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Abstract- Cells with characteristics of embryonic stem cells, and cancer stem cells are at the basis of both embryo development and the cancer process. At the same time, they share signaling pathways, such as the hedgehog, Notch, Wnt, TGF beta, among others. This knowledge is important for understanding the pulmonary regeneration process and for the development of new target therapies.

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Characteristics Shared between Lung Development and Tumorigenesis: Mini Review Article

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Abstract- **Cells with characteristics of embryonic stem cells, and cancer stem cells are at the basis of both embryo development and the cancer process. At the same time, they share signaling pathways, such as the hedgehog, Notch, Wnt, TGF beta, among others. This knowledge is important for understanding the pulmonary regeneration process and for the development of new target therapies.**

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Introduction

The understanding of lung development during embryogenesis and the knowledge of several cell populations is essential for regenerative medicine and for the recognition of the cell of origin of lung neoplasms.

Several evidences suggest that the human lung contains a population of characteristic stem cells. This statement is explained by the fact that most patients with small cell lung cancer (CPCP) already have metastases, resistance or refractoriness to chemotherapy treatment at the moment. Likewise, patients with adenocarcinomas that express tyrosine kinase (EGFR) mutations, and who are initially sensitive to therapy, also acquire resistance. (Kobayashi et al. 2005; Pao et al. 2005; Kosaka et al.2006).

Another piece of evidence was the identification of cells from the lateral population, isolated by their ability to efflux the Hoechst dye and which exhibit increased expression of drug transporters, tumor propagation capacity and resistance to multiple chemotherapies (Ho et al. 2007). It was identified that CD133 positive lung tumor cells formed self-renewing spheres in culture with tumor propagation, when transplanted subcutaneously in immunodeficient mice (Erasmo et al. 2008).

With this review we intend to define the cell types and molecular biology data of the lung in embryogenesis and in the adult lung, drawing points of comparison and trying to correlate with the development of neoplasms.

I. Pulmonary Development Stages

The lung has a large internal surface and an airway conduction system with several branches. Conductive airways are formed first, followed by the formation and enlargement of the gas exchange area. Alveolarization is the last stage of the fetal period and continues in the postnatal period.

In the embryonic period, between 4-7 gestational weeks organogenesis occurs. The left and right lungs have their own ring, an external pouch of the anterior intestine (Cardoso and Lu 2006). Each pulmonary bud initiates a repetitive process of growth and branched morphogenesis to form future airways (Schittny and Burri 2008). Epithelial cells are supported by a basement membrane, surrounded by an extracellular matrix that is produced by mesenchymal cells. The components of the extracellular matrix, including the basement membrane, are different in the terminal bud, in the branching points and in the most proximal portions of the bronchial tree, where epithelial differentiation has already started (Schittny and Burri2004). The branching is coordinated by epithelial and mesenchymal cells, growth factors and transcription factors that the cells are producing.

The fetal period includes the pseudoglandular, canalicular and saccular stages. The postnatal lung period comprises the stages of classic and continuous alveolarization, as well as microvascular maturation. As most processes during lung development begin in the proximal area and extend to the periphery, all phases of lung development overlap (Schittny and Burri 2008; Wood and Schittny 2016)

The expression of growth factors, such as fibroblast growth factor 10 (FGF-10), bone morphogenic protein 4 (BMP-4), Sonic Hedgehog (Shh), retinoic acid, Notch and TGF-β provide the instructions for

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ramification in the period of morphogenesis. (Cardoso and Lu 2006; Hines and Sun 2014; Schittny and Burri 2008)

The negative feedback mechanism involves signaling by Shh (Sonic hedgehog), its Ptc1 receptor (Patched 1) and transcription factors such as Gli1-3, belonging to the Shh signaling pathway. The Shh pathway acts by inhibiting local expression of Fgf10, preventing branching from occurring indefinitely. The process also depends on complex regulation by signaling pathways of the TgfB (Transforming Growth Factor Beta) family members, Wnt (Wingless- type) and Bmp4 (Bone Morphogenetic Protein 4, from the Tgf Beta family) (Park 1998; Rock and Hogan 2011; Katton and Morrisey 2014).

The Fgf (fibroblast Growth Factor) signaling pathway is activated by localized expression of Fgf10 in the mesoderm and its receptor Fgfr2 in the endoderm. This signaling induces branching, and Fgf10 stimulates the proliferation of epithelial cells. (Rock and Hogan 2011; Katton and Morrisey 2014).

Around the 10th gestational week, respiratory movements begin that cause additional stretching of the fetal lung tissue (Koos and Rajace2014). These stimuli positively regulate the release of serotonin, promoting epithelial differentiation (Pan et al 2006).

A continuous layer of positive cells for α smooth muscle actin begins to form around the future proximal airways, becoming discontinuous distally in the bronchial tree and ending in front of the terminal buds. These contractile cells begin to perform spontaneous contractions, pushing peristaltic waves of interbronchial fluid to the periphery. These movements, too, stimulate branched morphogenesis and prevent uncontrolled airway expansion as lung fluid is secreted into the lung (Schittny et al. 2000; Sparrow et al. 1994).

The canalicular stage occurs between 16-26 gestational weeks and comprises the differentiation of the epithelium that allows the morphological distinction between the airways (acino / ventilatory unit) (Winkelmann and Noack 2010).

At the junction of the bronchialveolar duct (BADJ), there is an abrupt change in the epithelium from hair cells and from Clear cells to type I and type II alveolar epithelial cells (Winkelmann and Noack 2010). This junction is formed at the canalicular stage, when epithelial differentiation occurs and is of particular importance, because it represents a niche of stem cells (McQualter et al. 2010). It has recently been shown that the junction bronchialveolar remains constant throughout the lung development in the generation of the airways, where it was originally formed (Barre et al. 2014, 2016).

The saccular stage occurs between 24-38 gestational weeks and represents an intermediate stage, when the branching morphogenesis ceases and the alveolarization has not yet started (Cardoso and Lu 2006; Morrisey et al. 2013). they are coated by type 1 and type 2 cells (Cardoso; 2006; Rock and Hogan, 2011).

At the end of the saccular stage, the mesenchyme located between the future airways contains a loose three-dimensional vascular network in proliferation, due to intense angiogenesis, conferring a high capillary density. The future airways that will become alveolar ducts grow in width and length, change shape and appear as "canaliculi", which form the canalization of the mesenchyma through the airways and capillaries. The growth of the airways and apoptosis cause condensation of the mesenchyme., where the volume and the total number of mesenchymal cells decrease (Rogelj et al. 1989).

In parallel with alveolarization, the double layer capillary network of immature septa merges with a single layer network, resulting in an optimized configuration for gas exchange. Alveolarization still continues, because, in places where new septa are shedding pre-existing mature septa, the second necessary capillary layer will be formed instantly by angiogenesis, confirming a lifelong alveolarization capacity, which is important for any type of lung regeneration.

The lung mesoderm represents a source of essential paracrine instructional signals that regulate the proliferation and differentiation of the endoderm progenitor and also contributes to the various lung structures, including airway smooth muscle, vascular smooth muscle, endothelial cells, mesothelial cells and many less known mesodermal strains, such as pericytes, alveolar fibroblasts and lipofibroblasts. The lung mesoderm is believed to originate from the initial mesoderm that surrounds the ventral anterior intestine.

II. Pulmonary Cell Types

a) Embryonic Lung Cells

The embryonic pulmonary epithelium differentiates into hair, serous secretory cells, goblet cells, clear cells, basal cells and neuroendocrine (NE) cells. The proportions of these cells vary along the proximal-distal axis. In bronchioles, clear cells are more abundant than the ciliated ones, with some groupings of NE cells, called neuroepithelial bodies or NEBs. Goblet cells are marked by the expression of the transcription factor SPDEF and mucin-5ac (Muc5ac). (Morrisey and Hoghan, 2010).

Neuroendocrine (NE) cells are the first epithelial cells to appear in the lung and are more abundant in fetal and neonatal lungs than in the adult lung. basic ID2 helix loop. These multipotent cells have the ability to give rise to all major types of respiratory epithelial cells, including PNECs (pulmonary neuroendocrine cells) (Rawlins et al 2009).

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The evidence suggests that the specification of the fate of PNECs is controlled by interference between bHlH activating and repressing genes, a conserved mechanism between Drosophila and mammals (Ito et al 2006).

The ASCL1 complex activates NE differentiation, while the HES 1 gene suppresses this pathway, inhibiting the formation of the ASCL1 / TCF3 complex.

Notch signaling was also important in specifying the PNEC lineage. The delta-like Notch ligand 1 (DLL1) is expressed in NE cells in the proximal airways. Its activity may be under the control of ASCL1.Notch 2 mediates the fate of clear hair cells.

Finally, the migration control program for normal pulmonary neuroendocrine cells and malignant cells is extremely relevant for the understanding and treatment of metastasis of small cell lung cancer. Recently, a new form of epithelial cell migration shown by normal pulmonary neuroendocrine cells during pulmonary epithelial development has been demonstrated, called 'sliding', which is used to organize neuroendocrine cells into stereotyped groups (Kou 2015). The normal sliding program involves the transient activation of an epithelial-mesenchymal transition (EMT), in which the pulmonary neuroendocrine cells migrate over and around other epithelial cells to meet, without ever invading the lung mesenchyma. The pulmonary NE cells are distributed throughout the bronchial epithelium, interspersed between secretory cells (Claras) and hair cells, the two main types of airway epithelial cells (Rock and Hogan, 2011; Semenova 2015). The clusters of NE or (NEBs) are highly innervated (Brouns et al., 2008) and have sensory and neurosecretory functions; stem cell function, which helps to replace the bronchial epithelium after severe injury (Guha et al., 2012; Reynolds et al., 2000; Song et al., 2012); and function of small cell lung cancer cell initiator (Song et al., 2012; Kuo 2015).

Further investigation into the sliding program is likely to reveal molecular dependencies directed at small cell carcinoma to attenuate or perhaps even prevent metastasis to extrapulmonary organs, which is the main cause of patient death (Semenova 2015; Kuo, 2015)

III. Pulmonary Cells of Adults

Pulmonary epithelial cells are largely subdivided into airways (tracheal / bronchiolar) and alveolar types. The tracheobronchial airways are lined with pseudostratified epithelium in which each cell comes into contact with the basement membrane. Below the basement membrane are blood and lymph vessels, smooth muscle, cartilage, fibroblasts and nerves (Hogan et al., 2014). The most distal intrapulmonary conduction airways are lined by simple columnar epithelium. The gas exchange is performed inside the alveolar epithelium.

PNECs represent only 0.4% of adult epithelial cells and have endocrine and neuronal cell properties. They express neural markers, such as NCAM1 and ASCL1 neural cell adhesion molecules (Chanda et al. 2014). They are associated with intraepithelial nerve fibers and can transmit signals to the central nervous system. Generally, it contains electron-dense vesicles, which accumulate peptides, related to the bombesin and calcitonin gene (CGRP), which acts as a vasodilator; and to the amines, represented by serotonin, which act as a vasoconstrictor. The functions of PNECs include control of airway tone, pulmonary blood flow and immunomodulation.

Brush cells make up less than 1% of the airway epithelium and have recently been shown to have a chemosensory role that can allow the detection of bacterial infections (Tizzano et al., 2011). Basal cells are stem cells that self-renew and differentiate into secretory and hair cells during homeostasis and repair (Teixeira et al., 2013; Watson et al., 2015). Secretory cells are predominantly of the mucous subtype. It is not clear whether mucus-secreting cells retain the ability to proliferate and function as stem / progenitor cells (Teixeira et al., 2013).

The alveolar epithelium consists of type I and type II alveolar cells (AT1 and AT2 cells) that are surrounded by capillaries and fibroblasts (Weibel, 2015). AT1 cells are flat, highly extended and specialized for gas exchange. AT2 cells are cuboidal, more common and specialized in the production of surfactant, a complex mixture of proteins and phospholipids that reduces surface tension in the alveolar region (Crapo et al., 1982; Hogan et al., 2014; Weibel, 2015; Williams, 2003). AT2 cells are the main alveolar epithelial stem cells and can self-renew and differentiate into AT1 cells (Barkauskas et al., 2013; Desai et al., 2014; Rock et al., 2011).

Traditionally, alveolar fibroblasts have been characterized mainly as myofibroblasts and lipofibroblasts, but their exact roles have not yet been defined and there are controversies about the existence of lipofibroblasts in human lungs. (Bhattacharya and Westphalen, 2016).

The lung also contains a resident population of immune cells and alveolar macrophages, which play important roles in surfactant homeostasis and innate immunity (Bhattacharya and Westphalen, 2016).

IV. Molecular Regulation in Embryogenesis

The first indication of the respiratory precursor in the endoderm of the primitive intestinal tube is registered by the expression of TTF1 (Thyroid Transcriptional factor 1, homeobox or NKx2.1 type transcription factor) where the thyroid and lungs will be formed (Cardoso and Lu 2006).

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CK8 / CK18 cytokeratins are the first keratins to appear in embryogenesis, already in pre-implantation embryos and also appear to be the oldest keratins during phylogenesis (Jackson, 1980; Blumenberg 1988). With respect to malignant tumors, K8 and K18 flush strongly the majority of adenocarcinomas, hepatocellular carcinomas, renal cell carcinomas and neuroendocrine carcinomas. These keratins can be useful in diagnostic immunohistochemistry in cases of carcinomas with low keratin content, such as small cell lung cancer, to prove their epithelial nature (Moll, 2008). P63 plays a prominent role in controlling the functions of epithelial stem cells and in differentiating and stratifying tissue derived from ectoderm during embryonic development. (Guerrini, 2011)

The transcription factor Sox2 marks proximal epithelial progenitors and Sox9 marks distal epithelial progenitors. Additional markers of Sox9 positive distal progenitor cells include surfactant proteins, such as surfactant protein C (Sftpc), the transcription factor Id2. Lineage screening studies have suggested that positive distal Id2 cells can generate distal and proximal cell lines. This capacity for multipotent differentiation is subsequently lost, and positive Id2 progenitor cells may form only distal alveolar epithelia (Rawlins 2018).

All early events in lung development are controlled by a variety of signaling pathways, including Fgf, Tgfb, Wnt, SOX, Hedgehog (Shh-Sonic hedgehog, its Patched 1 receptor and transcription factors like Gli1-3), Notch and acid retinoic (Rock and Hogan 2011; Katton and Morrisey 2014).

The process also depends on a complex regulation by signaling pathways that includes members of the TgfB (Transforming Growth Factor Beta) and Wnt (Wingless-type) family, Bmp4 (Bone Morphogenetic Protein 4, of the Tgf Beta family). Notch signaling plays an important role in controlling cell differentiation (Tsao 2011).

On the tenth day of the embryonic period, mesenchymal cells begin to express abundant vascular endothelial growth factor (VEGF) (White et al., 2007), which is an important ligand for the VEGF 2 receptor (VEGFR2) in vasculogenesis and angiogenesis (Chung and Ferrara, 2011; Karaman et al., 2018; Apte et al., 2019). VEGF expression stimulates the alveolar capillary network. FGF10 derived from the mesenchyme also stimulates mTORC1 / Spry2 epithelial signaling, and this signaling triggers the production of VEGF in the epithelium (Scott et al., 2010).

Columnar, non-ciliated epithelial cells are identified by the expression of the product CC10 (Clara Cell Secretory Prootein 10KD) (Reynolds 2002).

Interleukins, IL4 and IL13, Foxa2 and Spdef transcription factors (Sam pointed Domain-containing etc. Transcription Factor) influence the differentiation of goblet cells (Chen 2009) that develop only in the postnatal period (Pack 1980) and are evaluated by the expression of Muc5ac (Main Mucina Constituent of mucus) and Spdef.

The transcription factor called Foxj1 (Forklvad Box Trancription Factor) identifies respiratory progenitors that will give rise to hair cells (Rawlins 2007).

NE cells are identified using ACCGRP (Calcitonin Gene Related Peptide) and PGP9.5 (Protein Gene Product 9.5). Mash 1 9Achaete-Scute-Complex-lLike1) is a transcription factor of the basic helix-loop-helix family) that is fundamental in the formation of this cell type (Guilhemont 1993).

Basal cells are identified by the expression of specific molecular markers Trp-63 (Transcription Factor Transformation-related Protein or P63), cytokeratin 14 (Krt14) and cytokeratin 5 (Krt5) (School 2004)

Evidence indicates that basal cells comprise a population of multipotent parents (Rowlins and Hogan 2006).

Antigens such as ICAM-I (Intercellular Adhesion Molecule) are abundantly expressed by type I pneumocytes and by expression of Type I Caveolins (Transmembrane Proteins).Type II pneumocytes express proteins associated with pulmonary surfactants, such as SP-A, SP-B, SP-C and SP-D (Costa 2001). Transcription factors such as cat-6, TTF1, Hnf3 / 3, C / ebpa, hormones glucocorticoids and Fgfs are involved in the differentiation of pneumocyte II (Cardoso 1997).

With aging, human lung functions decrease at a rate of 1% per year after the age of 25, even without lung diseases (Janssens et al., 1999; Sharma and Goodwin, 2006). The lung starts to exhibit several changes, including increased secretion of pro-inflammatory cytokines, attenuated immune response and changes in the structural proteins of the extracellular membrane (Meiners et al., 2015; Navarro and Driscoll, 2017). Structural changes occur, such as spaces increased air space, loss of surface area and decreased static elastic recoil, with the most significant decline in the number and functions of capillary endothelial cells (Thurlbeck and Angus, 1975).

Fases do desenvolvimento pulmonary e mediadores

V. Epigenetic Regulators of Fate and Differentiation of Pulmonary Epithelial Cells

Recent studies have also identified epigenetic mechanisms of histone changes in the control of lung development. Acetylation through Histone acetyltransferase (HATs) promotes genetic transcription, and deacetylated histone (HDACs) removes the acetyl group, leading to genetic silencing (Choudhary et al., 2009). There is evidence that HATs are necessary for embryonic lung development. The loss of Hdac in the pulmonary epithelium results in reduced expression of Sox2, preventing the development of multiple types of proximal cells (Wang et al., 2013). This change in Sox2

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expression is, in part, mediated by increased expression of Bmp4, which also contributes to the severe branching defects seen in Hdac mutants. It has also been shown that hyperoxia during neonatal development results in decreased hdac activity, leading to alveolar hyperplasia and interrupted alveolarization (Zhu et al., 2012).

Although histone acetylation is known to play an important role in the lung, little is known about the roles of other epigenetic complexes during lung development. The methyltransferases Suv39H1 and Suv39H2, which induce transcriptional silencing through histone H3 lysine 9 methylation, directly repress the expression of the surfactant protein SP-A (Sftpa1) during hypoxia (Benlhabib and Mendelson, 2011). Suv39H1 and Suv39H2 are also highly expressed in early lung development, suggesting that they may inhibit SP-A transcription until later in development. During pulmonary fibrosis, DNA methylation by Dnmt1 represses the transcription of miR17~92, a microRNA cluster that regulates lung development (Dakhlallah et al., 2013). Likewise, Dnmt1 mediates the progression of lung cancer through the methylation of several promoter regions (Dakhlallah et al., 2013).

VI. Conclusion

Recent studies demonstrate that cell signaling and gene expression pathways, including PTEN, protein kinase C (iota), Wnt, hedgehog, c-kit, Akt and others that can play important roles in the transformation of endogenous progenitor cells into cancer cells lung.

Pluripotent stem cells (PSCs) can be derived from the internal cell mass of the initial embryo (in the case of embryonic stem cells, ESCs) or can be reprogrammed from fully differentiated cells (in the case of iPSCs). They retain the potential to differentiate into any type of cell in the body. For this reason, we can say that our organoid system provides a genetically treatable tool and, therefore, specific human characteristics of lung development should be investigated investigated. (Nicolic 2017).

Disclosure Statement

The authors declare no conflict of interest

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