MOLECULAR AND HISTOLOGICAL CHANGES IN AIRWAY BASAL STEM CELLS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Airway basal stem cell changes in COPD including hyperplasia, squamous cell metaplasia, epithel-mesenchymal transition, impairment of cilia and secretory non mucosal cell differentiation, and junctional barrier integrity disturbances that lead to histological changes. There are also molecular changes such as disturbances in gene expression, cytokines, inflammation factor and dysregulation of basal cell transcriptome in locus 19q13.2. This article is aimed to review airway basal cell changes in COPD. By understanding initial changes of airway basal stem cell in COPD, hopefully can help to develop stem cell therapy in COPD treatment. The research aims to explore molecular and histological changes in airway basal stem cells on chronic obstructive pulmonary disease. The researchers used literature review as the way to verify their arguments on the issue discussed by analyzing the results of scientific sources, especially from trusted sources such as Google Scholar and Science Direct. The study continues by stating that regenerative therapy using stem cells has started to evolve with the advancement of stem cell technology and is anticipated to improve and treat this illness. Only preclinical and phase 2 clinical trials have seen recent advancements in the use of stem cells for treating COPD.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a disease of the respiratory organs characterized by persistent respiratory symptoms and airflow limitation due to abnormalities in the airways and/or alveoli which are usually caused by exposure to harmful particles or gases such as cigarette smoke, vehicle exhaust, or air pollution (Brandsma et al., 2020; Mirza et al., 2018). In addition to these harmful particles or gases which are risk factors for COPD, host factors such as genetic abnormalities, abnormalities in lung development, and the aging process also play a role in COPD. Respiratory symptoms that are quite common are dyspnea, cough and/or excessive sputum production. These symptoms are usually marked by a period of acute worsening called an exacerbation. In almost all patients, COPD is associated with other chronic diseases which will increase morbidity and mortality.

In 1990, Lopez and Murray explained that at that time COPD was ranked 12th in the world and was expected to be ranked 5th in 2020 and 3rd in 2030 (Global Initiative for Chronic Obstructive Lung Disease, 2018). In Indonesia, COPD in 2009 was ranked 9th based on WHO data (2009) and its ranking is increasing where in 2016 it has reached the 5th rank as the disease that causes the most death in Indonesia (IHME, 2023). With these data showing that COPD is a disease that causes death quite often and judging by its ranking which is increasing over time, there is a possibility...
that COPD treatment has not been able to reduce the impact on morbidity and mortality so that it is necessary to evaluate how to treat it better and more effectively to reduce COPD morbidity and mortality. Current management of COPD is generally symptomatic and preventive to reduce exacerbations. With the development of molecular and cellular-based science, research has begun on how the cellular and molecular processes that occur cause changes in the histological structure of the airways in patients with COPD.

Histologically, normally the respiratory organs are divided into conducting units and respiratory units with various types of constituent cells that support the functions of the respiratory organs (Amatngalim & Hiemstra, 2018). The function of the respiratory organs in delivering oxygen and mediating the exchange of oxygen and carbon dioxide between the air we breathe and our body requires constant pressure because the air Inhaled also contains various particles, gases, and microorganisms that can cause injury and infection in the respiratory tract and lungs. Removal and neutralization of these potentially hazardous substances in the airways is played by the airway epithelium. Whereas in the lungs it is played by alveolar macrophages and other immune system molecules.

The airway epithelium is a pseudostratified epithelial layer consisting of several main cells, namely goblet cells, ciliated columnar cells, brush cells, serous cells, neuroendocrine cells (DNES), and basal cells. Basal cells are stem/progenitor cells that can differentiate into other cells (Amatngalim & Hiemstra, 2018; Mescher, 2000). These basal cells are generally inactive, but are active in case of injury/trauma so as to maintain homeostasis in the airways. In COPD, dysfunction of the airway basal epithelium which is the airway stem/progenitor cell is the initial change that initiates the occurrence of this disease apart from the role of inflammation and immune processes in its pathogenesis. Several studies support that basal cells also function as sensory and cellular sources for various cytokines and growth factors associated with airway injury associated with molecular and histological changes in COPD pathogenesis. Histological changes that occur in the basal cells in COPD include hyperplasia, squamous cell metaplasia, epithelial-mesenchymal transition (EMT), disruption of differentiation of ciliated cells and non-mucous secretory cells, and disruption of the integrity of the junctional barrier. Meanwhile, molecular changes in basal cells can be in the form of gene dysregulation that is specific to the COPD locus. By understanding that early changes in basal cells that result in epithelial dysfunction are important in the pathogenesis of COPD, it is hoped that cell-based therapeutic and/or prevention approaches for COPD can be developed which in the future can reduce the number of patients, morbidity and mortality due to COPD.

The researchers aimed to study molecular and histological changes in airway basal stem cells on chronic obstructive pulmonary disease. The study is expected to contribute to a wider range of knowledge regarding the issue discussed, especially in COPD.

METHOD

By reading journals and references about chronic obstructive pulmonary disease, molecular and histology, and airway basal stem cells, this article used literature review to convey the aimed
results. The researchers used databases such as Google Scholar, Science Direct, Springer Link, Emerald Insight, and Proquest. Prioritizing literatures published between 2014-2023, the researchers attempted to gather reliable and most recent studies on the topic discussed. Older references were used as supporting statements.

RESULT AND DISCUSSION
Normal Respiratory System Histology

The respiratory system, which includes the lungs and a set of airways, functions to provide oxygen and remove carbon dioxide from body cells, which is known as respiration. Respiration can take place in the respiratory system and through the internal circulation and respiratory systems that take place in all body tissues. The respiratory system is histologically divided into two main parts, namely the conduction part and the respiratory part. The conducting portion which is located both outside and inside the lung will transport air from the outside environment into the lung, while the respiratory section is located inside the lung which will function in exchanging oxygen and carbon dioxide.

The conducting portion of the respiratory system consists of the airways composed of the nasal cavity, oral cavity, nasopharynx, pharynx, larynx, trachea, primary bronchi, secondary bronchi (lobar bronchi), tertiary bronchi (segmental bronchi), bronchioles and terminal bronchioles. This arrangement is not only for transporting air, but also for filtering, humidifying and for warming inspired air before it reaches the respiratory portion of the lungs. To ensure that there is no obstruction, the structure of the airway is unique and the combination of cartilage, elastin and collagen fibers and smooth muscle makes the conducting section a rigid structure while remaining flexible and extensible. In addition, the conduction portion of the airways in supporting its role in filtering respiratory air, is mostly lined by respiratory epithelium which plays an important role in mucociliary clearance (Amatngalim & Hiemstra, 2018; Mescher, 2000).

Respiratory or respiratory epithelium is a stratified epithelium consisting of six types of cells, namely goblet cells, ciliated columnar cells, basal cells, brush cells, serous cells, and neuroendocrine cells (DNES). All of these cell types are associated with the basement membrane but not all reach the lumen. Goblet cells amount to about 30% of the total epithelial population which produce a mucinogen which when it is hydrated is known as mucin. These goblet cells appear to have stalks at the base and contain secretory granules in the dilated parts of the theca. Ciliated columnar cells number approx

30% of the total respiratory epithelial cell population are slender, tall, with a cell nucleus at the base and protrusions of cilia and microvilli in the apical part of the cell membrane. These cells move mucus and trapped particles and through ciliary action push them towards the nasopharynx to be expelled. Brush cells make up about 3% of the total cell population which are small granular, narrow cylindrical mucous cells with tall microvilli. Its function is thought to be in sensory systems that express some signal transduction components such as gustatory cells and have afferent nerve endings on their basal surfaces that are chemosensory receptors. Other researchers also believe that these cells are goblet cells that have released their mucinogens. Serous cells make up 3% of
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the respiratory epithelium which contains an electron-dense secret, a serous fluid of unknown composition. While DNES cells, also known as small granular cells or Kulchitsky cells, numbering 3-4%, have long protrusions towards the lumen and are believed to have the ability to monitor oxygen and carbon dioxide levels in the lumen of the airways. These DNES cells also have many granules in the basal part of their cytoplasm which contain pharmacological agents, such as amino peptides, acetylcholine and adenosine triphosphate. In a state of hypoxia, the agent will be released, not only into the lumen but also into the connective tissue spaces in the lamina propria which will play a paracrine role and can inform the hypoxic state to the respiratory control center in the medulla oblongata. Lastly are the basal cells which make up 30% of all respiratory epithelial cells which are located directly above the basement membrane but the apical surface of the cells does not reach the lumen. These basal cells are undifferentiated cells and are stem cells that will proliferate to replace goblet cells, cylindrical cells and brush cells.

Basal Cells As Stem/Progenitor Cells in the Respiratory Epithelium

Basal cells are cuboidal cells with positive keratin 5 attached to the basement membrane. Unlike ciliated respiratory cells and secretory cells, basal cells are not very prominent, have a high nuclear-to-cytoplasmic ratio with few organelles and with scattered microvilli. Basal cells have the largest proportion in the large airways and progressively decrease in the tracheobronchial branches with a proportion of 34% in the trachea, 27% in the large airways and 10% in the small airways. Basal cells so that the cell surface does not reach the lumen consist of undifferentiated cells which are believed to be stem cells that will proliferate to replace goblet cells, cylindrical cells, and brush cells.

Under physiological conditions, the airway epithelium in normal adult humans changes slowly about every 1-4 months. Under these conditions, basal cells are usually in a relatively quiescent or inactive state, but under conditions of injury and stress, basal cells will respond by proliferating, forming clonal patterns, expanding intermediate cells, and in the presence of various other factors in the microenvironment will regenerate, differentiate into normal luminal airway epithelial cells, or under certain conditions may produce a distinct or histologically abnormal phenotype. In this differentiation process several molecules play a role in producing the histological phenotype of the airway epithelium from basal cells, including transcription factors and regulators FOXJ1, multicilin, cyclin O, Myb, and RFX proteins play a role in the process of differentiation of basal cells into ciliated columnar cells, whereas Secretory cells require mediation of the Notch pathway and mucus-producing goblet cells depending on the activation of the transcription factors SPDEF and FOXA3 (Crystal, 2014).

Several studies have shown that basal cells are one of the respiratory stem/progenitor cells using both animal and human cells. A stem cell or progenitor cell has one of the characteristics of self-renewal and can differentiate to produce different progeny from one or more cell types. Adult stem cells are also supposed to be able to completely repopulate tissues and maintain them for a long time, in the form of a culture of airway basal cells with immunohistochemical staining showing 95% of the population of basal cells expressing cytokeratin markers 5, p63, and CD151.
and showing mesenchymal markers N-cadherin, mucin marker 5A and trefoil factor 3 for secretory cells, marker b-tubulin IV and dynein intermediate chain 1 for ciliated cells, chromogranin A and calcitonin gene-related polypeptide for all negative neuroendocrine cells. Then in this study to show that the basal cells are true stem/progenitor cells, cultures were carried out on the basal cell population on type IV collagen with an "air-liquid interface" culture which positioned the basal cells at their base on the growth medium and their apical parts on air. On day 28 these basal cells were isolated and yielded fully differentiated airway epithelial cells with a progressive increase in the number of ciliary and secretory cells, tight tau, and increased transepithelial resistance.

Normal basal cells not only have the ability to proliferate and differentiate to produce other types of cells, but also can secrete proteins that can affect surrounding cells and have receptors that can be influenced by products from other cells. In normal airway basal cell transcriptome studies, the expression of 1100 genes was found, which is five times more than that of the differentiated epithelial cells. These basal cells are also characterized by the presence of growth factor-encoding genes, growth factor receptors, extracellular matrix components, G protein coupled receptors, neuroactive ligands and other receptors and ion channels. In the basal cell culture, when the supernatant was taken and examined, it turned out that the basal cells secreted various growth factors (vascular endothelial growth factors A and C, angiopoietin, platelet-derived growth factors A and C, placental growth factor, bone morphogenetic proteins 1 and 2), transforming growth factors 1 and 2, fibroblast growth factors 2 and 11, endothelin, IL-1b and IL-8, and the Notch ligand Jagged) and their transcriptional analysis showed airway basal cells express receptors for epidermal growth factor, transforming growth factor, tumor necrosis factors, ephrin, leptin, vasopressin, histamine, serotonin, IL-1, and low-density lipoprotein. This suggests that airway basal cells can communicate with and influence the surrounding environment by producing polypeptides and are influenced by cells in the surrounding environment with the expression of various receptors so that airway basal cells play a role in maintaining airway homeostasis through their ability to proliferate and differentiate.

**Chronic Obstructive Pulmonary Disease (COPD)**

COPD is a chronic lung disease characterized by progressive non-reversible or partially reversible airflow obstruction in the airways. COPD consists of chronic bronchitis and emphysema or a combination of both. Smoking is the most common and important risk factor compared to other causes such as exposure to pollutants and other harmful gases. In addition, risk factors such as genetic factors (alpha 1-antitrypsin deficiency), age and gender, presence of asthma and airway hypersensitivity, chronic infection and inflammation also contribute to the occurrence of COPD.

Spirometry is used to diagnose COPD to confirm persistent air resistance after bronchodilator use. In patients with dyspnea, chronic cough with chronic mucus production, with or without exposure to risk factors, COPD is suspected. Spirometry shows FEV1/FVC < 0.7 post bronchodilator confirming persistent air resistance and coupled with other signs and symptoms, other supporting examinations and exposure to risk factors can be diagnosed with COPD. Classification of severity of airflow limitation based on GOLD criteria is divided into gold 1 (mild)
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with an estimated FEV1 ≥ 80%, gold 2 (moderate) with FEV1 50% to 79%, gold 3 (severe) with FEV1 30% to 49%, and gold 4 (very severe) if FEV1 < 30%. Meanwhile, the severity of symptoms can be checked using the Modified British Medical Research Council (mMRC) criteria or the COPD assessment test (CAT). An assessment of the severity of airflow obstruction and an assessment of existing symptoms are then combined to determine the appropriate treatment.

Current management of COPD includes education, oxygen therapy, mechanical ventilation, nutrition, rehabilitation, and medications which differ from individual to individual and depend on stable or exacerbating symptoms. Drugs such as bronchodilators, anti-inflammatories, antibiotics, antioxidants, mucolytics, antitussives, corticosteroids and other drugs are used taking into account the side effects that exist to reduce symptoms, prevent recurrent exacerbations, and in order to improve the quality of life of sufferers, but have not been able to treat them. Pneumococcal vaccination can also be used to reduce the chance of developing a serious disease.

In the pathogenesis of COPD, apart from the role of chronic inflammation involving the immune system, pathological changes in the airways both histologically and molecularly also play an important role in the early stages of COPD. Changes in the airway epithelium (respiratory epithelium) are also found in the conducting portions of the airways. Pathological changes that often occur are goblet cell metaplasia and squamous cell metaplasia in the stratified epithelium of the larger airways and goblet cell metaplasia in ciliated columnar epithelial cells in the small airways (Berg & Wright, 2016). It has been described previously that the respiratory epithelium consists of various cell types, one of the only basal cell which is a stem cell in the respiratory epithelium of the respiratory tract which plays a role in the regeneration of respiratory epithelial cells whose changes in the early stages of COPD histologically and molecularly cause airflow obstruction in the airways in patients with COPD.

**Changes in Airway Basal Epithelial Cells in COPD**

It is well known that airway basal cells play an important role in airway homeostasis, with their ability to proliferate and differentiate as well as communication between basal cells and surrounding cells in terms of cytokines and growth factors. However, under certain conditions, there may be changes in various cytokines and growth factors such as IL1a, IL33, and TGF-b which are overregulated in basal cells which can cause abnormal proliferation and differentiation leading to disease (Crystal, 2014; Rock et al., 2010). In COPD, duct epithelial dysfunction occurs. breath due to the presence of noxious particles that injure the airways and interfere with the defense function of the airway epithelium. In general, the dysfunction of the airway epithelium includes three things, namely the occurrence of physical barrier dysfunction, chemical barrier dysfunction, and immune system dysfunction.

The physical barrier involves junctional proteins and ion channels that regulate epithelial permeability in addition to dysfunction of the role of ciliary cells and mucus-secreting cells which play a role in eliminating harmful particles. While the chemical barrier involves mucus-producing proteins and the epithelium will secrete a number of chemical products based on antimicrobials and antioxidants. While the epithelial immune response involves innate and adaptive immunity.
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Healthy epithelial cells will produce a good physical, chemical and immune system barrier and can restore normal function if there is injury played by airway basal cells.

In COPD, there are changes in the histological composition/structure of the airway epithelium starting from changes in the airway basal cells that act as stem/progenitor cells. Abnormal changes that occur in the basal cells begin with basal cell hyperplasia followed by loss of ciliated cells, shortening of cilia, hyperplasia of mucous cells, squamous cell metaplasia, and loss of cell junctions. supported by changes in the microenvironment of the airways. In COPD, these changes are irreversible because changes at the basal cell level are usually difficult to treat because the progenitor cells which will later proliferate and differentiate to create homeostasis in the airways themselves are already disturbed or even damaged.

Basal cell changes in epithelial dysfunction mainly play a role in disruption of the physical barrier which includes leakage of junctions between cells, mucociliary dysfunction, and dysfunction of repair mechanisms in the airways. In the epithelium there are tight junctions/zonula occludens (tight junctions), adherent junctions/adherent zonules (adherens junction), and desmosomes composed of molecules and proteins such as claudins, occludins, and cadherin/β-catenin complexes which play a role in signaling as well as processes of proliferation and differentiation supported by intact polarity. In addition, E-cadherin will also interact with the epidermal growth factor (EGFR) receptor which in response to injury plays a role in promoting mitosis, cell migration processes, and epithelial cell differentiation. In COPD, increased EGFR will result in pathological processes such as breaking of the epithelial barrier, goblet cell hyperplasia/metaplasia, mucus hypersecretion, and EMT. This causes leakage in the lining of the respiratory epithelial cells. The existence of these leaks has an effect on the susceptibility to infection and colonization of bacteria such as Streptococcus pneumoniae, Pseudomonas aeruginosa, and Haemophilus influenzae in COPD and disrupts the signaling process which results in disruption of the proliferation and differentiation processes.

Under normal conditions, the mechanism for removing harmful particles from the airways is played by ciliated epithelium and secretory-producing cells to produce airway surface liquid (ASL). The ASL consists of two parts, an upper viscoelastic portion that secretes mucin, and a periciliary layer composed of membrane-bound glycoproteins that provide lubrication of the ciliated cells. So that the particles can be stuck in the layer. In order to function properly, apart from the quality, quantity and composition of the lubricating fluid, intact ciliary function is also needed to expel particles that are entangled in mucus out of the airways. In COPD, mucociliary dysfunction occurs in various ways that will change the composition and pH of the mucin, coupled with reduced cilia, the mucus in the airways will increase and can clog the airways. This condition with mucus hypersecretion is common in patients with chronic bronchitis in which goblet cells in the bronchial and bronchiolar epithelium produce excess secretions.

In COPD, the predominant condition of EMT type II occurs, which is characterized by the disappearance of E-cadherin markers and increased mesenchymal markers such as vimentin, desmin, specific protein 1/S100A4, and alpha smooth muscle actin. This EMT will cause a loss of cell polarity, disruption of intercellular adhesion and changes in the interaction of cells with their...
extracellular matrix which can affect the response to various inflammatory signals. In COPD there is also squamous cell metaplasia which is influenced by increased IL-1b which also affects polarity and adhesion through EFGR activation. which causes fibroblast proliferation, secretory cell hyperplasia, and smooth muscle hypertrophy. All of these processes, including disruption of barrier function and disruption of mucociliary clearance, play a role in COPD conditions that contribute to chronic scarring that requires extensive tissue repair and changes in the histological makeup that occur in COPD. As this process continues, the airway lumen narrows in response to inflammation and mucin infiltration of the airways.

The Effect of Gene Dysregulation on Basal Cell Changes

Chronic obstructive pulmonary disease (COPD) often occurs in the elderly with the assumption that chronic exposure to harmful particles can stimulate changes in the structure of the airways. However, not everyone exposed to the same agents will develop COPD and there are early changes in airway basal cells. One of the other important concepts presented in the incidence of COPD is evidence that smoking is at risk for the occurrence of COPD and in smokers, only 20% become sick fibrosis with similar symptoms. This raises the question of whether there is dysregulation of certain genes along with life and exposure to these harmful particles (Crystal, 2014; Shaykhiev & Crystal, 2014).

There is an association between genetic risk factors for COPD and airway basal cells, which are the first cell population to undergo histological changes. However, not all of these genetic risk factors are inherited. There are also conditions where dysregulation occurs, which is induced by harmful particles, especially cigarette smoke, so that the basal cells do not function properly. Because basal cells are stem/progenitor cells that function in the regeneration of other airway epithelial cells, somatic variations in these cells can lead to disruption of their normal structure. A study conducted by comparing the exome sequences in the basal cell DNA of smokers compared to the exome DNA sequences in the blood of the same smokers showed a higher somatic mutation in the basal cells compared to the blood of these smokers.

As basal cells play an important role in the early pathogenesis of COPD, it has been hypothesized that exposure to harmful particles such as cigarette smoke and genetic changes in basal cells may modulate COPD risk factors. Research in 2014 tried to assess this hypothesis and it turned out that there was 25% dysregulation in genes located on chromosome 19, where 13 of these genes are located at 19q13.2 which is the locus for COPD. These thirteen genes were up-regulated in basal cells and 4 of them (EGLN2, LTBP4, TGFBI, and NFKB1B) were also studied with genomwide association which is a risk factor for COPD (Crystal, 2014; Ryan et al., 2014; Shaykhiev & Crystal, 2014).

TGFBI will encode TGF-b which is a growth factor that is detected high enough in smokers with COPD which is associated with airway obstruction and plays a role in changes in airway epithelial cells by causing squamous cell metaplasia and airway fibrosis. LTBP4 which is a binding protein that binds to TGF-b and targets the extracellular matrix plays an important role in maintaining the distal lung architecture. EGLN2 will code for a prolyl hydrolase which functions
as a cellular oxygen sensor that plays a role in response to hypoxic conditions. Impaired expression of EGLN2 is associated with increased proliferation of epithelial cells and impaired junctional barrier function in the epithelium. Meanwhile, NFKBIB which encodes NF-κB inhibitor b is associated with the occurrence of oxidative stress in smokers.

**Transition from the Normal Airway to the Airway of a Patient with COPD**

Exposure such as smoking that takes place chronically in the long term causes basal cells to be disrupted and regress to become more primitive, susceptible to gene changes, and lose their capacity to regenerate epithelium. In someone who is continuously exposed to risk factors for harmful particles, even though he looks normal on the outside before COPD occurs, it turns out that he has already experienced changes at the cellular level. Basal cells of the airways will experience fatigue (stem/progenitor fatigue). A study by Staudt, et al showed that when basal cells placed at the air-liquid interface could differentiate into mucociliary epithelial cells within 28 days, 88% of the samples differentiated into non-smokers, whereas in healthy smokers only 64% differentiated and in smokers who become COPD there is only a 44% differentiation.

The inability of the basal cells to maintain their ability to differentiate will cause the integrity of the respiratory epithelium to be disturbed which causes infection and inflammation which will develop chronically into COPD. In smokers and people with COPD, there are changes in the microenvironment that induce genetic changes in the basal cells that cause a reduction in the regenerative capacity of these cells. Chronic inflammation and infection due to repeated exposure over a long period of time will produce stress mediators such as EGF and amphiregulin (AREG) which cause basal cells to become fatigued and basal cell DNA methylation occurs. As a result, the basal cells become more primitive, their ability to regenerate decreases, and histological changes occur in the airway structure according to the characterization of COPD which causes symptoms of chronic bronchitis and pulmonary emphysema.

**Stem Cell Therapy in COPD**

Stem cells are currently being developed for regenerative therapy, one of which is for regenerative therapy for lung diseases such as COPD. With the development of stem cell technology, many studies have been carried out in this field and some have even claimed that stem cell therapy has been proven effective, although it is not clear how far clinical trials for disease therapy with stem cells have progressed. Stem cells are expected to differentiate into several types of lung cells and airways damaged by exposure to hazardous substances. In pre-clinical studies with experimental animals, it is thought that there is improvement in structures such as the alveoli, and a reduced inflammatory response, but this has only been shown to work well in animal models with acute injury. Based on several published journals, recent developments in stem cell therapy for COPD have only reached phase II clinical trials.

Lung regeneration therapy is currently divided into *in vitro* tissue/progenitor cells engineering and transplanting, cellular and gene therapy, as well as pharmacological manipulation which is divided into extrinsic and intrinsic therapy strategies. The basis for the development of...
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lung and airway regeneration research for transplantation is based on the existence of the pneumonectomy model in which the lung also has the ability to regenerate if an injury occurs, although its capacity is limited. Therefore, research has begun to be developed based on the mechanisms and molecular changes that occur during lung reveolization and regeneration. Cell extrinsic therapy is carried out by infusion of embryonic stem cells (ESCs), induced pleuripotent stem cells (iPSSs), mesenchymal stem cells (MSCs), and/or human lung stem cells (hLSCs). While the intrinsic therapy strategy is by transferring small molecules (such as retinoid components which are currently being studied) which can stimulate lung and airway stem/progenitor cells to regenerate and replace damaged structures.

Although some studies with stem cells have been successful, research in phase two clinical trials has yet to show different results. Several studies that have successfully shown improvement are known to improve symptoms, reduce exacerbations and reduce inflammatory markers, but are still unable to correct structural changes. It is known that the injected stem cells cannot differentiate and replace damaged cells, but reduce inflammatory markers and reduce symptoms. This could be due to the paracrine effect of stem cells which have anti-inflammatory and immunomodulatory effects. In clinical trials that have not shown significant results, it could be because the development of COPD has passed its acute phase where reprogramming of basal cells has occurred which plays an important role in the early stages of COPD (Balkissoon, 2018; Cao & Xiao, 2018; Oh et al., 2017).

CONCLUSION

Chronic Obstructive Pulmonary Disease is a disease that causes high morbidity and mortality in Indonesia and the world. Current therapy is still limited to improving symptoms and reducing exacerbations, but there is still no therapy that can improve or cure COPD. Recent developments in the pathogenesis of COPD disease are known that there is an important role for changes in the histological and molecular structure of the airways played by basal cells. Changes in the basal cells are the starting point for histological and molecular structural changes that have been proven from several published studies. With the development of stem cell technology, regenerative therapy with stem cells has begun to be developed which is expected to improve and cure this disease. Recent developments in stem cell therapy in COPD are only limited to preclinical and phase 2 clinical trials. In the future, further research is still needed for stem cell therapy, especially in COPD, by considering changes in basal cells, molecularly and histologically, which are the initial stages of COPD.

REFERENCE


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