Short Communication

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Inactivation of JNK1/2 Promotes Lung Squamous Cell Carcinoma in *Lkb1* Deficiency Mice

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ABSTRACT

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Lung cancer is the leading cause of cancer-associated mortality worldwide. In the last two decades, great efforts were made to search for effective treatments by identifying drug-targetable biomarkers based on multiple levels of genomic and epigenomic investigations. Histologically, lung cancer can be classified as two major subtypes, namely adenocarcinoma (ADC) and squamous cell carcinoma (SCC), together they account for more than 80% of cases. Although more than 50% of lung cancers showed a mix of the subtypes indicating a high degree of heterogeneity of these tumors [1,2], the ADC and SCC are shown to possess a distinct pattern of genomic abnormalities [3,4]. By mimicking genomic alterations of human cancer in mice, the whole process of tumorigenesis from initial to advanced stages can be dissected and studied in a spatial and temporal manner. Thereby it is possible to recapitulate, validate, and identify new targets for therapeutics. Importantly, the generated mouse models can be applied for testing new therapeutic strategy as well as drug resistance management.

Unlike previous Lung SCC (LSCC) models in which compound mutations and depletions were involved such as $Kras^{G12D}$ / $Lkb1^{loss}$, $Sox2^{ox}$ / $Lkb1^{loss}$, or $Pten^{loss}$ / $Lkb1^{loss}$ [5,7], Jian Liu et al. were able to show that *Lkb1* deficiency by itself was sufficient to induce LSCC in 11-14 months after application of $CCSP^{iCre}$ in $Lkb1^{f/f}$ mice with a penetrance of 32.8% of LSCC and its initial lesions (*Nature Communication*, 10:1-16, 2019) [8]. Impressively the process of tumorigenesis was accelerated to 7-8 months when $Jnk1^{d/d}$ / $Jnk2^{-/-}$ was combined and a 100% penetrance of LSCC and its initial lesions was achieved!

In human, LSCC is initiated from epithelial hyperplasia and squamous cell metaplasia in bronchus/bronchiole, followed by dysplasia and carcinoma. Jian Liu et al. succeeded in mimicking this process and demonstrated sequential lesions of hyperplasia, squamous cell metaplasia, and SCC in the large airway of LKb1 deficiency mice. Importantly the lesions recapitulated the characteristics of human LSCC such as expression of ΔNp63/P63 and CK5 and had a high degree of a positive relationship with human LSCC in transcriptome profiling. Furthermore, in GSEA (Gene Set Enrichment Analysis) the authors identified the JNK1/2 phosphorylation-induced pathway that was the top enriched pathway and was negatively associated with the *Lkb1* deficiency gene signature.

To address JNK1/2 as major suppressors for *Lkb1*-dependent LSCC initiation and progression, the authors conducted *in vitro* and *in vivo* investigations by ablating JNK1/2 in mLSCC cells and knocking JNK1/2 out in *Lkb1* deficiency mice. The results thereby showed increased cell growth *in vitro* and acceleration of LSCC development with a full penetrance *in vivo*. In this context, they were able to associate *Jnk1/2* knockout or inactivation with activation of $\Delta Np63$ / $p63$ pathways that led to LSCC initiation and progress. Conversely, Jian Liu et al. utilized JNK1/2 activators such as Anisomycin for pharmaceutical activation of JNK1/2 in mice that resulted in a decrease of expression of $\Delta Np63$ / $p63$ and consequently a lower incidence of LSCC. Thereby they elucidated a negative regulation of JNK1/2 on the Np63/p63 pathway involving in LSCC development. The negative relationship between

JNK1/2 activation and P63 expression could be clinically relevant for prediction and treatment of LSCC patients when low JNK1/2 phosphorylation level is evident.

As shown by Jian Liu et al. and others [9], high inflammatory responses were present in mouse models of LSCC that resembled the human counterpart. Further investigations in the role of JNK1/2 and its regulation by cytokines will add more insight into the significance of the tumor microenvironment involving in tumor initiation and progress, which may provide new approaches towards LSCC management.

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