**CDK12 is hyperactivated and a synthetic lethal target in BRAF-mutated melanoma**

Thibault Houles, Geneviève Lavoie *et al. Nat Commun. 2022 Oct 29;13(1):6457.*

**Presenter:** Chih-Ling Chen                 **Date/Time:** 2023/09/14, 15:00 -16:00

**Commentator:** Po-Han Chen, Ph.D.        **Location:** Room 601, Med College Building

**Background:**

Melanoma is an aggressive malignancy originating from pigment-producing melanocytes localized at the epidermal-dermal junction in human skin. Melanoma accounts for a large majority of skin cancer-related deaths due to the lack of clinical efficacy of current treatments. Melanomas often harbor mutations including the Ser/Thr kinase BRAF, the small GTPase NRAS, the negative regulator of RAS neurofibromin 1 (NF1), and phosphatase and tensin homolog (PTEN). Most of these mutations caused the increase of RAS/mitogen-activated protein kinase (MAPK) signaling, which is involved in drug resistance.

Cyclin-dependent kinase 12 (CDK12) belongs to the cyclin-dependent kinase (CDK) family of Ser/Thr kinases and has multiple roles in gene expression and tumorigenesis. CDK12 is a transcriptional CDK required for genomic stability and suppresses intronic polyadenylation. Although CDK12 was shown to be required for proper execution of the DNA damage response, the mechanisms involved in CDK12 regulation remain unknown.

**Objective/Hypothesis:**

To investigate the molecular mechanisms of how the RAS/MAPK pathway promotes resistance to conventional chemotherapeutic drugs by modulating the DNA damage response.

**Results:**

The author performed a proteomics study to identify new effectors to the RAS/MAPK pathway. By using the biotin identification (BioID) screen with mass spectrometry (MS), the author identified 179 proteins as potential proximity interactors, which 56 proteins were previously found to be phosphorylated in an ERK1/2-dependent manner. Among these, CDK12 is directly phosphorylated by ERK1/2 and the RAS/MAPK pathway positively regulates CDK12 activity. Consistent with this, the author found that several BRAF-mutated melanoma cell lines showed high levels of CDK12 activity. Characterized the transcriptional program controlled by CDK12 in melanoma and found that CDK12 regulates gene expression based on gene length. Since CDK12 plays a role in transcription elongation, the author found that CDK12 inhibition decreases the expression of long genes containing multiple exons, including the genes involved in DNA repair. Besides, CDK12 inhibition promotes the expression of short genes with few exons, such as some growth-promoting genes regulate by AP-1 and NF-κB transcription factors. The inhibition of these pathways sensitizes melanoma cells to CDK12 inhibition in vitro and in vivo.

**Conclusion:**

CDK12 is hyperactivated in BRAF-mutated melanoma, the inhibition of DNA damage, AP-1, and NF-κB pathways strongly synergize with CDK12 inhibitors to inhibit melanoma growth, suggesting potential combinations for the treatment of melanoma patients.