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

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**Abstract**

Although Lkb1 has been reported to involve in LSCC development under another genetic background, such as Kras<sup>G12D</sup>, Sox2<sup>d/d</sup>, and Pten<sup>d/d</sup>, the role of Lkb1 in determining LSCC development has been undermined since no phenotype was found after ablation of Lkb1 using viral Cre<sup>[4-6]</sup>. Considering the potential limit of the viral Cre, Jian Liu et al. generated a Cre mouse, named CCSP<sup>Cre</sup><sup>+</sup>, 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 (<p53, Pten, Errf1, Smad4, and Kras><sup>G12D</sup>) 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 expression, 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<sup>d/d</sup>, Lkb1<sup>d/d</sup>Js<sup>d/d</sup>Nk1<sup>d/d</sup>Nk2<sup>-/-</sup> and Lkb1<sup>d/d</sup>Pten<sup>d/d</sup>) 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.

References


