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The way a stretch of DNA is organized inside the cell—whether it is loosely or compactly packaged by associated proteins—is believed to reflect the activity level of the genes it contains. The Risca lab studies how the 3-D architecture of the mammalian genome helps to precisely control transcriptional programs and genome maintenance in both healthy cells undergoing differentiation and in cancer cells under targeted therapy.

The 46 chromosomes of the human genome would measure almost two meters if stretched out end-to-end as pure DNA. To fit into the roughly five-micron-wide cell nucleus, DNA is wrapped around histone proteins into repeating bobbin-like structures called nucleosomes, which make up the chromatin fiber. Chromatin organizes the genome within the nucleus to control transcription, DNA replication, and DNA repair. Defects in chromatin organization can perturb gene expression, leading to serious consequences that include developmental disorders and cancer.

The Risca lab investigates the 3-D architecture of chromatin and the basic biophysical mechanisms by which it defines and maintains stable states in the regulation of transcription and other DNA-based processes.

Risca's postdoctoral studies helped to fill a significant gap in the field of chromatin biology: The high density of chromatin packing made it challenging to study how nearby nucleosomes fold together in the chromatin fiber. Risca and her colleagues developed a technique, called RICC-seq, capable of examining the configuration of one to three nucleosomes. This length scale is particularly important because it corresponds to the length of genetic elements that contain binding sites for transcription factors.

RICC-seq uses ionizing radiation to create spatially distinct clusters of DNA strand breaks within intact cells. DNA fragments spanning break sites are sequenced and the resulting data aggregated across many cells to create a high-resolution map of DNA folding. Using RICC-seq, Risca and colleagues uncovered accordion-like compaction of chromatin fibers within repressed regions of chromosomes. Meanwhile, within active regions, they found evidence of a looser folding with few contacts between neighboring nucleosomes, consistent with previous data.

In addition to RICC-seq, the Risca lab uses computer simulation, microscopy, and other sequencing-based methods to study genome architecture in order to understand how it is regulated and how it, in turn, controls regulatory molecules' access to DNA.

To better understand these relationships, the lab investigates differences between cell types and studies senescence, a state in which cells irreversibly exit the cell cycle and undergo associated changes in genome organization. Because senescence can shut down the replication of cells in response to DNA damage or oncogene activation, it acts as a first line of defense against cancer. It has also emerged as a mechanism by which targeted cancer therapies may be slowing or reversing tumor progression. The Risca lab collaborates with cancer biologists to understand how changes in chromatin architecture drive or reinforce this response to therapy.

The new mechanistic insights that result from this work may make it possible to better understand how cells respond to perturbations brought on by mutations or chromatin-targeting drugs, potentially leading to more precise tailoring of cancer therapies and control of cell differentiation.

EDUCATION

B.S. in physics, 2004
Stanford University

Ph.D. in biophysics, 2012
University of California, Berkeley

POSTDOC

Stanford University School of Medicine, 2012–2018

POSITIONS

Assistant Professor, 2019–
The Rockefeller University

AWARDS

V Scholar, 2019

Rita Allen Foundation Scholar, 2021

NIH Director's New Innovator Award, 2022

SELECTED PUBLICATIONS

Kim D.S., et al. The dynamic, combinatorial cis-regulatory lexicon of epidermal differentiation. *Nature Genetics*, 53, 1564–1576 (2021).

Bell, J.C. et al. Chromatin-associated RNA sequencing (ChAR-seq) maps genome-wide RNA-to-DNA contacts. *Elife* 7, e27024 (2018).

Chiou, S.H. et al. BLIMP1 induces transient metastatic heterogeneity in pancreatic cancer. *Cancer Discov* 7, 1184–1199 (2017).

Risca, V.I. et al. Variable chromatin structure revealed by in situ spatially correlated DNA cleavage mapping. *Nature* 541, 237–241 (2017).

Risca, V.I. et al. Actin filament curvature biases branching direction. *Proc. Natl. Acad. Sci. U.S.A.* 109, 2913–2918 (2012).