ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

DIPARTIMENTO
DI FARMACIA
E BIOTECNOLOGIE

AVVISO DI SEMINARIO

Il giorno **17 Giugno 2024**
alle ore **14:00**

Prof. Berkley Gryder

Assistant Professor - Case Western Reserve University

(ospite di Dr. Giorgio Milazzo e Prof Giovanni Perini)

terrà un seminario in lingua inglese dal titolo:

Chromatin mechanisms of gene control in cancer

Area tematica:
Cancer Biology; Drug discovery and development; Genomics

in presenza:
Aula A Farmacologia, via Irnerio 48, Bologna BO

Colleghi e studenti sono cordialmente invitati

ABSTRACT

Core regulatory transcription factors (CR TFs) orchestrate the placement of super enhancers (SEs) to activate transcription of cell-identity specifying gene networks and are critical in promoting cancer. We discovered the core regulatory circuitry of fusion positive rhabdomyosarcoma (FP-RMS, a cancer of childhood that resembles myoblasts) in primary tumors and cell lines, which includes PAX3-FOXO1 (P3F), MYOD1, SOX8, MYOG, MYCN and others. We also discovered that the fusion creates an “infinite loop” of enhancer logic, preventing FP-RMS cells from differentiating down the muscle lineage.

To find chemical probes able to selectively inhibit CR TF transcription, we screened the Structural Genomics Consortium epigenetic probe set by RNA-seq. We found that chemical probes along the acetylation-axis, and not the methylation-axis, are able to cause selective disruption of CR TF transcription. Inhibitors of HDACs (acetylation erasers), BRD4 (acetylation readers) and CBP/p300 (acetylation writers) were all able to selectively halt CR TF transcription.

For HDACs, this raised a conundrum: why would too much histone acetylation, an active chromatin mark, stop transcription at CR TFs? ChIP-seq showed that CR TFs build SEs that have the largest quantities of histone acetylation and the enzymes that write acetylation (i.e., p300), yet paradoxically also harbor the highest amounts of the opposing histone deacetylases (HDACs). To investigate the architectural effects of disabling HDACs and causing hyper acetylation, we developed Absolute Quantification of Architecture (AQuA) HiChIP, revealing erosion of native SE contacts at CR TFs, and extensive aberrant contacts. This did not cause an elongation defect, but rather removed RNA Pol2 from core regulatory genetic elements and eliminated RNA-Pol2 phase condensates in 20 minutes.

Using HAT inhibitors/degraders, we discovered a profound dependence on CBP/p300 for clustering of Pol2 loops that connect P3F to its target genes. In the absence of CBP/p300, Pol2 long range enhancer loops collapse, Pol2 accumulates in CpG islands and fails to exit the gene body. These results reveal a potential novel axis for therapeutic interference with P3F in FP-RMS and clarify the molecular relationship of P3F and CBP/p300 in sustaining active Pol2 clusters essential for oncogenic transcription.

In multiple contexts, we propose Pol2 Un-Loading Ratio (PULR) as a new key metric to quantify and explain the drug induced defects in CR TF transcription. Overall, our data reveals a SE-specific need for balancing histone acetylation states to maintain SE architecture, Pol2 clustering in 3D, and CR TF transcription.

BIOGRAPHICAL SKETCHES

Dr. Berkley Gryder focuses on the epigenetic mechanism of gene regulation in 3D, and chemical genomics. He is a chemist who retrained as a molecular biologist and computer scientist. His lab is passionate about understanding how cancer cells control their genes, and developing new chemical strategies to stop cancer cells’ addiction to transcription. Along the way, he has proposed paradigm shifts and surprises that are explaining old conundrums. The Gryder lab combines synthetic chemistry, 3D computational biology, nascent transcriptomics, and genetic engineering, to develop new chemical and biological tools and rigorously evaluate the epigenetic mechanisms of gene regulation.