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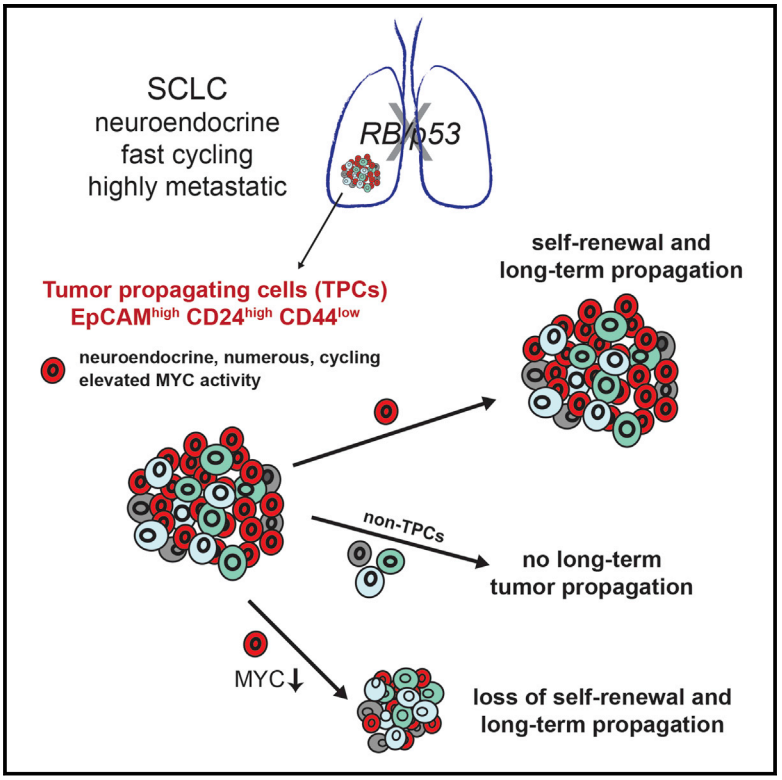
Identification and Targeting of Long-Term Tumor-Propagating Cells in Small Cell Lung Cancer

Graphical Abstract



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In Brief

Jahchan et al. use a genetically engineered mouse model of small cell lung cancer (SCLC) to functionally characterize cancer stem cells (tumor-propagating cells, TPCs). SCLC TPCs are numerous in tumors, cycle quickly, are chemosensitive, and depend on elevated MYC activity for their ability to propagate tumors.

Highlights

- $CD24^{High}$ $CD44^{Low}$ $EpCAM^{High}$ mark tumor-propagating cells (TPCs) in mouse SCLC
- SCLC TPCs generate non-TPCs and are proliferative and abundant but not chemoresistant
- Elevated MYC activity is required for the maintenance of TPCs in SCLC tumors
- A low dose of the transcriptional inhibitor JQ1 inhibits long-term SCLC growth

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Identification and Targeting of Long-Term Tumor-Propagating Cells in Small Cell Lung Cancer

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SUMMARY

Small cell lung cancer (SCLC) is a neuroendocrine lung cancer characterized by fast growth, early dissemination, and rapid resistance to chemotherapy. We identified a population of long-term tumor-propagating cells (TPCs) in a mouse model of SCLC. This population, marked by high levels of EpCAM and CD24, is also prevalent in human primary SCLC tumors. Murine SCLC TPCs are numerous and highly proliferative but not intrinsically chemoresistant, indicating that not all clinical features of SCLC are linked to TPCs. SCLC TPCs possess a distinct transcriptional profile compared to non-TPCs, including elevated MYC activity. Genetic and pharmacological inhibition of MYC in SCLC cells to non-TPC levels inhibits long-term propagation but not short-term growth. These studies identify a highly tumorigenic population of SCLC cells in mouse models, cell lines, and patient tumors and a means to target them in this most fatal form of lung cancer.

INTRODUCTION

Small cell lung cancer (SCLC), which represents ~15% of lung cancers, is characterized by small cells with neuroendocrine features (Wistuba and Gazdar, 2006). Close to 200,000 people die from SCLC every year worldwide, and the 5-year survival rate is a dismal 5%–10%. SCLC disseminates early and is usually detected late when patients present with extensive metastases. Patients often respond well initially to chemotherapy (usually a combination of etoposide and a platinum-based agent), but they almost invariably relapse with disease that is resistant to their primary therapy and other agents. Despite numerous clinical trials, no new treatment has been approved in two decades and SCLC remains the most lethal form of lung cancer (Pietanza et al., 2015).

The cancer stem cell model assumes a hierarchical organization in which a subset of tumor cells is responsible for sustaining tumorigenesis and establishing the cellular heterogeneity of a primary tumor (Beck and Blanpain, 2013; Clarke et al., 2006; Magee et al., 2012; Visvader and Lindeman, 2012). Not all tumors may be organized in such a hierarchical manner (Meacham and Morrison, 2013; Quintana et al., 2010). The aggressive and highly metastatic nature of SCLC tumors suggests that SCLC tumors may harbor highly tumorigenic cells. However, the study of SCLC is challenging in patients because of the inherent complex genetic and environmental diversity of these patients. SCLC patients rarely undergo surgery, and primary human material is scarce. Moreover, the establishment of SCLC cell lines and patient-derived xenografts can select for the growth of specific populations of tumor cells (Daniel et al., 2009; Leong et al., 2014), which may bias the analysis of cancer cell subpopulations. In contrast, relevant mouse models allow for the analysis of large number of independent primary tumors. The first mouse model for SCLC was developed based on the observation that human SCLCs are mutant for both the p53 and the RB tumor suppressors (Meuwissen et al., 2003). The additional deletion of the *p130* gene (also known as *Rbl2*) enhances SCLC development (Schaffer et al., 2010). Tumors that are triple knockout (TKO) for *Rb* (also known as *Rb1*), *p130*, and *p53* (also known as *Tp53*) have histopathological features of human SCLC, including an initial relative chemosensitivity followed by the acquisition of chemoresistance (Gazdar et al., 2015; Jahchan et al., 2013; Park et al., 2011).

Here we use mouse models and human SCLC cells to investigate tumor heterogeneity in SCLC. Because cancer stem cells may not possess the exact and full repertoire of normal tissue stem cell properties, we instead use the term tumor-propagating cells (TPCs). We define TPCs as cells that are highly tumorigenic