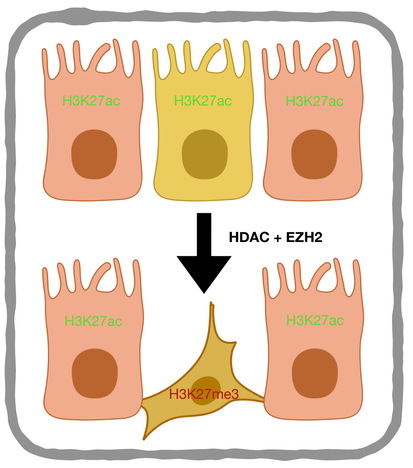
Investigating the role of histone marks in alternative splicing during EMT

Background

Cancer cells exploit alternative splicing (AS) for enhanced proteome diversity, allowing them to adapt to changing micro environments. However, the regulation of cancer-specific splicing programs remains poorly understood. We have uncovered a novel regulatory mechanism for dynamic splicing changes. This mechanism also occurs during the Epithelial-to-Mesenchymal Transition (EMT), a key process in cancer progression and metastasis.

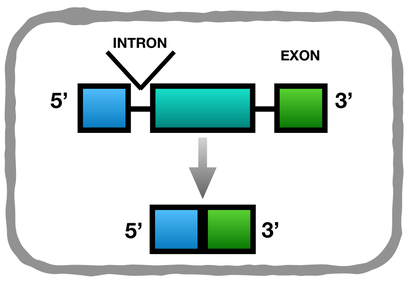
What is EMT ?

Epithelial-to-Mesenchymal Transition (EMT) is a dynamic cellular process in which epithelial cells undergo reprogramming to acquire mesenchymal characteristics. It plays a pivotal role in cancer progression and metastasis by enabling cells to adapt to new micro environments, enhancing their invasive and migratory properties.



What is AS ?

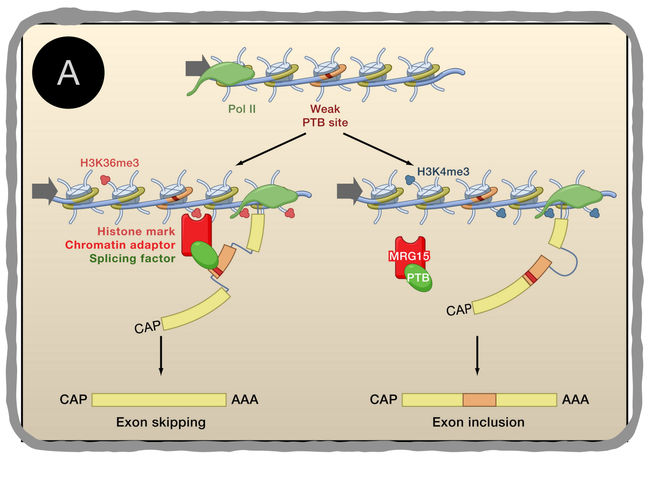
Alternative Splicing (AS) is a complex cellular process that allows a single gene to encode multiple protein isoforms. This is achieved by splicing different exons (coding segments of DNA) from a single gene, leading to the production of different proteins with varying functions.

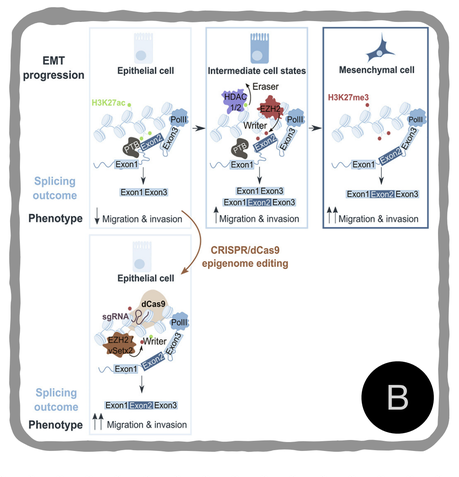


Our discoveries

A. Exon-specific changes in histone marks H3K27ac and H3K27me3 drive splicing changes during EMT.

B. CRISPR/dCas9 epigenetic editing tools can reverse splicing changes, impacting cell invasiveness.





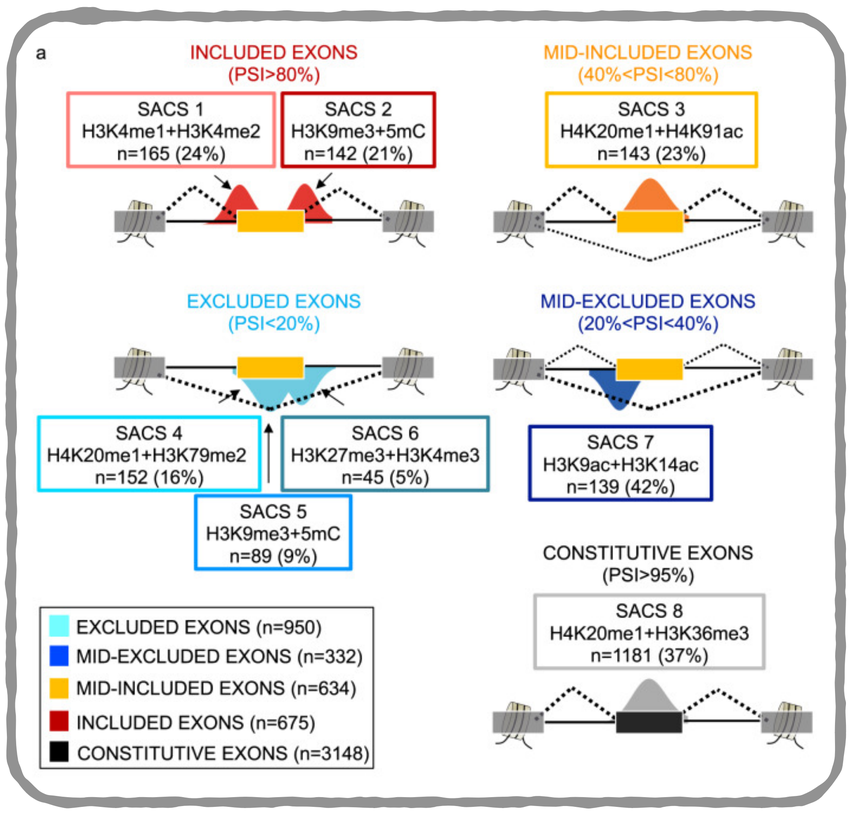
Project goals

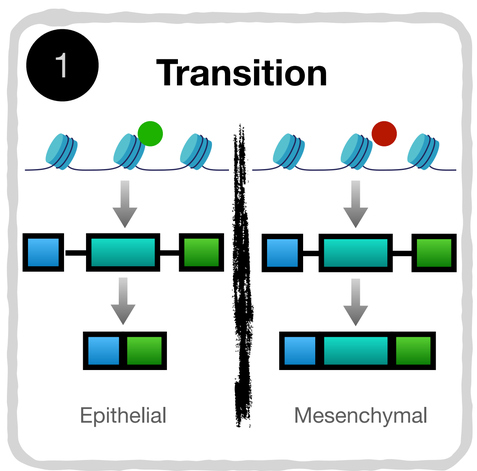
1. Identify exons with splicing changes and histone mark changes in EMT

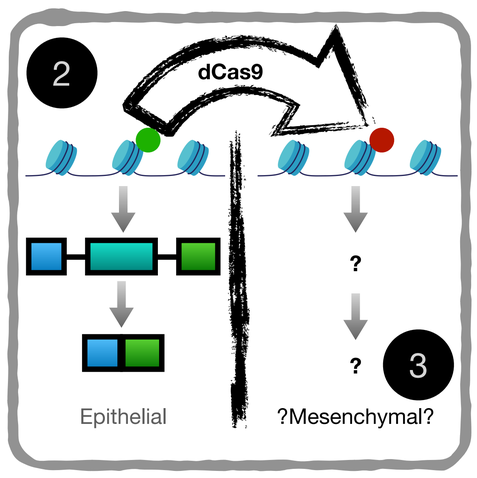
2. Use dCas9 fusions to epigenetically edit H3K27ac/me3 levels at these exons

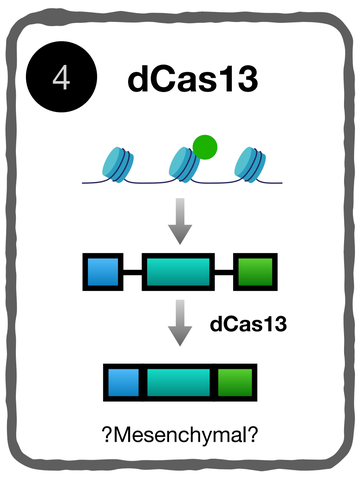
3. Assess impact on EMT splicing patterns and phenotypes

4. Compare to directly editing splicing with dCas13









The lab already succeeded to create groups of epigenetic marks that are able to predict whether an exon is more likely to be included or excluded from the final transcript. I will have to use these different groups to achieve the goals of my project.

Expected outcomes

To gain a deeper understanding of the molecular mechanisms that govern EMT and develop novel therapeutic strategies to target EMT-associated cancers, we aim to identify the critical alternatively spliced exons (ASEs) that are essential for this process.

Unraveling new splicing patterns that are dependent on epigenetic marks will provide new insights into the crosstalk between the epigenome and the transcriptome, which is crucial for developing effective therapeutic strategies for cancer and other diseases.

Perspectives

Develop novel therapeutic agents that modulate histone marks to regulate AS and inhibit EMT.

Utilize CRISPR/dCas9 epigenetic editing tools to precisely manipulate histone marks and AS patterns in cancer cells.

Investigate the crosstalk between histone marks and other regulatory mechanisms, such as microRNAs and transcription factors, in shaping AS patterns

Epigenetics in Alternative Pre-mRNA Splicing, Reini F. Luco, Mariano Allo, Cell
Histone marks regulate the epithelial-to-mesenchymal transition via alternative splicing, Alexandre Segelle, Yaiza Núñez-Álvarez, Cell
Splicing-associated chromatin signatures: a combinatorial and position-dependent role for histone marks in splicing definition, Eneritz Agirre, Andrew J. Oldfield, Nature

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