

Nanomedicine for Respiratory Diseases

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INTRODUCTION

Development of a wide spectrum of nanoscale technologies is starting to make fundamental changes in diagnosis, treatment and prevention of diseases. Nanotechnology includes a wide variety of sciences and it is fundamentally based on manipulation of molecules and atoms that form nanoscale structures measuring 100 nanometer or smaller in size that still carry all the physicochemical properties of that specific element. In fact, we may very well demonstrate the physical and chemical properties of materials if we minimize them in size to reach a small cluster of atoms (1).

Nanometer is one billionth of a meter. In order to understand its actual size the following example by John Miller may be helpful (2). Size of an American Dime is 1000 micron. One tenth of it is the size of a human ovule which is equal to 100 micron. A red blood cell is approximately one tenth of it or equal to 10 micron. A neural axon has a thickness one tenth of it which is equal to one micron. This axon can host ten viruses. So far we have discussed 100 nanometer. Cell membrane has a thickness one tenth of it and a DNA thread has one fifth of this thickness. Size of an aminoacid is about one third of it. We are now discussing one nanometer scale and this hypothetical nanoparticle like an aminoacid preserves all the physical and chemical properties (2).

Nanotechnology has been extensively used in various fields of science and technology such as spatial, terrestrial and naval/marine industries, food industries, military and

security affairs, agriculture, animal husbandry and health sciences. One of the most important applications of nanotechnology is in the field of medicine known as nanomedicine (3,4).

The innovation of nanotechnology in the field of medicine based on this new technique has been named as nanomedicine by the American National Institute of Health (NIH) (5). One of the most important applications of nanotechnology is in medicine. This technology is capable of employing molecular genomics and proteomics-based discoveries for treatment of a wide range of diseases.

This new field of science has become increasingly popular for diagnosis, treatment, prevention and follow ups of diseases (6,7). Nanomedicine is still in its infancy and has been noticed only recently in the past few years. However, searching PubMed and other databases revealed that many articles are now published weekly in medical journals on this subject. Our understanding about the molecular structure and nanoscale particles in the human body has greatly improved during the recent years. However, the aspects related to diagnosis, treatment or prevention of chronic or severe diseases have not advanced significantly. Diseases like cancer, diabetes, chronic pulmonary diseases, cardiovascular diseases, chronic inflammatory diseases (autoimmune and others), neurologic disorders, renal diseases and infection are big challenge that are faced by medical scientists. Multidisciplinary approaches that link material science

specialists to medical scientists may help in findings efficient diagnostic and therapeutic intervention.

Nanoscale materials manifest specific physical, chemical and biologic properties (7,8). Nanoscale synthetic structures like nanoparticles and nanodevices that are about the same size as their biologic substitutes can easily react with natural biologic substances on the cell surface or intracellular. Nanomedicine has been investigated for various applications. On one hand, quantum dots can be used for molecular diagnostic and imaging purposes and on the other hand, we can benefit from its therapeutic value by using nanocarrier and integrated medical nanosystem. More importantly, by using nanosystem we can enhance healing and accelerate repair in injured tissue (9). However, as mentioned efficient advancement and development of this field of science require a multidisciplinary approach (10,11).

All nanoparticles do not act the same. They manifest different behaviors in a biologic microenvironment. Their stability, survival and intra- and extra-cellular distribution differ as well. The mentioned factors depend on their chemical structure, morphology and size. In most cases, nanoparticles are used for a single purpose. However, their multipurpose application has also been reported in some studies (7).

Multidisciplinary cooperation in nanomedicine can also be used in the field of chronic pulmonary diseases and acceptable reports can be found in the literature regarding the three domains of molecular diagnosis, targeted drug delivery and reconstruction (8). In this review, we focus on a summary of application of nanomedicine in respiratory diseases. Before reading this review, we invite our valuable readers to refer to an article published in the Iranian Journal of Pathology (12).

PULMONARY DISEASES AND NANOMEDICINE

Respiratory diseases include a wide spectrum of illnesses affecting individuals in all age groups from the fetal period to the elderly. By increased life expectancy,

hope for a comfortable life for elderly becomes specially important, and nanomedicine may help. The lung is a very suitable target for drug delivery due to easy, non-invasive and safe administration via inhalation aerosols. Direct delivery to the site of action for the treatment of lung disease and injuries, and because of availability of lavage surface areas for local drug action and systemic absorption of drugs (13,14). In this regard, nanomedicine researchers by considering three basic principles in this subject, respiratory disease, namely:

1. Diagnosis and imaging based on nanotechnology
2. Targeted drug delivery
3. Reconstructive surgery

were able to benefit from nanomedicine technology in some chronic pulmonary diseases (8). Since nanocarrier systems can be easily transferred to the airways (14), many respiratory diseases has been treated. Pulmonary diseases that have so far been searched for this purpose are a large list, including chronic Obstructive pulmonary disease, cystic fibrosis and some other genetic disorders, tuberculosis and Infectious diseases, cancer, and pediatric diseases and we are reviewing some of them.

OBSTRUCTIVE PULMONARY DISEASES

Among obstructive pulmonary diseases, bronchial asthma and COPD are among global health hazards in terms of mortality and morbidity. It is estimated that COPD will be ranked the third cause of death by 2020. Although the mentioned two diseases have significant differences with each other; there are lots of similarities between the two. Characteristics of the infection in these two diseases are different. The basis of nanomedicine activities in diseases were discussed in a study by John et al. in Ann Arbor, MI (15). Considering the role of selectin in pulmonary infections leading to bronchial asthma and creation of airway hyper-reactivity (AHR), they evaluated the role of a protein nanoparticle P-selectin antagonist with anti-inflammatory effects in allergic airways disease in in-vitro asthmatic models (15). Using the same concept, Kumar et al. in Florida were able to obtain good results by

using Chitosan IFN-genome-pDNA nanoparticles (CIN) therapy for diagnosis and treatment of allergic asthma in an animal model (16). Kong et al. used the same model for asthma (17). Although a suitable model has not been presented for COPD, some researches, discussed for the role of nanomedicine in COPD (17).

CYSTIC FIBROSIS

Cystic fibrosis is usually manifested as an autosomal recessive disease. It is caused by the dysfunction of the epithelial chloride channel cells due to the mutation in cystic fibrosis trans-membrane regulator gene (CFTR). Since the CFTR gene was discovered in 1989 more than 1900 mutations have been reported to cause CF and significant effort has been put forth in to gene therapy to find a mutation independent cure for CF (18). In addition to gastrointestinal system, respiratory system is another target for this disease. Over- production and altered composition and consistency of the mucous secreted in the lungs results in airway obstruction making the lungs susceptible to recurrent infections resulting in eventual death of patients.

Airway changes as the result of mucous secretions in this disease lead to hyperplasia and metaplasia of bronchial gland cells and superficial goblet cells which per se in a vicious cycle cause overproduction of mucous and subsequent destruction of mucociliary system. Eventually, mucous plugs cause obstruction of airway and make the lungs susceptible to infection. It has been proved that the airway mucus composition is widely variable. The most important type is a large oligomeric gel-forming mucin glycoprotein with a molecular mass of 10 to 40 million Daltons.

In the respiratory system, mucin is secreted by two main sources. For instance, MUC5AC or MUC2 are secreted by the superficial epithelial goblet cells while MUC7 and MUC5B are mainly secreted by the glandular cells. However, the glandular mucin can also be secreted by the superficial cells under special circumstances i.e. inflammation. Among these mucins, MUC5B and

MUC5AC are the most important gel-forming mucin glycoproteins. Biochemical differences have been demonstrated between the natural mucin and CF mucin. Also, the latter is heterogeneous.

The goal of nanotechnology is firstly to affect and manipulate CFTR gene by employing nanospheres DNA which is still under investigation. A transfection study has demonstrated that the nanoparticles implanted in the tracheal lining (9HTEa) with a plasmid-containing nanosphere resulted in expression of CFTR in 50% of cells. Another theory is that the delivery of nanoparticles that can change the composition of mucin based on this nanosystem may be an interesting candidate for the delivery of therapeutic nanoparticles in this disease (7,8,18).

PULMONARY TUBERCULOSIS

Some experimental studies have evaluated the potential efficacy of nanoparticles used in antimicrobial treatments. Application of nanotechnology for treatment of tuberculosis was the subject of primary studies. Pandey and coworkers in India have reported the effect of direct delivery of anti-tuberculosis drugs by nanoparticles in several studies (19). Pandey's group directly entered anti-tuberculosis drug nanoparticles fabricated through multiple emulsion vacuum-dried method into the lungs of guinea pigs by nebulization. One time nebulized administration of drug kept the drug level high for 6 to 8 days in the blood stream and up to 11 days in the lungs. In this method, half-life of the drug and its bioavailability were higher compared to its oral administration or injection of drugs. This effect for rifampin, isoniazid and pirazinamid was 12.7, 32.8 and 14.7 times, respectively. In this experiment, by five times application of Poly (D,L-lactide-co-glycolide) (PLG) as a carrier in drug inhalation at 10 days interval the guinea pig become completely free from the TB bacilli. In comparison, by oral administration of drug, this result could be achieved after 46 times of administration (19). Bhardwaj and coworkers in India used a combination of chemotherapeutic agent-loaded vesicular

system to overcome TB. They developed ligand appended liposome with Dry Powder Inhaler (DPI), using various in vitro and in vivo parameter and reported good result (20). Several other studies have also evaluated the use of anti-TB nanoparticle drugs delivery. The obtained results all mentioned the following advantages:

- Shortening the treatment course
- Targeted drug delivery and therapy
- Use of minimum required drug dosages
- Preventing drug side effects

Ventilator-associated pneumonia (VAP), a device related pneumonia which is directly related to the colonization of endotracheal tube (ETT) during long term mechanical ventilation. The diagnosis of VAP is difficult because of unspecific radiographic and clinical signs. Machado et al. used nanomodified coatings on ETT provided an effective strategy to prevent biofilm formation and ETT colonization. They used selenium and iron oxide nanoparticles to penetrate into biofilm reaching the cells (21).

LUNG CANCER

Researchers in the recent years have focused on the application of gene therapy in lung cancer offering various encouraging strategies. Clinical phase I and phase II programs have been implemented as well. However, it has not exceeded the treatment of small local tumors. An important problem was the fact that drug delivery with carriers was temporary and transient and was not sufficiently efficacious.

However, nanosystems have been reported to target and deliver the drug in situ to selectively kill cancer cells, decreasing toxicity on healthy organs and tissues as well as side effects. Some nanoparticles have been reported to overcome tumor resistance. Several nanosystem for the diagnosis and treatment, such as dendrimer, polymeric micelles, super paramagnetic iron oxide cores, gold nanoparticles, liposomes and other lipid nanoparticles have been reported with reasonable results (22, 23).

Gopalan et al. (24) Prabha et al. (25) and others achieved successful results in this domain by using nanosystem. However, treatment of lung cancers is still limited to local tumors. One reason is the immunologic reactions against virus and gene carriers. Nevertheless, for nanoparticles, due to their small size and biocompatibility, they can reach the target site without being detected by the immune system and suffer cellular uptake or deliver the drug in the tumor vicinity (22).

Gopalan et al. (24) suggested another technique for gene transfer which was effective and non immunogenic and had systemic application. They used a non-viral nanoparticles carrier named DOTAP/ cholesterol that could deliver tumor suppressing genes directly to the tumor with a controlled release program at the tumor site. Prabha et al. (25) conducted a similar study and used PLGA and anti-proliferative gene P53 in breast cancer cells. Gopalan used systemic DOTAP/cholesterol nanoparticles even for treatment of disseminated tumors (24). Broza et al. demonstrated the feasibility of nanomaterials-based sensors for identifying the breath-print of early-stage lung cancer and for short-term follow up after lung cancer resection (26). Barash et al. demonstrated histological lung cancer classification by using gold nanoparticles (GNP) sensors with a device profiles volatile organic compounds (VOCs) for detection lung cancer specific pattern (27).

CONCLUSION

This review tried to briefly discuss the importance and application of nanomedicine technology in diagnosis, treatment and prevention of human illnesses especially some respiratory diseases.

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