Deciphering the Molecular Mechanisms of LIN28B in Tumor Progression in Squamous Cell Lung Carcinoma

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Summary

Lung cancer represents the most malignant cancer entity with the highest cases of deaths worldwide. Generally, lung cancer is histologically divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). After the adenocarcinoma, squamous cell lung carcinoma (SQCLC) is the second most common NSCLC subtype with 30 % from all lung cancer cases.

The LIN28B protein, a conserved RNA-binding protein normally expressed in embryonic cells, targets a broad range of microRNAs (miRNA) and messenger RNAs (mRNAs) modulating their maturation and activity, whereby the most prominent family are the let-7 miRNAs. By repressing their biogenesis, it promotes the translation of several proto-oncogenes and cell-cycle progression factors provoking the blockade of differentiation and the stimulation of proliferation, angiogenesis and epithelial-to mesenchymal transition (EMT), generally leading to a stem cell-like phenotype. However, in adult tissues LIN28B may be abnormally upregulated facilitating the development of several diseases and above all cancer. With a fraction of 12% among SQCLC patients showing LIN28B overexpression, the limited therapeutic options and the fact that until now the molecular function of LIN28B expression in SQCLC are quite illusive, the investigation of LIN28B's effects in SQCLC represents a promising occasion to deepen the understanding of the molecular mechanisms in SQCLC and to expand the prognostic and therapeutic potential for SQCLC patients.

In the first part of the present work, we investigated LIN28B's impact on tumorigenesis in SQCLC. We showed that although LIN28B expression in SQCLC cells did not promote tumor growth per se, it increased the occurrence of distant metastases. Here, bone metastases displayed the most prominent fraction of all distant metastases. Next, we examined the ability of LIN28B to equip the tumor cells with immunomodulatory functions. We identified the cytokine interleukin-6 (IL-6) which is significantly upregulated and secreted in LIN28B expressing SQCLC cells. Further *in vitro* experiments showed that upon IL-6 stimulation, the PD-L1 expression of tumor cells was facilitated. Finally, we aimed to identify LIN28B as a molecular driver of decisive oncogenic pathways contributing to improved prognostic and therapeutic options of SQCLC patients. Our data revealed the activated canonical Wnt signaling pathway accompanied by an elevated phosphorylation status of the Wnt co-receptor Ryk and an increased Wnt ligand secretion in SQCLC cells, when LIN28B is expressed. Last

but not least, the analysis of publically available data sets suggests that LIN28B characterizes a subset of patients which first shortly quitted smoking.
Taken together, our findings highlight the role of LIN28B in cancer and will likely improve the prognostic and therapeutic perspectives for SQCLC patients.