Review

Biomedical Applications of Biopolymers in Airway Disease

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- Lung tissue engineering
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SUMMARY

Airway disease is a group of devastating conditions the prevalence of which has increased substantially in past decades despite the advanced therapeutic interventions. The term describes several events that lead to lung tissue scarring, poor lung circulation, and airway obstruction that prevent the lungs from working properly. Biodegradable polymers have emerged as significant advancements of modern medicine. In this review, we sought to discuss the clinical potential of biopolymers in airway disease. First, we describe succinctly the biosynthesis of biomaterials, their use in lung tissue scaffolding, and their use as substrates for *in vitro* culture of respiratory epithelial cells. We then discuss their utilization as bio-absorbable nanostructured drug delivery systems that combat lung cancer and prevent metastasis by targeting lung cancer stem-like cells. Additionally, we review the use of biopolymers as substitutes of pulmonary surfactant in acute respiratory distress syndrome. We bring forward the use of biopolymers as surgical implants in lung blood vessels. Also, the encapsulation of plasmids or antibiotics in polymer-based nanoparticles is discussed for pulmonary gene therapy in the context of modulating the function of alveolar macrophages, dendritic cells and adaptive immune responses. The use of nanoparticles for nasal, bronchial and lung vaccine administration is also reviewed as a novel method to induce favorable immune responses at the respiratory mucosa with the potential to induce systemic immunity. This review summarizes the most recent advances in the field over the past decade, specifically highlighting new and interesting applications in airway disease.

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INTRODUCTION

The term biopolymer includes high molecular weight polymeric structured produced by living organisms with biological methods as opposed to synthetic polymers that are produced by chemical methods. Biodegrad-

able biopolymers have gained a great deal of scientific and industrial interest because they can be produced by a wide range of sources and be used in a growing range of biomedical applications. The organic bioplastics, i.e. biopolymers, are derived from renewable biomass sources such as vegetable oils, starch, proteins, etc., as opposed to petroleum-derived fossil fuels. Biopolymers provide the dual benefits of conserving mineral resources and reducing CO_2 emissions, which make them an important innovation for sustainable development[1].

BIOSYNTHESIS OF POLYMERS

Polyesters

Biodegradable polyesters providing a sustainable alternative to petroleum-originated plastics consist of ester, amide and other functional groups that can be categorized into four classes, based on their synthesis process: i) natural polymers of plants and animals origin e.g. cellulose, chitosan, starch, and proteins, ii) microbial biopolymers like polyhydroxyalkanoates (PHAs), iii) polymers synthesized from natural monomers like polylactic acid (PLA), and iv) conventional polymers chemically synthesized from monomers produced from petrochemical products e.g. polycaprolactone[1,2]. Additionally, the properties of these biodegradable polymers are usually altered and improved through blending[3]. The potential sources for their biosynthesis varies from different sorts of biomass, including proteins, lipids and polysaccharides (such as cellulose- and starch- based biopolymers, chitosan) (Figure 1).

Proteins

In this category of biopolymers, the proteins that often are used are albumin, casein, collagen, feather meal (by product of poultry processing), gelatin, gluten, meal soy, peanuts, whey, and zein (a class of prolamine protein found in corn). Collagen is a naturally occurring structural extra-cellular matrix polymer and the predominant component of the mammalian body connective tissue, which is highly conserved across species. Biopolymers synthesized by collagen are often the best candidates for synthetic replacement of connective tissues due to their excellent structural and mechanical properties. Collagen biomedical applications in regenerative medicine are described in detail elsewhere[4].

A gelatinous protein mixture used for many applications and known with the commercial name matrigel is secreted by Engelbreth-Holm-Swarm mouse sarcoma cells, produced and commercialized by Corning Life Sciences and BD Biosciences. Matrigel is utilized by cell biologists as a matrix for cell culturing due to its resemblance to the complex extracellular environment that lies in various tissues. Gel foam is another gelatin-derived biomaterial that is used as an efficient hemostatic agent during surgical procedures.

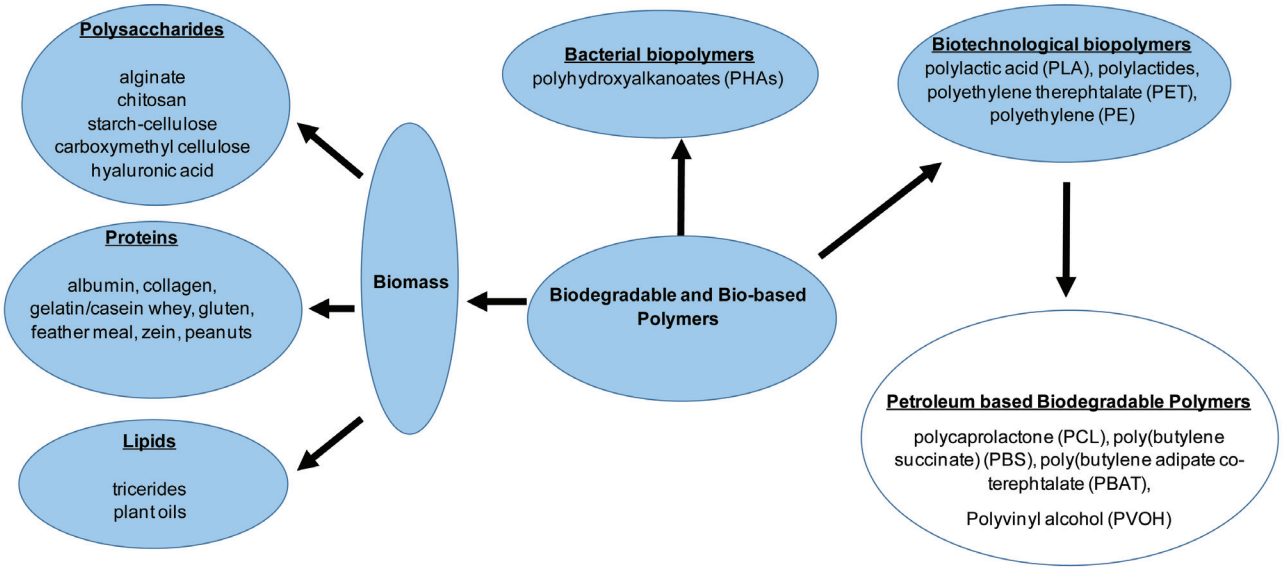

FIGURE 1. Biosynthesis of polymers that are used to treat airway diseases.

Polysaccharides

Chitosan is a natural polysaccharide, with cationic and biocompatible properties constituted of co-monomeric units, 2-deoxy-2-acetamido-D-glucose and 2-deoxy-2-amino-D-glucose. The major advantage of chitosan is its mild antimicrobial activity that is attributed to its cationic residue, making it an important biomaterial since it suppresses bacterial growth by adhering to the bacterial cell wall. Furthermore, chitosan is biocompatible with human tissues and biodegrades *in vivo*. Its functional groups (hydroxyl, amine and amide) can be chemically modified to synthesize polyhydroxyalkanoates/chitosan mixtures that are applicable in wide range of biomedical applications.

Microbial polymers

Polyhydroxyalkanoates (PHAs) belong to a family of microbial polyesters and constitute the only bioplastics, synthesized by several Gram-negative and Gram-positive bacteria. PHAs serve as both source of energy for bacterial cultures and carbon storage. We have shown that PHAs can be synthesized in *Thermus thermophilus* under nutrient starvation conditions[5-7]. PHAs can be combined with more than 150 different monomers and give rise to a wide range of biomaterials with various properties making them ideal candidates for a number of biomedical applications[8-11]. Depending on their chemical structure, PHAs display flexible mechanical, structural, and thermal properties, biodegradability, biocompatibility and they are environmentally friendly. PHAs are often used in medicine as biodegradable and biocompatible implants and drug delivery capsules[3,12].

Poly-α-hydroxy acids

The most well-known poly-α-hydroxy acid is polyglycolideor poly(glycolic acid) (PGA). It constitutes the simplest linear, aliphatic polyester that is ranked among the biodegradable, thermoplastic polymers. Its biosynthesis takes place through polycondensation or ring-opening polymerization of the smallest α-hydroxy acid (AHA), or by solid-state polycondensation of halogenoacetates. Initially PGA had very limited use due to its tough fiber-forming structure and its rapid hydrolysis rate compared to other polymers[13]. However, when PGA is coated with L-lysine and N-laurin, it makes an ideal soft bio-absorbable material for sub- and intra- cutaneous sutures and closures, respectively, in abdominal and thoracic surgeries. In the past decades PGA has been co-polymerized with a number of other different monomers such as lactic acid, trimethylene carbonate, e-caprolactone to bioengineer implantable medical devices including anastomosis rings, pins, rods, plates and screws[14].

Table 1 summarizes the biosynthesis and current applications of biopolymers used in airway diseases.

APPLICATIONS IN AIRWAY DISEASE

Lung Tissue Engineering

Engineering of lung tissue is part of the regenerative medicine that aims to reconstruct tissue parts and repair physiological functions of the lung rendered dysfunctional after lung injury or lung disease. Although there has been some progress in the *de novo* lung tissue engineering and transplantation of live human cells into patients to confront several respiratory diseases, it is not yet a clinical reality. Considerable effort has been placed to design matrices that can support 3-D structure, lung cell differentiation, and tissue development[15]. Biopolymers such as collagen[16,17], gel foam[18] and matrigel[19] have been employed in lung tissue engineering and have been shown to allow lung tissue growth, albeit the development of a whole functioning organ has not been substantiated so far.

The biomaterials used for these purposes are expected to be biocompatible and their adsorption kinetics must be such so that the biopolymers will remain long enough to allow cell colonization and differentiation, without impeding the mechanical properties of the bioengineered tissue. It is now realized that the complexity of the human lung cannot be mimicked by a single biomaterial and development of a hybrid of biopolymers is required to generate lung tissue and different pulmonary cell types that can replicate the specific functions of the lung[20]. For example, Club cells (Clara cells) that are found in the lung bronchioles, the function of which is to protect the bronchial epithelium, have been shown to differentiate from mouse embryonic stem cells on several biopolymers such as gelatine, collagen types I, IV, and VI either in submerged or air-liquid interface cultures[21]. Another example is the alveolar type II pneumocytes; these produce the pulmonary surfactant that has critical role in reducing the surface tension formed at the air-liquid interface of the alveoli. We have shown that type II cells can maintain their phenotype *in vitro* in 3-D cultures system when grown on mixture of matrigel and collagen[22]. We have also shown that upper airway nasal epithelial cells maintain their ciliated phenotype when grown *in vitro* in collagen IV coated air-liquid surfaces[23].

TABLE 1. Biopolymers used in airway disease, their origin and their biosynthesis.

Biopolymers	Application	Origin	Biosynthesis References
Chitosan	Synthetic surfactants, nanovaccinology	*Mucorrouxii*	62
Collagen types i, iv, and vi	Cartilage graft, 3-D cultures system	Porcine	63
DODAC:DOPE (dioleoyl-dimethyl-ammonium chloride: dioleoyl-phosphatidyl-ethanolamine)	Nanobeads	Liposomes	64
Gel foam	Lung tissue engineering, hemostatic agent	Porcine skin gelatin	65
Gelatine	Lung tissue engineering	*Acetobacterxylinum*	66
HYAFF-11	Nasal Cartilage Graft	*Streptococcus zooepidemicus*	67
Matrigel	*In vitro* airway cell culture	Mouse	68
Polyethylene glycol (PEG)-substituted polylysine/ PEBP-b-PBYP-g-PEG	Nanostructured drug delivery systems	Chemical agent	32
Poly-amino acids	Nanoparticles	Plants	69
Polyethylene imine (PEI)	Nanovaccinology	Chemical agent	70
Poly-hydroxy alkanoic acids (PHAs)	Nanoparticles	Plants, *Thermus thermophilus*	5, 6, 7
Poly-lactic-co-glycolic acid (PLGA)	Cartilage graft engineering, Nanovaccinology	Chemical agent	71
Polylysine/glycocylated polylysine and polyethylenimine	Nanoparticles	*Streptomyces albulus*	72
Polysaccharides	Nanovaccinology	*Leuconostocmesenteroides*, starch	73
Poly-α-hydroxy acids	Nanoparticles	Chemical agent	74

Bio-absorbable Nanostructured Drug Delivery Systems

Lung cancer is by far the commonest form of cancer worldwide, with 1.7 million new cases just in 2012, a 13% annual incidence, and a leading cause of cancer death among both sexes. It is estimated that more people die of lung cancer than breast, prostate and colon cancers combined[24]. Surgery and radiotherapy are the most common methods to remove and treat local, non-metastatic malignancies, while chemotherapy is employed to treat the metastatic cases of lung cancer. One of the major drawbacks of chemotherapy is that although the anti-cancer drugs are designed to target the fast dividing cells, they are not highly specific for just cancer cells, and often this lack of selectivity results in damage of healthy cells and adverse side effects. Furthermore, the half-life of these anti-lung cancer drugs is very transient in the blood stream, with low efficacies, and therefore higher doses of chemicals are needed with concomitant dire side effects. In this sense, customized bio-absorbable nanostructured drug delivery systems (DDS) can offer great breakthroughs in the fight against lung cancer.

DDS have a wide range of advantages compared to regular chemotherapy. Not only they can deliver anti-cancer agents in a controlled time and release rate but they can be customized to target lung specific cells and tissues and maintain efficient therapeutic drug levels[25]. Polymeric DDS can be bioengineered in different forms

(liposomes, micelles, micro- and nano- particles) infused with the appropriate anti-lung cancer agent and administered in different routes such as oral (inhaled DDS), injectable gels (blood stream DDS) and surgical implants (DDS scaffolds, foams, films/sheets)[26]. An additional feature of the bio-absorbable DDS is that after they deliver the desired anti-cancer agents, the biopolymers themselves can be metabolized by the patient's body.

An example of increased efficacy of biopolymers is the PLGA nanoparticles loaded with the anti-lung cancer agent suberoylanilidehydroxamic acid (SAHA). It was shown *in vitro* that these particles were able to release an initial burst of SAHA followed by sustained release for up to 50 h, showing higher antineoplastic activity compared to direct SAHA administration in human adenocarcinomic alveolar basal epithelial A549 cells[27]. Another example of utilization of biopolymers to increase specificity in lung cancer cells is the bioengineering of PLGA nanoparticles coated with vascular endothelial growth factor receptor (VEGFR) on their outside surface and their infusion with paclitalex, a tubulin-binding agent, which is widely used for the treatment of non-small cell lung cancer[28]. The concept is that since vascular endothelial growth factor is over expressed in lung cancer cells, the coating of the nanoparticles with the receptor (VEGFR) facilitates the specific conjugation of the nanoparticles to the cancer cells and subsequent increased inhibitory activity of tumor growth compared to native paclitalex or paclitalex-loaded PLGA nanoparticles in the A549 cell line. Additionally, *in vivo* mouse studies showed that biopolymeric DDS can be used to prevent lung cancer metastasis to other organs. *Yang et al* identified a peptide that specifically binds to pulmonary adenocarcinoma tissue, and conjugated it to PLA particles encapsulated with anti-cancer agent docetaxel. These nanoparticles were shown to specifically target the lung cancer stem-like cells, eliminate them and prevent metastasis to the liver[29]. *Long et al.* used the same concept and showed in mouse studies that inhalation of thiolated gelatin nanoparticles carrying a specific epidermal growth factor receptor (EGFR) binding peptide and encapsulated with doxorubicin, not only were specifically internalized by lung cancer cells but they also released high doses of the anti-cancer agents for more than 24h post inhalation resulting in 90% increased efficacy[30].

Another interesting use of biopolymers is that of micelles, which serve as vehicles for delivering insoluble hydrophobic anti-cancer chemicals. Micelles are bioengineering as organized auto-assembly amphiphilic copolymers formed in a liquid, composed of solvophilic and solvophobic blocks. The core of micelles is hydrophobic, and the place where water insoluble drugs are loaded, while the outside of micelle is comprised of a hydrophilic polymer that renders the whole micelle stable and biocompatible with tissues and blood. Albumin nanocarriers were used to deliver niclosamide, a very potent anti-lung cancer agent that is normally hydrophobic, and therefore cannot be delivered systemically to the patient. *In vitro* trials showed that the albumin coated nanoparticles were hydrophilic and were are able to deliver efficiently the agent, resulting in significant tumor inhibition and apoptosis of cancer cells[31]. To augment the pharmacokinetics of paclitalex, *Zhang et al* generated a micelle cross-linked with amphiphilic terpolymer PEBP-b-PBYP-g-PEG formulating a shell, which was shown to increase paclitalex intra-tracheal delivery by 2400-fold, thus preventing lung metastasis of osteosarcoma in a mouse model[32].

Nanopolymers in Respiratory Gene Therapy

Gene therapy is currently used to treat several respiratory disorders such as cystic fibrosis (CF) and acute respiratory distress syndrome (ARDS). The overall concept is to replace a mutated gene that causes the disease with a healthy copy of the gene, inhibit or knock-out a mutated gene that is malfunctioning, or introduce a new gene that helps fight the disease, providing permanent therapeutic solutions rather than treating just the symptoms. The application of biodegradable nanoparticles as gene transferring agents is being currently evaluated for a wide range of airway diseases.

CF is a lethal autosomal disease, in which the cystic fibrosis transmembrane conductance regulator gene (CFTR) is malfunctioning. The CFTR channel is present on the apical surface of epithelial cells and is critical in the chloride (Cl^-) and bicarbonate (HCO_3^-) transport. These channels are important for the optimal levels of water and ion components of the mucosa. CFTR gene mutations result in epithelial cell dysfunction, mucus thickening, propagation of recalcitrant bacterial populations affecting not just the lung, but also the sinuses[33], intestines, pancreas and other organs[34]. In this direction glycocylated polylysine and polyethylenimine nanobeads carrying a functional CFTR gene were internalized in airway epithelial cell cultures. This was based on the fact that lectins, such as pulmonary surfactant protein A (SP-A) and D (SP-D), which are expressed in airway epithelial cells selectively bind and internalize the above glycoconjugates[35]. *In vivo* studies also showed that polylysine nanobeads loaded

with serpin-enzyme complex receptor (that binds to airway epithelia) and CFTR plasmid, restored the chloride ion transport in a CFTR knock-out mouse model[36]. In the same way, nanoparticles conjugated with shortpeptides resembling integrin-binding domains successfully delivered the CFTR gene via bronchoscopic administration in a porcine CF model[37]. Furthermore, clinical trials in CF patients have been conducted using polyethyleneglycol (PEG)-substituted polylysine nanoparticles delivering intranasally the correct CFTR gene. Correction of CFTR transfer channel has been confirmed by detecting plasmid-specific DNA and mRNA while the ion transfer was corrected in seven out of twelve of the patients[38].

The major advantage of the biodegradable nanobeads is their small size (18-25 nm), which allows them to enter the nuclear envelope by passive diffusion and deliver the CFTR plasmid for transcription. Another advantage of their small size is the possibility to be systemically delivered via intravenous (i.v.) injection which can lead to specific lung transfection. It has been shown that DODAC:DOPE (dioleoyl-dimethyl-ammonium chloride: dioleoyl-phosphatidyl-ethanolamine) nanoparticles infused with human cytokeratin 18 gene (KRT18) gene when administered i.v. can reach the left side of the heart and travel to the bronchial circulation which supplies the alveolar capillaries of the pulmonary circulation. There, the nanoparticles deliver the KRT18 plasmid to the alveolar epithelial cells, which mitigates the CF phenotype[39]. In addition, novel nebulization therapeutic modalities have been investigated to delivery polymeric gene vectors for several lung diseases. *Alton et al* showed that inhaled gene therapy has presented safety and effectiveness in phase 2b clinical trials. Liposome nanoparticles were biosynthesized containing the CFTR cDNA, nebulized and derived to the patients via inhalation resulting in significant stabilization in the lung function of CF patients[40]. The use of biopolymers in pulmonary gene therapy is currently being evaluated and it is expected, soon, to lead to efficient therapeutic interventions that address the mechanism of airway disease, therefore providing permanent solutions.

Biopolymers in Respiratory Distress Syndrome

Pulmonary surfactant (PS) is a mixture consisting of 90% lipids and 10% proteins that is produced by the alveolar type II cells. It's major bio-physiological function is to lower the surface tension that is formed at the air-liquid interface during the respiration process and prevent the alveolar collapse. Absence or deficiency of PS leads to respiratory distress syndrome (RDS)[41]. In preterm neonates, the lungs are not fully developed and the lack of PS production leads to neonatal RDS (NRDS). Natural and synthetic surfactants have been used successfully to alleviate RDS. In the case of synthetic surfactants, it has been found that supplementation with biopolymers enhances the surface activity of the synthetic lipids and prevents the inhibition of the natural PS in the lungs. For example, although dipalmitoyl-phosphatidylcholine (DPPC) and phosphatidyl-glycerol (PG) are natural components of PS, when administered exogenously in neonatal rabbit lungs, they proved ineffective. Supplementation of DPPC and PG with tyloxapol (a nonionic liquid polymer of the alkylaryl polyether alcohol) facilitated dispersion of the synthetic surfactant and prevention of NRDS. This synthetic surfactant supplement is FDA-approved and used in clinic (Exosurf)[42]. The biopolymers that have been tested so far with the intent to improve the surface activity of synthetic surfactants include nonionic, such as polyethylene glycol (PEG)[43] and dextran[44], anionic, such as hyaluronan[45], and cationic polymers (e.g. chitosan)[46]. Another advantage of these polymers is that their addition reduces surfactant inhibition and improves lung function after pulmonary injury[47]. PS inhibition takes place when surfactant encounters plasma proteins, meconium (fetal feces aspiration during gestation), and cholesterol, conditions that are associated with acute lung injury (ALI), acute respiratory *distress* syndrome (ARDS), NRDS, and pulmonary edema. The use of low cost, hydrophilic biopolymers as surfactant substitutes and additives has proven to be an effective approach to treat RDS.

Nanovaccinology

Traditional vaccines usually contain attenuated pathogens, and although they have been proven effective in preventing contagious diseases, they are not safe for immunocompromised individuals. To address these issues, components of pathogens such as bacterial lipopolysaccharides, viral proteins, or even naked DNA encoding a protective antigen, have been utilized to manufacture less reactogenic vaccines. These were proven to be less immunogenic. Although their addition resulted in enhanced immunogenicity, they also increased the topical reactions. In this direction, nanotechnology has come to introduce a new era in vaccinology. Nanovaccines are defined as the bioengineered nanoparticles that are formulated to either encapsulate within or absorb on their surface specific antigens to elicit a desired adaptive immune response. They induce cellular memory, which is central to protection

against pathogens, and generate long-term protective immunity. Nanotechnology and biomedical engineering are now facilitating cross-disciplinary research that has come to increase the biocompatibility, permeability, solubility and stability of vaccines[48].

Nanoparticles can be prepared by a range of biodegradable polymers such as poly-α-hydroxyacids, polyhydroxyalkanoates, poly-amino acids, or polysaccharides to generate a vesicle that either contains or displays on its surface the antigen of interest. The most commonly used biomaterials are poly-lactic-co-glycolic acid (PLGA) and poly-lactic acid (PLA)[49]. Also, chitosan nanoparticles apart from being biodegradable and non-toxic, they are particularly useful for vaccinology since their small size allows them to pass through the tight junctions of epithelial cells and deliver the antigen[50]. *In vivo* studies have shown that the delivery and uptake of nanoparticles by the antigen presenting cells such as dendritic cells (DCs) increased by 30- fold compared to the soluble antigen alone[51]. Another example is the chicken ovalbumin (OVA) challenge model for studying antigen-specific immune responses in mice. When mice were injected with polyaminoacid nanoparticles encapsulated with OVA they produced significantly higher levels of IgG, IgG1, and IgG2a compared to the injections of soluble OVA. *Mohr et al* showed that the nanoparticles induced cellular and humoral immune responses by $CD8^+$ and $CD4^+$ T cell activation that produced interferon gamma (INF-γ) and polarization towards IgG2a[52]. Likewise, hepatitis B antigen encapsulated into a PLGA nanoparticle was shown to induce a significantly more pronounced immune response compared to the soluble virus antigen[53].

Moreover, shape and surface charge of nanoparticles are important for efficient delivery of antigens. Spherical nanoparticles compared to rod-like vehicles are more readily phagocytosed by macrophages and DCs. Also, positively charged biomaterials are taken up more easily by the anionic epithelial cell membranes[54,55]. In this concept nanoparticles composed of PLGA and polyethylene imine (PEI) were encapsulated with naked DNA encoding the *Mycobacterium tuberculosis* Rv1733c latency antigen. The bioengineered nanoparticles were small and positively charged and when endotracheally intubated in a mouse model, they adhered to the negatively charged lung mucosal membranes with subsequent epithelial cellular uptake. *M. tuberculosis* antigen was then expressed resulting in antigen presentation to DCs, T-cell proliferation, INF-γ production, secretion of interleukin 12 (*IL-12*), and tumor necrosis factor alpha (TNF-α) at levels comparable to lipopolysaccharides stimulation[56]. Taken together, the above demonstrate that biodegradable polymers are becoming the novel platforms for lung DNA vaccinations. However, given their short history in vaccinology applications, they have not established yet their safety for human use, thus further research needs to be carried out to assess their toxicity before they are incorporated in clinical trials.

IMPLANTS FOR LUNG CIRCULATION DISEASES

Without doubt, one of the most common uses of biopolymers has been the development of pulmonary cardiovascular products. In the 1990s poly (3HB) patches were developed to close pericardium during open heart surgery[57] and the same material was used for augmentation of pulmonary artery[58]. These biodegradable patches had sufficient strength to close the arteries and drove the formation of regenerative tissue that resembled the native atrial wall. Perhaps one of the most outstanding application of biopolymers is that of the development of tissue engineered cell-seeded pulmonary valves that was successfully applied in animal models[59]. Researchers have used bio-absorbable poly-4-hydroxybutyric acid patches with autologous vascular cell seeding as a feasible biomaterial to augment pulmonary circulation[60]. *Mettler et al* used a mixture of polyglycolic acid and poly-4-hydroxybutyrate biopolymer and seeded the biomaterial with ovine endothelial progenitor and mesenchymal stem cells for 5 days. The patches when implanted into the ovine pulmonary artery showed the successful creation of artificial bioengineered blood vessel[61].

DISCUSSION

Biopolymers are the natural metabolite products formed during the life cycle of animals, bacteria, fungi and plants. Because of their high biocompatibility, and their non-toxic degradation products they have come to be ideal biomaterials that found applications in a number of airway diseases, as they are summarized on Figure 2. We are expecting that in the near future a number of biomaterials will be utilized to bioengineer fully functional lung tissues from the very own stem cell lines of the recipient. It is without doubt that in the approximate future biopolymers will continue to find more biomedical applications in airway disease.

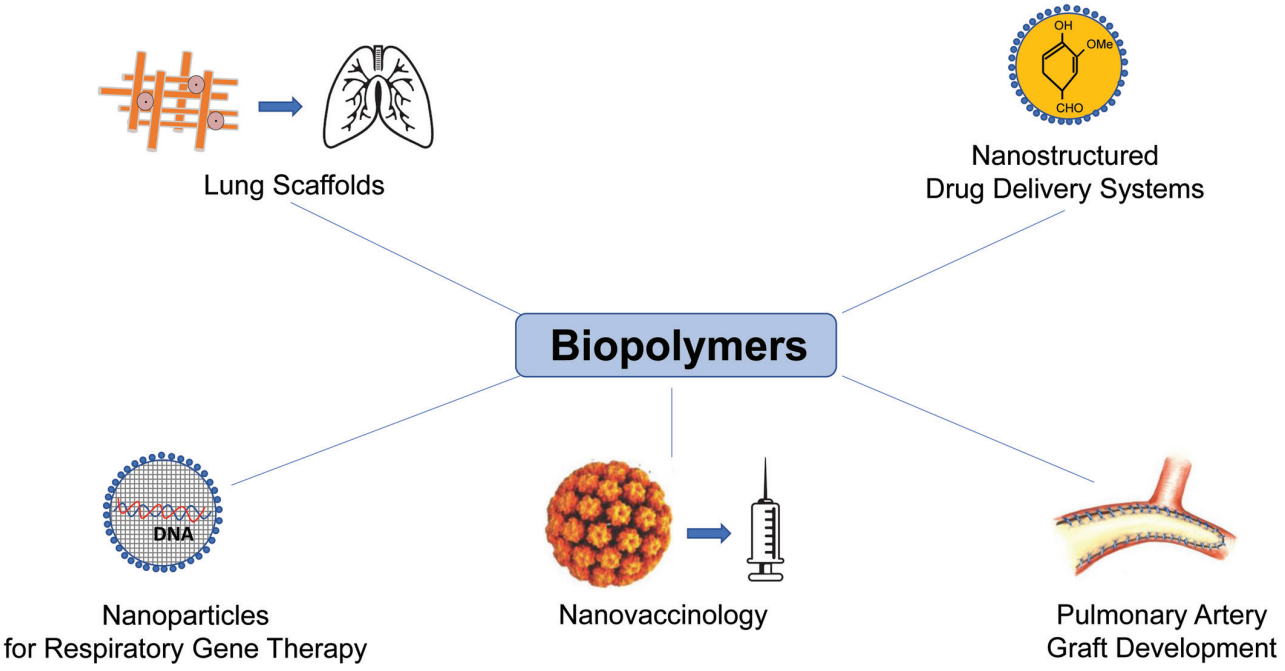

FIGURE 2. Schematic representation of biomedical applications of biopolymers in airway disease.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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DECLARATIONS

Ethics approval

This review article was evaluated and approved by the Arizona State University and Aristotle University.

Consent for publication

Not applicable.

Authors' contributions

GTN reviewed the relevant literature, designed the structure of the review article, integrated and synthesized published data, contributed to manuscript writing, prepared figures. AAP, contributed to manuscript writing, prepared figures, contributed to manuscript writing, and provided oversight to the entire review progress.

ΠΕΡΙΛΗΨΗ

Βιοϊατρικές εφαρμογές των βιοπολυμερών στη νόσο των αεραγωγών

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Ο όρος "νόσος των αεραγωγών" περιγράφει διάφορα γεγονότα που οδηγούν σε καταστροφή του πνευμονικού ιστού, κακή αιματική κυκλοφορία, και απόφραξη των αεραγωγών που εμποδίζουν τη λειτουργία των πνευμόνων. Πολυμερικά βιοϋλικά που είναι βιοαποικοδομήσιμα έχουν αναδυθεί ως σημαντικά επιτεύγματα της σύγχρονης ιατρικής. Σε αυτήν την ανασκόπηση, επιδιώξαμε να διερευνήσουμε το κλινικό δυναμικό των βιοπολυμερών στην ασθένεια των αεραγωγών. Αρχικά συζητούμε συνοπτικά τη βιοσύνθεση των βιοϋλικών και τη χρήση τους σε ικριώματα των ιστών των πνευμόνων, στη μηχανική των μοσχευμάτων χόνδρων και τη χρήση τους ως υποστρώματα για in vitro καλλιέργεια αναπνευστικών επιθηλιακών κυττάρων. Στη συνέχεια συζητάμε τη χρήση τους ως βιοαπορροφήσιμα νανοδομημένα συστήματα χορήγησης φαρμάκων που καταπολεμούν τον καρκίνο του πνεύμονα καθώς και την πρόληψη της μετάστασης με στόχο την παρεμπόδιση του πολλαπλασιασμού των καρκινικών πνευμονικών κύτταρων. Επιπλέον, αναφερόμαστε στη χρήση των βιοπολυμερών μαζί με λιπίδια ως υποκατάστατα του πνευμονικού επιφανειοδραστικού παράγοντα στο σύνδρομο οξείας αναπνευστικής δυσχέρειας. Προτείνουμε τη χρήση βιοπολυμερών ως χειρουργικά εμφυτεύματα σε αιμοφόρα αγγεία του πνεύμονα. Επίσης, η ενθυλάκωση πλασμιδίων ή αντιβιοτικών σε βιοπολυμερή νανοσωματίδια συζητείται για την γονιδιακή θεραπεία στο πλαίσιο της ρύθμισης της λειτουργίας των κυψελιδικών μακροφάγων, των δενδριτικών κυττάρων και των προσαρμοστικών ανοσοποιητικών αποκρίσεων στην κυστική ίνωση. Η χρήση νανοσωματιδίων για χορήγηση ρινικού, βρογχικού και πνευμονικού εμβολίου (νανοεμβολιολογία) επίσης καταγράφεται ως μια νέα μέθοδος για την πρόκληση ευνοϊκών ανοσοαποκρίσεων στον βλεννογόνο του αναπνευστικού συστήματος με πιθανότητα να επάγει συστημική ανοσία. Η παρούσα ανασκόπηση συνοψίζει τις πιο πρόσφατες εξελίξεις στον τομέα κατά την παρελθούσα δεκαετία, επισημαίνοντας συγκεκριμένα νέες και ενδιαφέρουσες εφαρμογές στις παθήσεις των αεραγωγών.

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Λέξεις - Κλειδιά: *πολυυδροξυαλκανοϊκά, νόσος των αεραγωγών, καταστροφή πνευμονικού ιστού, συστήματα απελευθέρωσης φαρμάκων, νανοεμβολιολογία*

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