of therapeutic agents to target organs, resulting in improved efficacy while minimizing drug toxicity [10,16]. Nanocarriers are particularly designed to target inflammation and cancer that have a permeable vasculature. A number of different strategies have been proposed for modification of nanoparticle characteristics to control their behavior within biological environments, like cell-specific targeted drug delivery or modified biological distribution of drugs, both at the cellular and organ level. Common nanoparticle systems include polymeric nanoparticles, lipid nanoparticles, polymeric emulsions through the chemical modification of the surface and inorganic nanoparticles.

These methods are particularly attractive for delivery of molecular targets in the setting of critical illnesses such as adult respiratory distress syndrome and sepsis. In particular these systems can overcome delivery mediated hurdles that are difficult to address with other traditional approaches such as small molecules or monoclonal antibodies. A desirable delivery system should lead to increased concentrations of therapeutic payloads at target sites, and should ultimately raise the therapeutic index.

2. Nanomedicine approach for acute respiratory distress syndrome

ARDS arises from direct and indirect injury to the lungs and results in a life-threatening form of respiratory failure with diffuse, bilateral lung injury and severe hypoxemia caused by non-cardiogenic pulmonary edema which affects approximately 1 million people world-wide annually [17]. Despite recent advances in diagnostic and therapeutic modalities ARDS still represent an unmet medical need because it is associated with appreciable morbidity and mortality (30–40%) and substantial medical expenditure. Hence, there is an urgent need to develop and test new drugs to treat this devastating disorder. Unfortunately, contemporary drug development approaches to address this challenge that center on mono-metabolic pathway inhibitors are hindered by diverse mechanisms underlying the complex pathogenesis of ARDS.

To overcome both barriers, we emulated in devising an innovative nanopharmacotherapeutic strategy consisting of long-acting and safe nanomedicines that selectively target and inhibit distinct key intracellular proinflammatory signaling cascades activated during lung inflammatory response. Accordingly, we have harnessed unique attributes of novel, long-acting, biocompatible, and biodegradable antiinflammatory nanomedicines [10,18,11,19]. They consist of amphipathic peptide drugs, human glucagon-like peptide-1 (GLP-1), [20], triggering receptor expressed on myeloid cells (TREM-1) peptide and 17-allylamino-17-demethoxygeldanamycin (17-AAG), a water-insoluble cytotoxic drug. This innovative approach consists of self-assembly of each drug with U.S. FDA-generally regarded as safe (GRAS) distearoylphosphatidylethanolamine covalently linked to polyethylene glycol of molecular weight 2000 (DSPE-PEG_{2000}), that forms long-acting, biocompatible, and biodegradable, sterically stabilized phospholipid nanomicelles (SSM) in aqueous milieu (size, ~15 nm; [18,21–23]).

In a recent study, we tested the efficacy of GLP-1 nanomicelles in a murine model of lipopolysaccharide (LPS)-induced lung injury [20]. In vivo administration of GLP1–SSM to mice with LPS-induced lung injury resulted in dose-dependent anti-inflammatory activity with significant downregulation of lung inflammation. Similar therapeutic activity was not detected in mice that were treated with control nanomicelles or with GLP-1 in saline, indicating that these nanocarriers played a critical role in protecting the enzyme-labile GLP-1 and delivering it to inflamed tissues in vivo. This was the first study to show that a lipid-based nanoformulation of GLP-1 is effective at attenuating inflammation in vivo in a murine model of ARDS [20]. We have also tested the efficacy of TREM-1, a pro-inflammatory superimmunoglobulin receptor [24] nanomicellar peptide in a model of LPS induced sepsis and lung injury and shown that TREM-1 nanomicelles are more efficacious than the naked peptide at abrogating inflammation [22].

One of the major effects of lung injury and inflammation entails inactivation of pulmonary surfactant because of inhibitors like albumin, fibrinogen, and serum [25–27]. Currently existing intratracheal surfactants are ineffective in this condition. Particles having an aerodynamic diameter of <2.5–3 μm can reach the bronchiolar and alveolar regions, whereas larger particles become trapped in the upper airways. 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. They employed a combination of dipalmitoyl phosphatidylcholine and dioleoyl phosphatidylethanolamine and optimized the nanovesicles for an improved airway patency in the presence of albumin and serum. By employing a murine model of acid-induced lung injury they showed that treatment with nanovesicle aerosols at a dose of 200 mg/kg, alveolar protein leakage decreased from 8.62 ± 0.97 μg/mL to 1.94 ± 0.74 μg/mL, whereas the airway patency of the bronchoalveolar lavage fluid increased from 0.6 ± 0.0% to 91.7 ± 1.05%. They demonstrated that the nanovesicle aerosols of nonlamellar lipids improved the resistance of pulmonary surfactants to inhibition and could be promising as a noninvasive aerosol therapy in acute lung injury [28]. Nanovesicle surfactants used in their study can also act as a suitable platform for noninvasive delivery of agents to the alveoli.

Vector based gene therapy has had major limitations with delivery and side effects from viral vectors. In a recent study Lin et al. investigated Polyethyleneimine (PEI) and DNA nanoparticle-based gene therapy in a mouse model of acute lung injury [29]. PEI is a cationic polymer with repeating units composed of an amine group and a two-carbon aliphatic spacer, with the molecular formula $(C_2H_5N)_n$. PEI can be in linear or branched forms which have been shown to be efficient for gene delivery in vivo mainly with alveolar epithelial cells as major targets. Lin et al. showed that nanoparticles formed by PEI/DNA can deliver genes

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