**CDKL1 potentiates the antitumor efficacy of radioimmunotherapy by binding to transcription factor YBX1 and blocking PD-L1 expression in lung cancer**

Li, Z., Xue, H., Li, J. et al. J Exp Clin Cancer Res 43, 89 (2024).

 **Presenter:** Liu-Chia Jung **Date/Time:** 2025/03/06, 16:20-17:10

 **Commentator:** Dr. Cheng-Hung Chi **Location:** Room 601, Med College Building

**Background:** Lung cancer is globally recognized as the leading cause of cancer-related deaths and has the highest mortality rate among cancers. Checkpoint blockade immunotherapies, targeting PD-1 and PD-L1, provide long-term clinical benefits to NSCLC patients. Localized RT can shift tumors from an immunologically cold phenotype to a hot phenotype, enhancing immunotherapy effectiveness. However, combining immunotherapy with RT yields unsatisfactory clinical outcomes. Tumor immune evasion via PD-L1 contributes to resistance to radioimmunotherapy in lung cancer patients, but the precise molecular mechanisms regulating PD-L1 remain unclear. CDKL1, a member of the cyclin-dependent kinase family, is expressed in the lungs, brain, and ovaries. It is involved in cilia formation, cilia length regulation, brain development, and cancer progression. YBX1, a cold-shock domain protein, regulates tumor immunity and can bind to the PD-L1 promoter region, promoting PD-L1 transcription and immune evasion in chemo-resistant liver cancer cells. However, its mechanism in lung cancer remains unclear.

**Objective/Hypothesis:** To investigate the role of cyclin-dependent kinase-like 1 (CDKL1) in the modulation of PD-L1 expression and the response to radioimmunotherapy in lung cancer.

**Result:** First, they observed that CDKL1 may act as a tumor suppressor protein in lung cancer. Second, CDKL1 was found to enhance the DNA damage response (DDR), as demonstrated by a neutral comet assay. An aberrant DDR is a crucial factor contributing to the development of radiation resistance in tumor cells. Moreover, an animal study confirmed that CDKL1 increases the radiosensitivity of lung cancer in vivo. Third, they discovered that CDKL1 interacts with the transcription factor YBX1, as identified through tandem affinity purification (TAP) and mass spectrometry (MS). Additionally, ChIP-PCR experiments demonstrated that in lung cancer, CDKL1 overexpression downregulates PD-L1. Subsequently, animal experiments and flow cytometry revealed that CDKL1 overexpression induces CD8+ T cell activation and enhances anti-tumor immune responses in lung cancer. Furthermore, mouse experiments showed that the combination of CDKL1 overexpression, radiotherapy (RT), and anti-PD-L1 antibody therapy achieves the greatest anti-tumor efficacy in lung cancer. Collectively, these findings suggest that the combined administration of CDKL1 overexpression, RT, and anti-PD-L1 antibody therapy exerts the strongest anti-tumor effect in lung cancer.

**Conclusion:** In summary, this study reveals that CDKL1 enhances radiosensitivity and inhibits immune evasion in lung cancer. CDKL1 interacts with YBX1, reducing its binding to the PD-L1 promoter, downregulating PD-L1, and activating CD8+ T cells, leading to radioimmunotherapy sensitization. These findings provide a novel molecular target and preclinical evidence for lung cancer treatment.