Editorial

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Molecular detection of lung cancer stem cells

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Editorial

According to the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS) and the European Respiratory Society (ERS), lung cancers are divided into two groups: SCLC: (Small cell lung cancer) and NSCLC: Non-Small Cell Lung Cancer.[1,2] Around 15% of the lung tumors are SCLC and appear in the bronchi, whereas the NSCLS are divided into three histological types: adenocarcinomas, squamous cell carcinoma, and large cell carcinomas. Adenocarcinomas account for about 40% of the lung cancers and usually occur in the peripheral lung tissue,[3] squamous carcinomas represent 25% and are generally located in the central bronchus and the large cell carcinomas (around 20% of lung cancers) appear to be derived from neuroendocrine cells and can be observed in combination with other types of NSCLC.[4]

Different types of genetic modification have been described in pulmonary tumors such as chromosomal abnormalities,[5] telomerase activation,[6] and mutations in oncogenes or tumor suppressor genes such as P53 (Tumor Protein p53),(RB1 Retino Blastoma 1), CDKN2A (Cyclin-Dependent Kinase Inhibitor 2A), KRAS and EGFR (Epidermal Growth Factor Receptor).[4] Some of these genes can be used as markers of the disease progression, others may have a direct role in the genesis of lung cancers.[7]

Cancer stem cells in the lungs may emerge from progenitor cells or differentiated cells that have acquired self-renewal capacity such as neuroendocrine cells.[8] Clara variant cells and neuroendocrine cells have been proposed as the cells responsible for bronchopulmonary cancers.[9] These phenomena are supported by the assumptions of stem cell plasticity, which is defined as the ability to cross the barrier of differentiated cell lines and to adopt phenotypes of other cell types,[10] as well as the hypothesis of Trans-differentiation.[11] The phenotypic heterogeneity observed between the different types of lung tumors suggests that the histological environment of the tumor profoundly affects the fate of cancer cells.[12] And the cell development program of a specific lineage can be altered by changing the signals in the local environment.[13]

The identification of cancer stem cells is based on their phenotype or on the functional characteristics. The SP (Side Population) for example, with its epithelial restorative capacity, has been shown to be resistant to chemotherapy in pulmonary cancers[14,15] and the over expression of its telomerase suggests that pulmonary SP may represent a source of cancer stem cells with unlimited proliferative potential.[14,15] Cancer stem cells can also be identified using the cell surface marker CD133 or prominin-1.[16] CD133 is expressed in hematopoietic, endothelial, neural and in many tumors such as brain and pulmonary tumors.[17] But the lack of specific markers of pulmonary progenitors represents a major problem in the isolation of pulmonary cancer stem cells. The markers known as CD133, ABCG2 (ATP Binding Cassette sub-family G member 2) and IL-6R (Interleukin 6 Receptor)[18] are not always effective in sorting for the population of cancer stem cells.[19]

Another method for the identification of tumor-derived pulmonary stem cells is the detection of the increased activity of ALDH (Aldehyde dehydrogenase). This enzyme is responsible for the intracellular oxidation of aldehydes and is over expressed in stem cells and cancer stem cells.[17,20] Furthermore, transcriptional deregulation can activate oncogenes and / or deactivate tumor suppressor genes.[21] RUNX (Runt-related transcription factors) genes, for example, have oncogenic and tumor suppressor characteristics. These genes encode transcription factors involved in normal tissue development. Many chromosomal translocations involving RUNX genes lead to the formation of oncogenic fusion proteins.[22] RUNX3 is an essential transcription factor in the late phase of pulmonary development. It is necessary for the control of the differentiation and proliferation of the bronchiolar epithelium.[23] Its sub-regulation by hyper-methylation has been observed in pulmonary adenocarcinomas[24,25] and has even been proposed as an early event in the development of pulmonary carcinomas by inhibiting the differentiation of progenitor cells.[23]

TTF1 (Thyroid transcription factor-1) may be a specific Oncogene of pulmonary adenocarcinomas[26] and BRF2 (B-Related Factor 2) a specific Oncogene of squamous cancers.[27] OCT4 (Octamer Binding Factor 4) is a transcriptional factor of embryonic stem cells that may induces apoptosis of cancer stem cells.[28] SOX2 (SRY (sex determining region Y)-box 2) controls the self-renewal and differentiation of stem cells and is involved in correct branching and lung morphogenesis.[29,30] SOX2 has been proposed as an Oncogene whose expression is essential in pulmonary tumor stem cells to induce carcinogenesis.[31,32]

In human, c-kit (Cell receptor tyrosine kinase) proved to be a promoter of tumor growth.[33,34] Patients with an over-expression of c-Kit in cancer stem cells have lower survival rates than those who do not and show evidence of resistance to chemotherapy.[35]The blockade of the c-Kit pathway inhibits the proliferation and survival of tumor stem cells after chemotherapy.[36] The knowledge of the signaling pathways of pulmonary cancer stem cells could lead to the development of new therapies capable of eliminating these cells. The methods developed for the detection of cancer stem cells described above and the coherence of the preclinical data on the transcription factors such as RUNX3, OCT4, SOX2, and c-Kit represent a major scientific development for the survival and healing of patients.

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None.

Conflict of interest

Author declares that there is no conflict of interest.

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