



Stem cells for lung cancer: impacts and future developments

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Received: 26 April 2019; Accepted: 05 August 2019; Published: 16 August 2019.

doi: 10.21037/shc.2019.08.01

View this article at: <http://dx.doi.org/10.21037/shc.2019.08.01>

Malignant pulmonary neoplasms are the most frequent cause of cancer-related death worldwide (1), accounting for more than 1.8 million newly diagnosed cancers and 1.6 million cancer-related deaths worldwide every year (2).

The whole amount of regulatory modifications leading to cancer development can originate from prolonged exposure to tobacco smoke, thus causing structural damages that can express as chronic obstructive pulmonary disease (COPD). Continuous smoke and environmental pollutants exposure can result into a well-defined series of structural modifications of the bronchial epithelium of the airway, ranging from basal cell hyperplasia to metaplasia, severe dysplasia and finally carcinoma (3).

A wide spectrum of primary lung tumors with several biological peculiarities exist, ranging from almost indolent and effectively treatable disease to highly aggressive lesions characterized by poor prognosis; nowadays it is mandatory to have a biological knowledge of lung tumors, particularly in advanced stage where local control by surgery and radiotherapy is not effective.

Considering that only a small amount of lung cancer patients can be diagnosed at an early stage, thus having a good prognosis and many effective treatments to be offered, exploration of new frontiers is constantly required.

Stem cells are cells that can differentiate into other types of cells, and can also divide in self-renewal to produce more of the same type of stem cells (4).

Mesenchymal stem cells—also defined as stromal cells—are undifferentiated cells presenting properties of self-renewal and the potential to differentiate *in vitro* and *in vivo* into a wide spectrum of cells, like chondrogenic, osteogenic

and adipogenic lineages when cultured in specific inducing culture media (4).

There are at least two types of stem cells: embryonic stem cells (EC), arising from the inner cell mass of blastocysts, and adult stem cells (AC), deriving from several tissues, like adipose tissue, blood, bone marrow and other sources (5). Many researchers have studied potential clinical applications of stem cells in several medical specialties—including thoracic surgery—although with controversial and still unclear results (6).

Two major aspects of potential application in clinical daily practice of stem cells in cardio-thoracic surgery have been studied: (I) regenerative and reparative medicine, representing a part of biomedical research in molecular biology as well as in tissue engineering, focusing on the possibility of replacing, engineering or regenerating of organs, tissues and cells to restore normal physiology; (II) drug-loading and drug-delivery, that is a new science branch, studying how stem cells may serve as vectors to deliver anti-neoplastic compounds for oncologic therapies (7). Mesenchymal stromal cells (MSC) disclosed the ability to accumulate within the cell and to release deliver many antineoplastic drugs, without any modifications of the cellular genome, thereby reducing tumor progression (8). Non-modified MSC are one of the most intriguing tools for antineoplastic drug delivery; in fact they can adapt to culture characteristics and target neoplastic sites when injected *in vivo* (8). MSC present several properties: first, they produce active soluble factors playing an active immune role; moreover they can pass through the blood brain barrier: for this reason they can be considered an appealing potential

tool for adult and pediatric cerebral tumors; on the contrary the aspect of whether MSC interacting with the tumor environment boost tumor suppression or instead favor tumor growth remains unclear (9); they can uptake and deliver—to target tissue—antineoplastic drugs both as free molecule and exosome associated drugs (10).

We have previously reported that bone marrow-derived MSC primed with paclitaxel—an anticancer drug targeting tubulin and stabilizing the microtubule polymer protecting it from disassembly—effectively block *in vitro* proliferation of malignant mesothelioma cells (11). However further experiments are required to confirm our initial *in vitro* results and to extend them to lung cancer therapy.

Although some concerns about safety of stem cell application in oncologic field have been reported (12), there are no definitive data about this aspect that should be further assessed (13).

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Giulia Sedda and Roberto Gasparri) for the series “A New Era in Lung Cancer Care: from Early Diagnosis to Personalized Treatment” published in *Shanghai Chest*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/shc.2019.08.01>). The series “A New Era in Lung Cancer Care: from Early Diagnosis to Personalized Treatment” was commissioned by the editorial office without any funding or sponsorship. FP serves as an unpaid editorial board member of *Shanghai Chest* from Jun 2018 to May 2020. The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/shc.2019.08.01

Cite this article as: Petrella F. Stem cells for lung cancer: impacts and future developments. *Shanghai Chest* 2019;3:44.