A143 · Quantitative Modeling of Transcription Factor Binding to UV-Damaged DNA, and Competition with UV-DDB

Presenter: Yuncheng Duan — UMass Chan Medical School

Authors: Yuncheng Duan, Hana I. Wasserman, Annie Paik, Miles A. Pufall, Raluca Gordan

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UV-induced mutagenesis is shaped by the formation of DNA photoproducts and their subsequent recognition and repair. Transcription factors (TFs) can influence both processes: TF-induced DNA distortions can alter formation of UV-induced cyclobutane pyrimidine dimer (CPD) lesions; subsequently, TF occupancy at damaged sites can impede lesion recognition by nucleotide excision repair proteins. Using CPD-seq data from UV-irradiated fibroblasts, combined with genome-wide TF binding site maps, we modeled the effects of TFs on CPD formation and repair across nearly 600 factors. We identified TF- and position-specific effects that linked either enhanced CPD formation, attenuated CPD repair, or both, to melanoma mutation hotspots. Because CPD lesions in TF binding sites can alter TF recognition, direct quantitative measurements of TF binding to CPD-containing DNA are needed to define lesion-dependent occupancy and to model competition between TFs and repair proteins. To address this gap, we are developing LesionSpec-seq, a new technique that combines Spec-seq (an assay for high-throughput measurements of protein-DNA interactions) with enzymatic cleavage-based identification of CPDs in individual DNA molecules. Using TF-specific libraries that systematically vary the binding-site sequence, we aim to model TF and UV-DDB binding affinities as functions of DNA sequence and CPD position. These models will then be integrated to predict TF-UV-DDB competition and its potential contribution to UV-induced mutagenesis in regulatory DNA, which will be validated against existing and new DNA damage and mutation data from UV-exposed human cells.

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