Nanotechnology based therapeutics in lung diseases: An update

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Abstract:The multidisciplinary field of nanomedicine study incorporates elements of traditional sciences such as chemistry, physics, biology, and materials science. Promising research findings indicate that nanomedicine will radically change medicine through the development of novel approaches to therapeutic agent delivery, vaccine development, and nanotechnology-based medical detections. Lung diseases, encompassing conditions such as asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, and lung cancer, represent a significant global health burden. Traditional therapeutic approaches often face challenges including limited drug efficacy, systemic side effects, and poor targeting. Current approaches to targeting lung diseases involving the relatively new "nanomedicines" have grown significantly during the last decade. It is abundantly clear that the application of nanotechnology in the detection and treatment of lung diseases will modify medical practice sooner rather than later through the development of nanoscale drug delivery systems, diagnostic tools, and regenerative therapies. This review explores the recent advancements in nanotechnology for treating lung diseases, focusing on nanoparticle drug delivery systems as well as cancer and infections of the lung. In conclusion, the integration of nanotechnology in pulmonary therapeutics holds promising potential for improving patient outcomes and revolutionizing the management of lung diseases.

Keywords: Nanotechnology, active targeting, lung cancer, tuberculosis.

INTRODUCTION

Among the leading causes of death worldwide [1], lung problems accounted for one in six deaths globally each year in 2018 (WHO report) and are poised to claim one in five deaths by 2030. Efforts to address this pressing clinical emergency have involved both the development of new therapeutic techniques and the improvement of current treatments. It is widely acknowledged that the use of nanotechnology in medicine, or "nanomedicine" will revolutionize the practice of medicine by facilitating the development of vaccines, new approaches to the delivery of therapeutic agents, the use of nanotechnology in medical detection and therapy (theranostics), and improved drug formulation in the field of personalized medicine [2]. Moreover, medication release can be controlled to acieve prolonged release, leading to higher efficacy and longer dosing intervals. These approaches can aid in the customization of nano medicine carriers to specifically target certain disease sites. Thus advances in the field of nanomedicine have made it possible for scientists to attain favorable results without having to alter existing prescribed drugs [3].

Applications of Nano-medicine in lung diseases:

Drug delivery, immunization, and disease diagnosis are the most developed areas of current nanotechnology inquiry, particularly in relation to the lung; in contrast, study of imaging, personalized medicine, and theranostics—the integration of therapeutic and diagnostic characteristics into a single nano-platform—is at a lower developmental stage. There is currently a substantial body of published research on the use of nanoparticles as a drug delivery system (DDS) to the lung [4, 5]. Since nearly 40% of currently available drugs are poorly water-soluble, a variety of nano-drug delivery systems (nano-DDS) offer a means to circumvent these solubility issues and extend the circulating half-life of the therapeutic agents. Biomacromolecular medications, including messenger RNA (mRNA), small interfering RNA (siRNA), and DNA, are frequently broken down in bodily fluids, making it difficult to administer therapeutic amounts to the intended organ. It has been demonstrated that using nanoparticles as DDS enhances the stability of biomacromolecular medications and inhibits their early disintegration and quick clearance in vivo, allowing for the delivery of

these medications. Moreover, compared to viral vectors, which are typically employed for biomacromolecular agents, nano-DDS, a non-viral vector, is less immunogenic and hazardous. Moreover, there are other ways to give nano-DDS, including intravenous, oral, and inhalation. When drug candidates are delivered using nanoparticles, their bioavailability can be increased and natural barriers like the mucosa can be bypassed. Taking advantage of the improved permeability and retention (EPR) effect, anti-cancer drugs contained in a nano-DDS may "passively target," or selectively accumulate in tumor tissue as compared to normal tissues. Because of the tumor's inadequate lymphatic drainage, the leaky tumor vasculature has interendothelial gaps, which allows nanotherapeutics to evade the bloodstream and locate them functionally inside the tumor tissue, causing EPR [6].

The creation of nanoparticles that are selectively targeted—a process known as "active targeting"—represents one of the most fascinating possibilities in nanomedicine as it relates to the lung [7]. Targeted nano-DDS is a precision medication that is intended to increase the accumulation of drug molecules in certain disease locations while minimizing exposure to healthy tissues. This lowers the amount that must be given to the patient and, consequently, the risk of adverse effects. Designing a targeted nanodrug delivery carrier most commonly involves conjugating specific moieties, such as antibodies, small molecules, proteins/peptides, and nucleic acids, to the surface of nanoparticles. Antibiotic-loaded nanoparticles directed towards the infection site have been demonstrated to greatly increase antibacterial efficacy. Furthermore, directing the nano-DDS to cancer cells is made possible by the over expression of surface markers on tumor cells that are missing on normal cells [8]. Encasing or conjugating the therapeutic compounds in polymeric, liposomal, micelle, or dendrimer nanoparticles enables the aforementioned nanomedicine uses. Figure 1 provides a schematic representation of the idea of passive and active targeting as well as the main benefits of targeted nano-DDS.

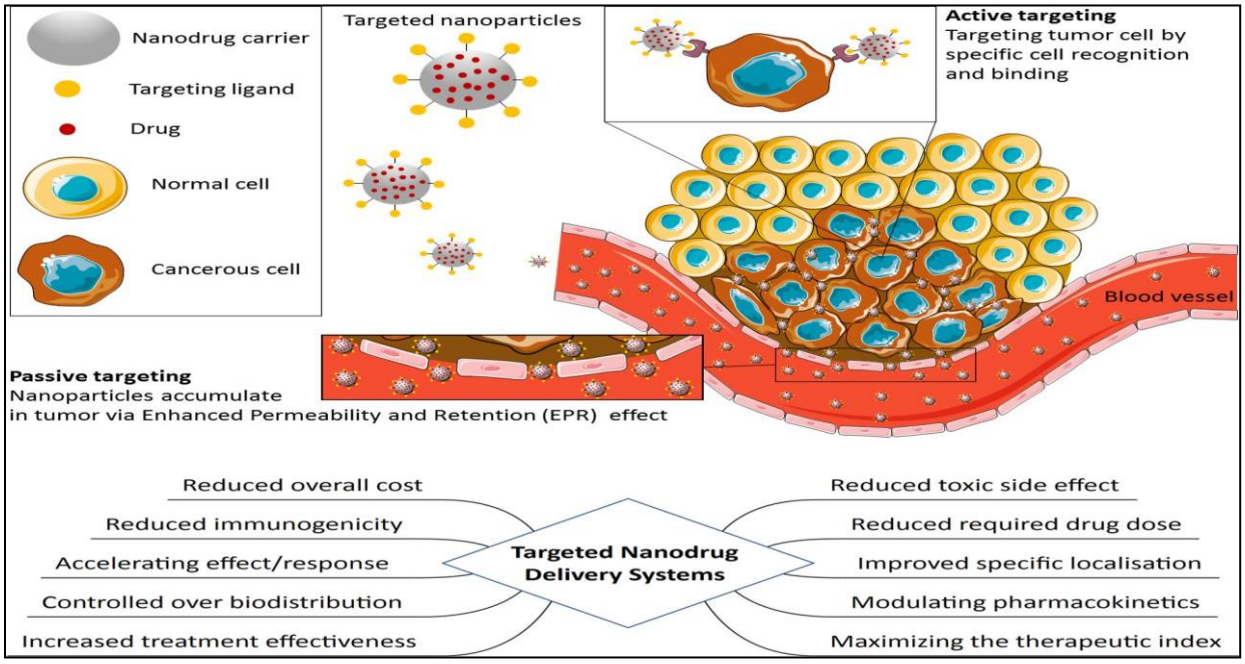

Figure 1: The advantages of attacking cancer cells both passively and actively

Figure 2 summarizes the use of nanomedicine in respiratory illnesses. It can be used as medication carriers, as well as diagnostic and detection instruments for a variety of lung ailments. Nanocarriers have the potential to be very sensitive and specific early illness diagnosis tools due to their regulated sizing and little toxicity. [9]

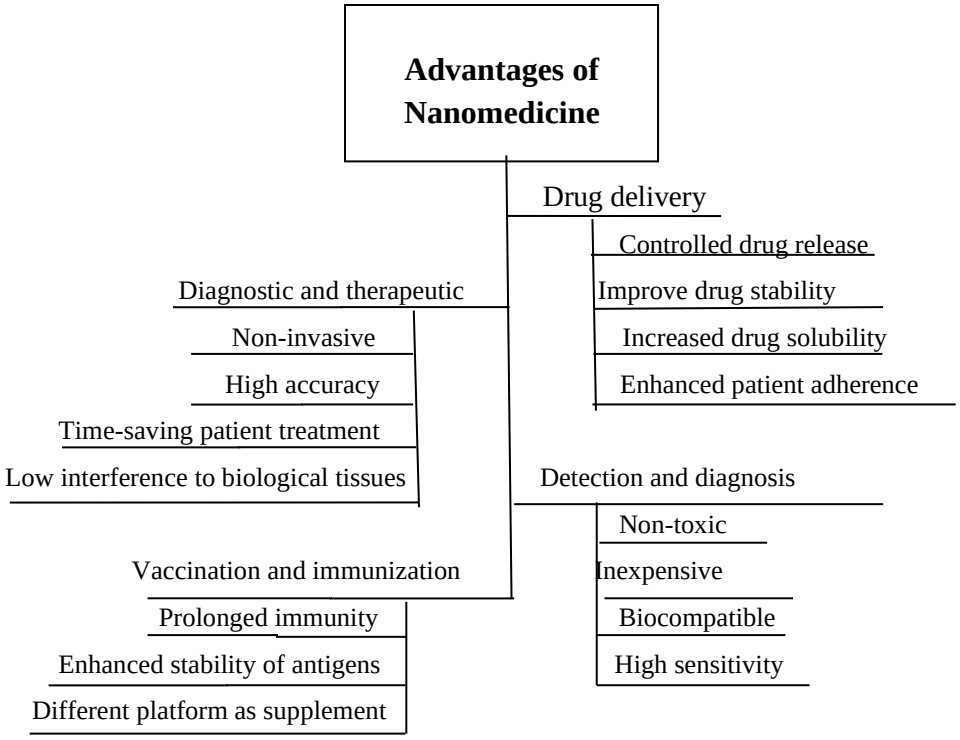

Figure 2: Benefits of using nanomedicine in the treatment of lung diseases

LUNG CANCER:

Anti-cancer drugs in nano sized formulations:

Lung cancer is the most prevalent cause of cancer-related deaths worldwide, accounting for around 1.6 million cancer-related deaths in 2012 [10]. More powerful anti-cancer drugs are being produced in an attempt to lessen this clinical burden. Nanotherapeutics have been utilized to treat cancer over more than 20 years, ever since Doxil was legalized in 1995 to treat Kaposi's disease related to AIDS. The reality that this was the first novel nanotherapeutics to be approved by the FDA has acted as a spur for ongoing research into novel nanotherapeutics for cancer treatment.

The potent chemotherapeutic drug paclitaxel is widely used to treat a range of solid tumors, including lung, breast, and ovarian cancer. Due to its' poor water solubility, it is administered with surfactants such as Cremophor EL as solubilizer to increase its bioavailability. However, excipients such as these have been connected to high levels of toxicity and adverse effects, such as hypersensitivity and neurotoxicity [11]. In order to treat non-small-cell lung cancer (NSCLC), Genexol-PM is a polymeric nano micelle formulation of paclitaxel wherein paclitaxel is encased in nanosized polymeric micelles. This enables a significantly higher dose of paclitaxel.

Immunotherapy in lung cancer

Immunotherapy has developed as a potent supplementary lung cancer treatment strategy. Programmed death ligand 1 (PD-L1) is an immune regulatory protein that plays a negative role in effector T-cell activation regulation. Immunotherapy studies have demonstrated that drugs that target programmed cell death 1 (PD-1) and its ligand, PD-L1, are highly effective in significantly extending patient survival in patients with advanced non-small cell lung cancer (NSCLC) [14]. A logical extension of these studies is currently being conducted to assess the efficacy of carboplatin + Abraxane in combination with cancer

immunotherapy. These trials include a phase II study in which patients with metastatic squamous non-small cell lung cancer are treated with the humanized monoclonal antibody atezolizumab (targeting PD-L1), and a phase III trial in which patients are treated with the humanized antibody pembrolizumab.

Active targeting of nanomedicine for lung cancer

The goal of "active targeting" is to minimize undesirable side effects while optimizing the concentration of the active therapeutic agent at the cancer site. This will result in improved patient compliance and treatment effectiveness. This is achieved by applying targeting ligands to the surface of the nanocarriers, which bind to specific tumor cell receptors that are absent on the surface of healthy cells. Docetaxel is contained in BIND-014, a polymeric nanodrug carrier that targets the prostate-specific membrane antigen. A phase II clinical trial for BIND-014 preclinical testing and clinical translation study showed a significant reduction in tumor volume in patients with cholangiocarcinoma and multiple lung metastases, while free docetaxel treatment for cholangiocarcinoma showed limited activity [15].

Cystic fibrosis:

Cystic fibrosis (CF) is caused by mutations in both copies of the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. It is the most prevalent autosomal recessive hereditary illness. Gene therapy has been actively used to fix the CFTR gene mutation at the cellular level, as the disease is caused by this mutation. This method involves inserting the right copies of the CFTR gene into the impacted airway epithelial cells. Viral and non-viral vectors are typically the two major kinds of vectors utilized in investigations to transfer the CFTR gene. [16] Non-viral vectors and such as nonmaterials, have a far longer shelf life, exhibit fewer immunomodulatory reactions, and tolerate repeated delivery better than viral vectors. They are also less difficult and expensive to create.

Since CF mucus contains high concentrations of negatively charged macromolecules like mucins and actin filaments, non-viral vectors are typically made to be positively charged in order to form an electrostatic bond with the adversely charged therapeutic nucleic acid and enhance particle immobilization. Non-viral vector based on polyethylene glycol nanoparticles and containing plasmid DNA encoding the CFTR gene was the subject of the first clinical investigation. The safety and gene transfer efficiency evaluation showed that nanoformulation is a successful vector for the transfer of genes, resulting in a partial nasal probable correction with no adverse effects.

BACTERIAL INFECTION:

According to the WHO, lower respiratory infections account for 3.2 million fatalities annually, making them the fourth most common cause of mortality. There is compelling evidence that, in both CF and non-CF infected patients, bacterial infections are associated with higher death rates, more frequent exacerbations, faster lung function loss, and more inflammation. [18]

Amikacin, a semi-synthetic amino glycoside antibiotic, developed from kanamycin A and is used to treat severe chronic lung infections caused by multidrug-resistant (MDR) organisms, such as Pseudomonas aeruginosa in patients with cystic fibrosis (CF) and non-CF patients. Amikacin is effective against a wide range of Gram-negative pathogens. Liposomal nanoparticles containing amikacin have been designed to extend the drug's therapeutic half-life while minimizing adverse effects. [19] Compared to free amikacin, encapsulated amikacin in liposomal nanoparticles offers prolonged release, quick administration, and medication protection from charged sputum.

Arikayce®, the nanopackaged amikacin is known by its general designation, liposomal amikacin for inhalation (LAI), which refers to its adaptation for aerosolized administration. It is important to note that aerosolized drug delivery techniques are thought to be a viable substitute approach that can maximize pulmonary drug concentration while lowering the possibility of systemic toxicity. Furthermore, LAI has made encouraging strides toward the creation of strong antibiotics to treat lung infections brought on by MDR pathogens. Because of the characteristics of its nanoformulation, the medicine releases more gradually and effectively while penetrating bacterial biofilms. The most prevalent non-tuberculous mycobacterium (NTM) species isolated from individuals with cystic fibrosis (CF), Mycobacterium avium complex biofilms, have been demonstrated to

be amenable to efficient LAI penetration. As compared to free amikacin, the drug's incorporation into the liposome caused pulmonary macrophages to absorb amikacin four times more.[20]

TUBERCULOSIS

The second most common infectious disease worldwide, tuberculosis (TB) is caused by *M. tuberculosis*. The need to take medication every day for up to nine months is a significant challenge in the treatment of the illness. This frequently results in patients not adhering to treatment plans, which poses a severe concern to public health due to its highly contagious nature in addition to endangering the patient's wellbeing. The current strategy for dealing with low adherence is called "direct observed treatment," in which patients are seen by a healthcare professional taking their prescription each day while undergoing treatment. This technique comes at a significant financial and scheduling cost to the healthcare system. [21]

In addition, the drugs currently used to treat tuberculosis have short plasma half-lives, rapid clearance, and serious adverse side effects such as hepatotoxicity. Because nanotechnology can regulate and maintain the release of pharmaceuticals from nanoparticles formulations, it can help lower the frequency of dosages linked to poor adherence. Clinical trials are still underway, although preclinical research has been done on a variety of nanocarriers as potential DDS for tuberculosis therapies. A lot of work has gone into developing nanotechnology for the diagnosis of tuberculosis. Early, prompt, and accurate diagnosis is essential to preventing the high prevalence of systemic illness and death among the patients. [22]

Asthma

The most common chronic inflammatory lung illness, asthma is characterized by bronchial hyper responsiveness, persistent airway inflammation, and intermittently reversible airway blockage. [23] The four inflammatory phenotypes of asthma, eosinophilic, neutrophilic, paucigranulocytic and mixed cellularity, have been well-described. These phenotypes are classified according to the counts of inflammatory cells in produced sputum. The characterization of asthma phenotypes is crucial for customized approaches to asthma medication, since it has been demonstrated that the inflammatory asthma phenotypes vary in terms of airway microbiology and even response to corticosteroid treatment. Recently, a highly accurate non-invasive evaluation method has been developed using nanotechnology to distinguish between patients with paucigranulocytic, neutrophilic and eosinophilic asthma phenotypes. Using an E-nose device, it is possible to distinguish between various inflammatory asthma phenotypes by using induced sputum analysis by analyzing their breath prints, according to the findings of a clinical experiment that evaluated the efficacy of this approach. The cutting-edge tool called Electronic nose (E-nose) is composed of nanosensors that can identify particular volatile organic compounds, also known as VOCs, in exhaled gas. Generally speaking, the main benefit of exhaled breath evaluation methods, such as E-nose, over other widely used procedures is the non-invasive identification of many disorders.

It was the first study to use pattern investigation of exhaled VOC mixtures by an E-nose in the field of asthma. Previous clinical studies demonstrated that the E-nose method can distinguish the exhaled breath of asthma patients from healthy controls and may create a difference between the degrees of asthma severity. Pulmonary illnesses are also detected and distinguished using the e-nose approach. [24]

Therapeutic substances have also been delivered by nanomedicine to treat asthma. One bronchodilator useful for both preventing and treating bronchoconstriction is salbutamol. But inadequate medication deposition in the lungs poses a constant and persistent problem for asthma management. Another salbutamol nanoformulation that will be studied in a clinical setting used niosomes, which are nanosized, non-ionic surfactant-based vesicles. Preclinical research revealed 8-hour duration for the drug's regulated release. The relative bioavailability for this nano-salbutamol and its sustained release are being investigated. [25]

Chronic obstructive pulmonary disease:

Like most chronic non-communicable diseases, COPD is the third biggest cause of mortality worldwide. Early detection of COPD has been shown to affect the rate at which the disease advances and the degree of lung functional impairment. Spirometry is

the most accurate method for identifying COPD and monitoring its progression [26], but it needs to be performed and evaluated by general practitioners with experience. Furthermore, in the early stages of COPD, breathing difficulties cannot manifest clinically. Previous studies have shown the efficacy of the nanosensors-based E-nose approach as a simple and user-friendly method of diagnosing COPD and differentiating patients with COPD from asthma (accuracy of 96%) and lung cancer from COPD (85%). The E-nose method was used to identify bacterial colonization in COPD patients as opposed to the quantitative culture of protected specimen brushes, which is the gold standard for identifying distal airway infections but requires invasive surgery. In this investigation, the accuracy of the E-nose approach in distinguishing between colonized and non-colonized COPD patients was 88%; however, their functional, demographic, and other features were similar. This study demonstrated how to identify bacterial colonization in COPD patients in a non-invasive, practical, reliable, and user-friendly manner using the E-nose tool. [27]

Current Challenges and Future Perspectives:

The field of nanomedicine offers a wealth of opportunities for both the development of novel treatment options and the fundamental enhancement of existing therapies for lung diseases that were previously thought to be incurable or difficult to cure. Though additional human data and significant investment are needed before nanomedicine in respiratory disease therapy can be considered a viable option for immunization, diagnosis, and treatment, we are still in the early phases of this field. Commercialization and industry encounter a number of obvious challenges, such as uneven size distribution, poor reproducibility, hygienic conditions, and the storage of large-scale output. [28] Even though it has been shown that the physicochemical characteristics of nanoparticles—such as size and surface charge—correlate directly with their biodistribution pattern, it is still challenging to consistently generate batches of nanoparticles with the same characteristics. These challenges may lead to amorphous structure/form, unclear surface chemistry, and eventually elevated risk of undesired biodistribution. To create a reliable and safe nanotherapeutics, techniques and instruments for describing the physicochemical properties of nanoparticles for medical use should be developed. Furthermore, in order to forecast how well nanoformulation will work in clinical trials looking into total body clearance, in vivo models are required. The buildup of nanotherapeutics in undesirable organs and tissues raises questions regarding their long-term harm. For instance, it is widely known that when treating lung illnesses, around 75% of intravenous liposomal nanotherapeutics accumulate in other parts of the body (liver, spleen, kidney, and heart) and are never found in the lung.

This may result in significant systemic unfavourable side effects and low treatment efficacy. Therefore, preclinical and clinical research should take into account determining the nanoparticles' biodistribution after systemic administration via any route. When it comes to cancer, the EPR effect—also known as passive targeting—makes nanoparticles more likely to gather in solid tumors. However, less than 1% of the nanotherapeutics has been discovered in the tumor, demonstrating the absolute ineffectiveness of passive targeting. [29] Active targeting of nanoparticles allows for the efficient regulation of biodistribution and, thus, a reduction in unfavorable effects by targeting precise cells or tissues.

CONCLUSION

In the context of chronic respiratory illnesses, this type of treatment reduces systemic toxicity by administering greater amounts of inhaled therapeutic payloads. This biological barrier can also be used to deliver monitored, suffered slow-release compounds with specific absorption characteristics that conquer the significant mucus and bacterial biofilms burden characteristics prevalent in numerous chronic respiratory diseases, which also explains why many of our current antimicrobial agents have poor lung penetration across it. All of these will lead to improved clinical treatment for patients.

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