Commentary

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LKB1, a Key Driver Gene of Human Lung Squamous Cell Carcinoma

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ABSTRACT

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Introduction

Identification of driver genes not only is a challenging work for cancer study, including lung cancer, but also is a foundation of precision medicine [1]. For example, the discovery of driver genes (e.g. *EGFR*, *ALK* and *ROS1*) in lung adenocarcinoma led to the development of molecular targeted therapies, significantly improving the treatment outcome. Unfortunately, similar targeted therapies have not been developed for the treatment of lung squamous cell carcinoma (LSCC), accounting for approximately 25-30% lung cancer patients. This may be due to a lack of evidence showing the key drivers of LSCC. Unlike that overexpression of single *EGFR* mutation in mice can induce lung adenocarcinoma, none of individual highly mutated genes in human LSCC tumors has been found to induce LSCC *in vivo* [2]. Therefore, the unaddressed key driver genes of LSCC prevent from developing its targeted therapy. Recently, Jian Liu et al. reported that *Lkb1* ablation alone in mouse lungs induced LSCC, providing the direct *in vivo* evidence of showing *Lkb1* to be the key driver gene of LSCC [3].

Although *Lkb1* has been reported to involve in LSCC development under another genetic background, such as $Kras^{G12D}$ [4], *Sox2* [5], and *Pten* [6], the role of *Lkb1* in determining LSCC development has been undermined since no phenotype was found after ablation of *Lkb1* using viral Cre [4-6]. Considering the potential limit of the viral Cre, Jian Liu et al. generated a Cre mouse, named $CCSP^{iCre}$ [7], to examine several candidate genes in their study. The advantage of this Cre is reported to have strong activity in the large airway epithelium, a major cell population responsible for human LSCC development. Notably, LSCC tumors were induced only after ablation of *Lkb1* using this Cre, whereas manipulation of other five frequent genetic mutations (*p*53, *Pten*, *Errfi1*, *Smad4*, and $Kras^{G12D}$) alone is unable to generate LSCC. This not only demonstrates *Lkb1* to be a key suppressor gene in LSCC initiation and progression but also suggest this Cre mouse line as a valuable tool to explore the *de novo* functions of LSCC regulators.

Mechanistically, Jian Liu et al. showed that *Lkb1* deficiency resulted in decreased expression of MKK7, a reduction of JNK1/2 phosphorylation, lower JNK1/2 activities and elevated ΔNp63 signaling, which subsequently led to initiation and progression of LSCC *in vivo*. Moreover, the authors revealed that the secondary genetic alterations beyond *Lkb1* alternation might be necessary for stimulation of LSCC formation. For example, Jnk1/2 loss accelerated *Lkb1*-null induced LSCC development and JNK1/2 activation attenuated mouse LSCC development. Therefore, more genetic regulators of LSCC are expected to be identified in a combination of *Lkb1* deletion. Clinically, Jian Liu et al. also reported that JNK1/2 was inactivated in a large proportion of LSCC patients and higher JNK1/2 activities had a better survival rate and longer relapse-free survival. JNK1/2 activators, such as Anisomycin or its derivatives, might benefit LSCC patients with low JNK1/2 activities through simulation of JNK1/2 signaling. Interestingly, JNK1/2 activities also exhibited a positive relationship with the survival rate of the cervical or head and neck SCC patients. Thus, activation of JNK1/2 in LSCC patients with lower JNK1/2 gene signature will be attractive clinical trials.

Besides, several LSCC mouse models generated in this study (e.g $Lkb1^{d/d}$, $Lkb1^{d/d}Jnk1^{d/d}Jnk2^{-/-}$ and $Lkb1^{d/d}Pten^{d/d}$) show the different stages of LSCC development, including the initial hyperplasia and squamous metaplasia. Further investigation of these development stages of LSCC using single cell sequence can help identify the

cellular origins and the track of genetic evolutionary dynamics during LSCC development. Despite this progress, it is noteworthy that LSCC tumors in an advanced stage, even in early stage, have complex genetic alterations other than one single genetic disorder. This dysregulated genetic complex poses a tremendous challenge to effectively provide LSCC targeted treatment. For example, tyrosine kinase inhibitors (e.g. Taselisib targeting PI3K, Palbociclib targeting cell cycle gene alteration, and AZD4547 targeting FGFR) have been specifically applied in treating human LSCC tumors with the related genetic alternations, but the outcome is disappointed, evidenced by the low response rates (<7%) and median progression-free survival time (2.9, 1.7 and 2.7 months, respectively) [8-10]. Therefore, identification of more regulators of LSCC besides the key drivers (e.g. *Lkb1*) merits the urgent further investigation, which can significantly help develop the effective combination of targeted therapy and bring the clinical benefit to LSCC patients.

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