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Chronic Obstructive Lung Disease, Stem Cells and Telocytes: Review of Therapeutic

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Abstract

Chronic Obstructive Lung Disease (COLD) is responsible for leading causes of mortality and morbidity worldwide, and a major public health problem worldwide. In addition, COLD is associated with high costs. In the EU, the total direct costs of respiratory diseases are estimated at 6 % of total health care costs, and that COLD accounts for 56 % of these expenditures (38.6 billion euros). In the United States, the direct costs of COLD are 29.5 billion and indirect costs of the order of 20.4 billion dollars. In Brazil, it is estimated that 5 million Brazilians have COLD, according to the Brazilian Thoracic Society (BTS) and second DATASUS, COLD generated in 2010, the National Public Health System, 141,994 hospitalizations that led the 778,428 days of hospitalization. Cell therapy can be regarded in a broad and general manner to the use of cells for the treatment of COLD, mainly stem cells and telocytes. Although not a significant number of reports, involving lung and object of study in cell therapy in human patients, there is consistent data, both in humans and in animal models that show the migration of stem cells from bone marrow to the lung and the recovery of lung function in different experimental situations. The results, together with those of other research groups, allow to contemplate the possibility of application of cell therapy in patients with COLD.

Keywords: COLD; Stemcells; Telocytes; Cell therapy

Introduction

Epidemiologic data of Chronic Obstructive Lung Disease

Chronic Obstructive Lung Disease(COLD) is responsible for leading causes of mortality and morbidity worldwide, and a major public health problem worldwide. In 2000, according to the World Health Organization - WHO, COPD was the 5th leading cause of mortality worldwide, with 4.5% of deaths, second only in brain and heart, AIDS or AIDS-vascular diseases (Acquired Immunodeficiency Syndrome) [1-3]. In 2004, also according to the WHO, COPD became the 4th leading cause of death worldwide, with 5.1% of deaths, surpassing AIDS [4-7]. Moreover, when we consider the "burden of disease" (Burden of Disease) measured in QALYs (Quality Adjusted Life Years - metric involving the quantity and quality of years lived), it is estimated that COLD will the 13th pathology Ranking world in 2004 to 5th in 2030, possibly due to population aging and the industrialization of low-income countries [7-9].

In addition, COLD is associated with high costs. In the EU, the total direct costs of respiratory diseases are estimated at 6% of total health care costs, and that COLD accounts for 56% of these expenditures (38.6 billion euros). In the United States, the direct costs of COLD are 29.5 billion and indirect costs of the order of 20.4 billion dollars [10]. In Brazil, it is estimated that 5 million Brazilians have COLD, according to the Brazilian Thoracic Society (BTS) and second DATASUS, COLD generated in 2010, the National Public Health System, 141,994 hospitalizations that led the 778,428 days of hospitalization [11]. The total cost of these hospitalizations was R $ 92,434,415.51 and 7,937 deaths directly related to COLD. According to BTA, the prevalence of COLD in Brazil is 15.8% in adults older than 40 years [12].

The main issue related to COLD is cigarette smoking, which are associated with 95% of cases. Other causative factors include air pollution, occupational exposure to pollutants and also in alpha-1-antitrypsin [13-16] disability. In the epidemiological study called Proyecto Latinoamericano de Investigacion en pulmonary obstruction (PLATINUM, Latin American Project for the Investigation of Pulmonary Obstruction), designed for screening for COLD and conducted in São Paulo, it was found that 15,8% of individuals aged 40 years or older had COLD and that 12.5% of these individuals had never been exposed to tobacco smoke [17-21]. From these data, it appears that other risk factors for COLD than smoking, are important in Brazil, including AAT deficiency. A study in COLD patients present severe AAT deficiency in 2-3% of patients. According to the PLATINO study, there are 5 to 7 million with COLD in Brazil [22-26]. It is estimated. Epidemiological studies conducted worldwide have shown that AAT deficiency is about as frequent as cystic fibrosis, affecting one in every 2,000-5,000 individuals [27,28].

Obstructive diseases have high prevalence in humans and have been the subject of many clinical and experimental studies aimed at a broader understanding of its pathogenesis, pathophysiology, and especially the establishment of more rational forms of treatment [22-26]. As a result of this great effort, the concepts of obstructive diseases suffered an extraordinary expansion in recent years, involving the integration of mechanical factors, inflammatory agents, autonomic regulation of airways and environmental aspects [21-26].

According GOLD 2011 the main aspects of therapy of patients with COLD are: the abandonment of smoking in smokers, which may be obtained either by frequent counseling patients, as by therapeutic measures [28-31]. Smoking cessation is the measure with the greatest potential to prevent disease progression [22-24].

Significance

Clinical standard treatment

According to the "Global Initiative for Chronic Obstructive Lung Disease" (GOLD), COLD is a common, preventable and treatable disease, which is characterized by persistent limitation in lung air flow, usually progressive and associated with character with increased

inflammatory response of the airways and lungs to noxious particles and gases [31-38]. Exacerbations and comorbidities contribute to the overall disease severity [39-42].

Moreover, the chronic airflow limitation characteristic of COLD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), and the contribution of each of these processes varies from individual to individual [43-51]. Chronic inflammation causes structural changes and narrowing of small airways [51-54]. The destruction of the lung parenchyma, also by inflammatory processes, leads to a loss of adhesion of the small airways and alveoli pathways decrease the elasticity of these pathways, which consequently leads to a decreased ability of these remain open during expiration [55-59]. The airflow limitation is best measured by spirometry, and this is the most available and reproducible tool to assess lung function test [60-65].

Many previous definitions of COLD have emphasized the terms "emphysema" and "chronic bronchitis", which are not included in the definitions used in GOLD. Emphysema, or destruction of the surface of pulmonary gas exchange (alveoli), is a term that is often pathological (but incorrectly) and used clinically only describes one of several structural abnormalities present in patients with COLD [66-70]. Chronic bronchitis, or the presence of productive cough for at least 3 months a year for two consecutive years, remains a term clinically and epidemiologically useful [71-73]. However, it is important to recognize that chronic productive cough (chronic bronchitis) is an independent disease entity that may precede or follow the development of airflow limitation and may be associated with the development or acceleration of chronic airflow limitations [74-78].

Currently, COLD is classified into 4 stages of severity depending on the degree of airway obstruction as measured by forced expiratory volume in 1 second (FEV1) and the ratio of FEV1 and forced vital capacity (FVC) -VEF1/CVF. These stages are listed below: Mild FEV1/FVC<0.70; FEV1>=80% predicted, moderate FEV1/FVC<0.70; 50% <=FEV1<80% predicted, severe FEV1/FVC<0.70; 30%<=FEV1<50% predicted, very serious FEV1/FVC<0.70; FEV1<30% predicted or FEV1<50% predicted plus chronic respiratory failure [79-81].

However, more recently these stages began to be called "degrees" and are used together with the level of symptoms presented by patients to classify them into four categories (A, B, C and D). According to the GOLD 2011, the purpose of the evaluation is to determine the COLD disease severity, its impact on patient health and the risk of future events (exacerbations, hospital admission and death) in order to guide therapy. Thus, the following aspects of the disease are used separately: symptoms, degree of airflow limitation (using spirometry), exacerbation risk, comorbidities [82-91].

Typical symptoms of COLD usually associated with hypersecretion of mucus and cough with fibrosis due to the attempted repair of chronic inflammation, obstruction of small airways because the lumen is reduced due to the formation of inflammatory exudate or by deposition collagen and emphysema with destruction of parenchyma, enlargement of the air, space narrowing and weakening of small airways with increased lymphoid follicles, loss of lung elasticity and closure of small airways. These presentations can be concurrent or not, and may show a variable degree [92-97].

Further, as treatment of COLD,vaccination against influenza and pneumococcal infections that decrease the executives responsible for periods of exacerbation. Measures of rehabilitation and physical conditioning that improve the quality of life of patients and their ability to perform physical activities. Using both drugs in the stable phase of the disease in order to decrease the intensity and frequency of seizures, the seizures in aiming the removal of the patient in this phase of acute exacerbation of the disease [76,77]. The pharmacotherapy used in the treatment of COLD consists of several classes of medications as: Beta 2 agonists, short and long action (LABA), anticholinergics short and long action (LAMA), systemic and inhaled corticosteroids (ICS), the nonspecific phosphodiesterase inhibitors (methylxanthines) specific phosphodiesterase 4 inhibitors (roflumilast), as well as various combinations of such drugs, according to the degree of the disease [77].

Cell Therapy – Advancements Stem Cells and Telocytes

Often cases of COLD are refractory to pharmacological treatments, then in order to meet such emergencies mortalities and morbidities and although cells, tissues and organs damaged by trauma or disease being recovered spontaneously by the body, the cell therapy regenerative medicine seeking to replace cells or tissues with severe injuries or senescent cells to regenerate and restore their functions [77,78]. The diseases that are targets of these treatments are the main causes of morbidity and mortality worldwide companies, taking as examples heart disease, diabetes, cancer, lung diseases, and genetic diseases.

Transplantation of hematopoietic adult stem cells in the bone marrow is still today the most used treatment for treatment of human stem cells and consists of the infusion of these cells to restore hematopoiesis in the recipient or even provide a greater quantity stem cells for promote tissue regeneration. The transplanted stem cells survive for long time maintaining their properties, being used for neoplastic and non-neoplastic diseases such as aplastic anemia, autoimmune diseases and lung diseases [70-79].

There is evidence that these cells can also transdifferentiate into other non-hematopoietic lineages such as endothelial and lung cells [70-82]. In addition to the hematopoietic stem cells in the bone marrow, there are mesenchymal stem cells around 0.01% to 0.001% which are multipotent cells capable of differentiating into various cells and tissues, increasing the therapeutic capacity of hematopoietic stem cells [80-82]. Despite a relatively small number of reported cases and the lung as an object of study in cell therapy, there is consistent data, both in humans and in animal models, which show the presence of stem cells labeled in the bone marrow lungs of animals or human patients undergoing bone marrow transplantation (Figure 1).

Others authors obtained promising results with regard to cell therapy in COLD [35]. These authors transplanted adherent cells derived from bone marrow of transgenic mice in wild-type mice subjected to lung injury by bleomycin and verified the presence of transplanted cells as type I pneumocytes in the lung of the recipient. Krause et al. 2001 [36], after irradiation of a female, transplanted stem cells from the bone marrow of a male mouse and observed the presence of these stem cells with Y chromosomes in several tissues, including the lung tissue.

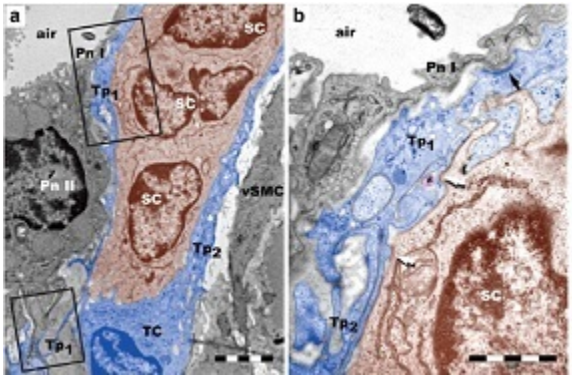

Figure 1: Telocytes and a possible stem cell niche at the level of the bronchoalveolar junction (mouse). A group of putative stem cells (SC), underneath the alveolar epithelial cells (Pn I, type I pneumocytes; Pn II, type II pneumocytes). The cluster of SCs (brown) is surrounded by telopodes (Tp1, Tp2; blue). TC, telocyte; vSMC, vascular smooth muscle cells. b Higher magnification of the upper boxed area in shows one telopode (Tp1, blue) in contact with a type I pneumocyte (Pn I, black arrow) and a brown-colored SC (white arrows). A shed vesicle visible in violet (asterisk) (From Popescu et.al. [95]).

Suratt et al. [71] selected lungs of women who have previously received allogeneic hematopoietic stem cell donor men and performed in situ hybridization studies, verifying the presence of the Y chromosome and endothelial and epithelial markers in these cells from the donors. Therefore found chimerism in human lung equivalent to 2.5 to 8% epithelial and 37.5 to 42.3% endothelial. Next, Ishizawa et al. 2004 [33] demonstrated, in elastase-induced emphysema model, treatment with retinoic acid and colony-stimulating factor granulocyte (GCSF) leads to the regeneration with the presence of alveolar bone marrow cells in the lung after treatment, indicating the mobilizing these cells could be of great importance in regeneration.

Also using the lung as an organ of interest, Yamada et al. [81] lung injury induced by lipopolysaccharide derived from Escherichia coli and analyzed the mobilization of bone marrow progenitor cells, finding a large number of receptors in donor cells with damaged lungs. However, there is no standardized therapeutic effective of these cells, with a stratification results inconclusive answers. You need to know and establish the appropriate niche for biological treatment of COLD and control variables of the clinical conditions of each patient to ensure the therapeutic effective of these cells (Figure 2).

Added to this, the author Popescu et al. [98-103] first demonstrated the importance of the presence of Telocytes(TC) with stem cells to increase the efficiency of cell therapy. The Telocytes is a new type of interstitial cells of mesenchymal origin, first described in 2005 by Popescu et al. Initially, they were named as Cajal interstitial cells, but when the lack of resemblancetothecanonical Cajal interstitial cells became obvious, the name Telocytes was introduced and is currently used.

The presence of TC has been documented in several organs and cavities in connective tissues (heart, the pericardium, the pulmonary vein, intestine, mesentery, gallbladder, uterus and fallopian tubes and non-cavitary organs (lung, trachea, pleural, skeletal muscle, exocrine pancreas, placenta, mammary gland and the [104-110].

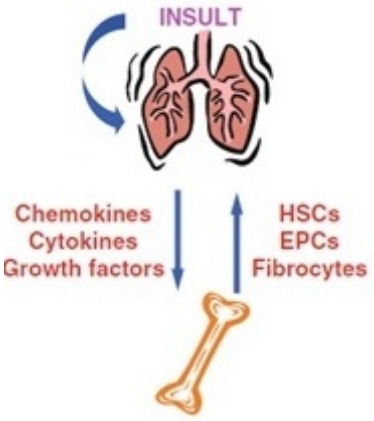

Figure 2: Injured lung infection or chemothera publztic processes. Such agents, radiation or other agents that may result in the production of chemokines, cytokines and growth factors through the lung. This in turn induces the release or "Call" progenitor cells from bone marrow into the damaged lung is defined as "homing" cell (From : M. Rojas, 2010. Stem Cells in the Respiratory System, Stem Cell Biology and Regenerative Medicine).

These are characterized by being very large, typically tens of micrometers, around a hundred micrometers or more. They are made by alternating dilated portions, called podoms and podomers. Podomers the thickness is usually very thin, below the resolving power of conventional light microscopy in sections, with the branch dichotomous extensive testing and immunohistochemistry with positive reactions for c-kit, vimentin and CD34 [111-113].

Apart from the conventional role of mechanical support for the TC network, we believe that the main role of TC is intercellular communication and regulation, with the existence of TP 3D network [114,115]. Thus, it is clear the location of TC and TP in close proximity to blood capillaries or nerve endings. We conclude that in adulthood, most of the TC has the fibroblastoid [104]. Immunocytochemical assays suggest that a variety of TC populations show different immunophenotypes may exist. Several papers were hypothesized to TC as mechanical function, intercellular signaling, guide immature cells during organogenesis, are precursors of many mesenchymal cells in adulthood [105-107]. However, none of these papers were also tested. Even so, it is proposed that TC can be acutely important in regeneration of tissues and organs [105,116-118].

These results, however, have been viewed with greater caution by some authors to question the acuraria of detection techniques employed [105,116-118]. The TC migration to the lung could have been overestimated, and therefore would be present in a much lower proportion than has been proposed, with questionable clinical significance [119,120]. Results in favor of this proposition were obtained by Xu et al. [83].

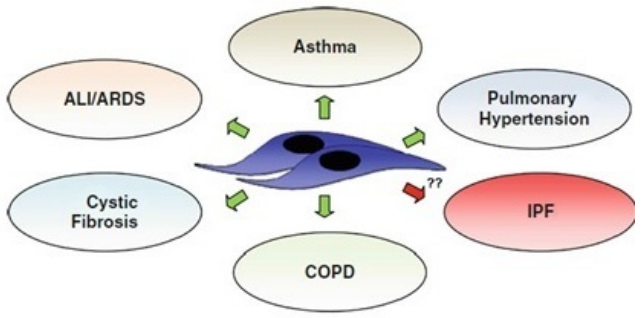

Figure 3: Action of mesenchymal stem cells (MSCs) in inflammatory lung diseases. MSCs are emerging as a therapeutic modality in many inflammatory lung diseases such as acute lung injury, chronic obstructive pulmonary disease, cystic fibrosis, pulmonary hypertension, and allergic diseases such as asthma. Due to its potential antifibrotic effects in vivo, MSC cannot represent a therapeutic option in patients with fibrotic lung diseases such as idiopathic pulmonary fibrosis (From: M. Rojas, 2010. Stem Cells in the Respiratory System, Stem Cell Biology and Regenerative Medicine).

These authors, after transplantation of mesenchymal stem cells in mice that had previously received intraperitoneal injection of lipopolysaccharide (LPS), not found in the immune histochemical analysis of lung tissue taken 14 days after transplantation, significant occurrence of cells with positive signal for mesenchymal stem cell - MSC [100, 104]. However, although they have not found evidence of effective integration of MSC to the lung tissue and the presence of derived cells with the phenotype of local cell types, the authors were able to prove that transplantation of stem cells has allowed a reduction in inflammation and pulmonary edema induced by LPS [120](Figure 3).

Conclusion

It was concluded that makes it important to adopt cell therapy as an alternative to conventional treatments for COLD, with the application of mesenchymal stem cells or hematopoietic stem cell associated with telocitos to better recovery of patients, emphasizing the improvement of quality of life.

Disclosure of potential conflicts of interest

The authors declare that they have no conflicts of interests.

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