세미나 초록

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발표 주제	Live-Cell Invasive Phenotyping Uncovers ALK2 as a Therapeutic Target in *LKB1*-Mutant Lung Cancer
발표 내용	The acquisition of invasive properties is a prerequisite for tumor progression and metastasis. Molecular subtypes of *KRAS*-driven lung cancer exhibit distinct modes of invasion that contribute to unique growth properties and therapeutic susceptibilities. Despite this, preclinical strategies designed to exploit growth within the context of invasion are lacking. To address this, we designed an experimental system to screen for targetable signaling pathways linked to active early 3D invasion phenotypes in different molecular subtypes of *KRAS*-driven lung adenocarcinoma. Combined live-cell imaging of human bronchial epithelial cells in a 3D invasion matrix and transcriptomic profiling identified mutant LKB1-specific upregulation of BMP6. LKB1 loss increased BMP6 signaling, which induced the canonical iron regulatory hormone hepcidin. Intact LKB1 was necessary to maintain BMP6 signaling homeostasis and restrict ALK2/BMP6-fueled growth. Preclinical studies in a *Kras*/*Lkb1*-mutant syngeneic mouse model and in a xenograft model showed potent growth suppression by inhibiting the ALK2/BMP6 signaling axis with single-agent inhibitors that are currently in clinical trials. Lastly, BMP6 expression was elevated in tumors of patients with *LKB1*-mutant early-stage lung cancer. These results are consistent with those of a model in which LKB1 acts as a “brake” to iron-regulated growth and suggest that ALK2 inhibition can be used for patients with *LKB1*-mutant tumors. ***Disclaimer:*** ***The views and content presented here are my own and do not necessarily reflect the views, policies, or positions of the Centers for Disease Control and Prevention (CDC).***