Super-enhancer Analysis Identifies Therapeutic Targets in Pancreatic Cancer

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Wednesday, May 3, 2017

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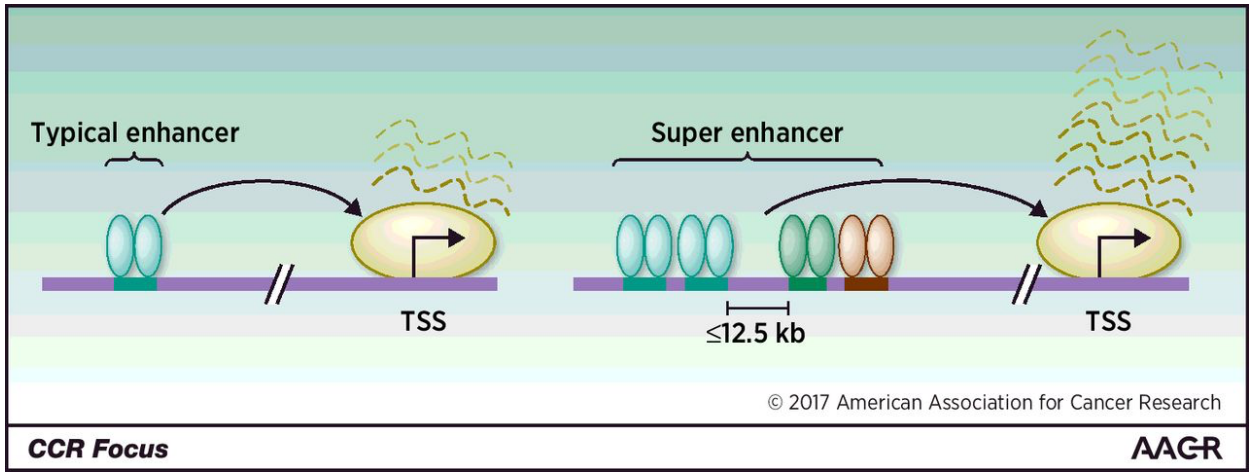
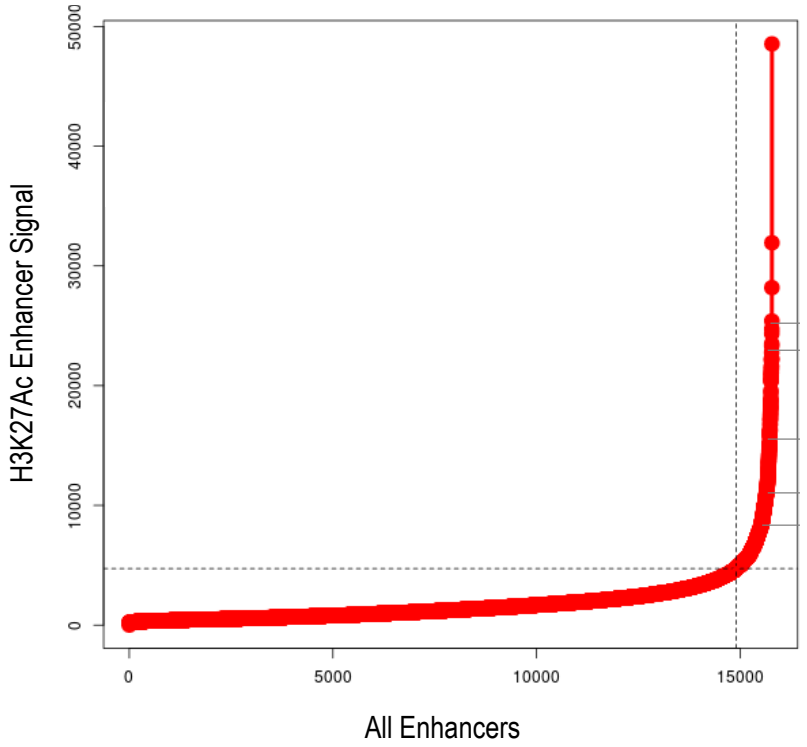
Super-enhancers

- Large non-coding regions of the genome made up of clusters of transcription regulators
- Rich acetylation of Histone H3 lysine 27 (H3K27ac) indicates high levels of SE activity
- Drive expression of genes that define cell type differentiation



G. Evan, et al. *Clinical Cancer Research*. April 2017.



Methods

Normal pancreas, primary PDAC, PDX tumors, PDX-derived organoids, PDAC cell lines

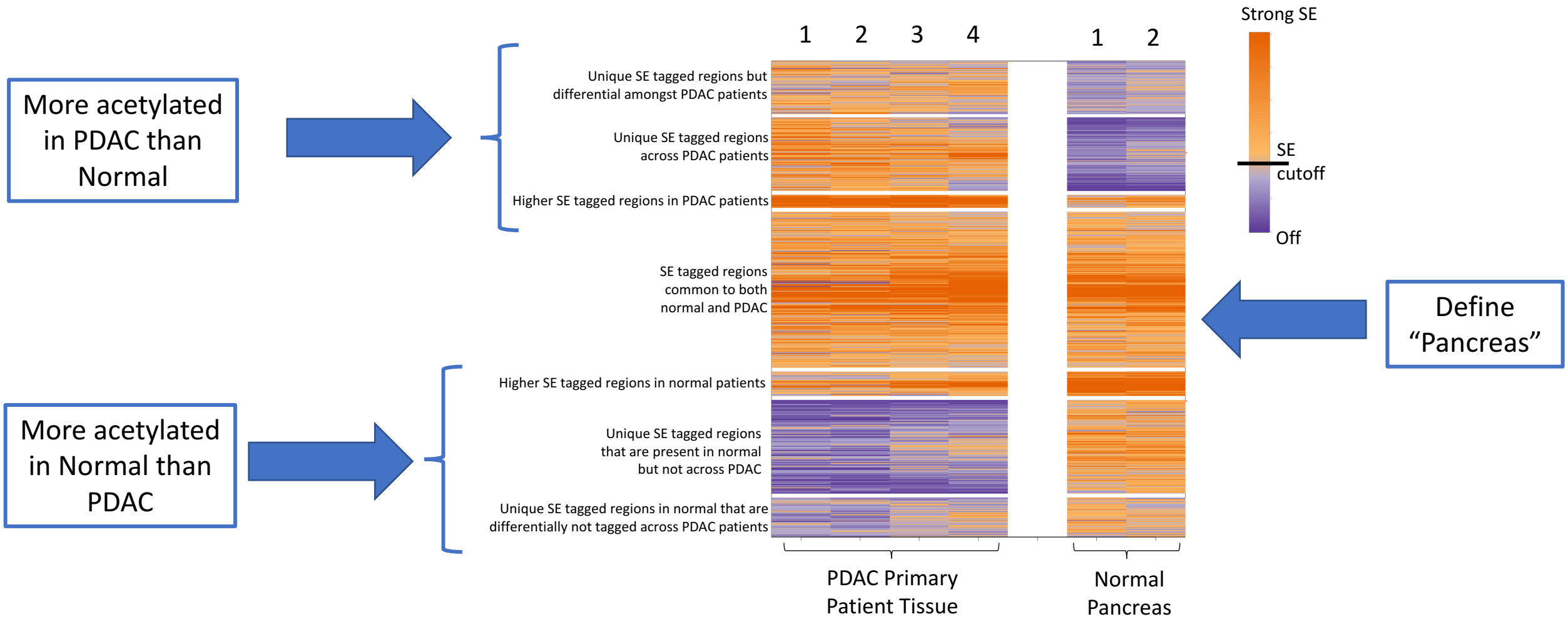
Dissociated and sorted into whole tumor, and epithelial, stromal, and immune populations

ChipSeq to identify SE regions (rich in H3K27ac)

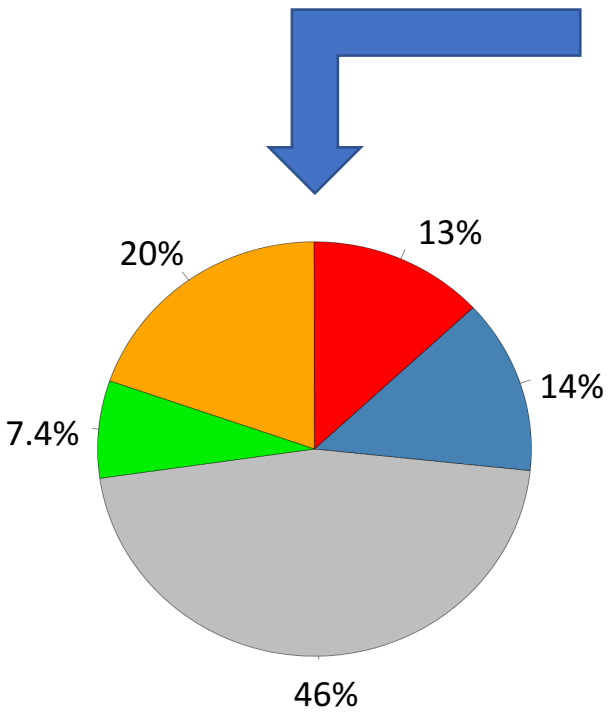
SE regions linked to specific genes

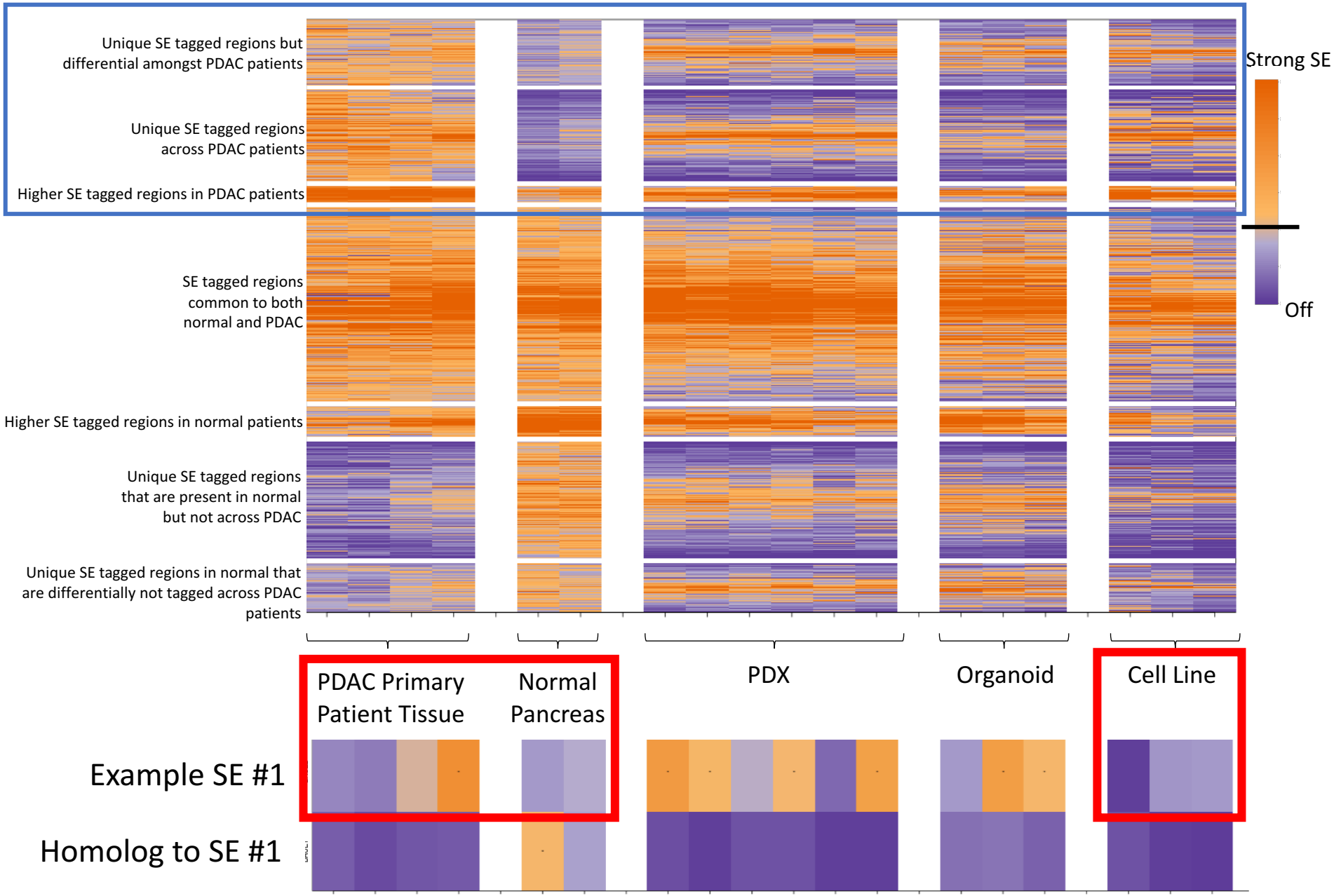
Genes linked to signaling pathways with Ingenuity Pathway Analysis

Primary PDAC samples have unique epigenetic landscapes compared to Normal Pancreas



There is variable maintenance of epigenetic landscape across PDAC models





Conclusions

- SE analysis can define key genes in the epithelial, stromal, and immune populations that may drive pancreatic cancer oncogenesis.

- SE analysis can be used to select and compare preclinical models of PDAC.
  - Majority of genes with SE status in primary PDAC that are lost in models are associated with immune signaling pathways
  - Consistent with the known loss of immune component in the models (only epithelial cells)

- These genes can hopefully be targeted for development of novel therapeutics.

- Validation of these putative and novel targets is ongoing.

Acknowledgements

Lowy Lab

Andrew Lowy, MD (PI)
Alex Cazes, PhD
Randall French, PhD
Dawn Jaquish
Francisco Mercado, PhD
Evangeline Mose
Shweta Sharma, PhD

Syros Pharmaceuticals

Tracey Lodie, PhD
Kathryn Austgen, PhD
Cindy Collins, MS
Chris Fiore, PhD
Brian Johnston, MS
Sofija Miljovska, MS
David Orlando, PhD

Funding/Grant Support

NCI/NIH Award Number T32-CA121938
Cancer Therapeutics Training (CT2) Fellowship Program

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