Navigating multiomics in clear cell renal cell carcinoma-ccRCC: Network analyses on DNA methylation-5mC, DNA hydroxymethylation-5hmC, messenger RNA-mRNA, and microRNA-miRNA expression

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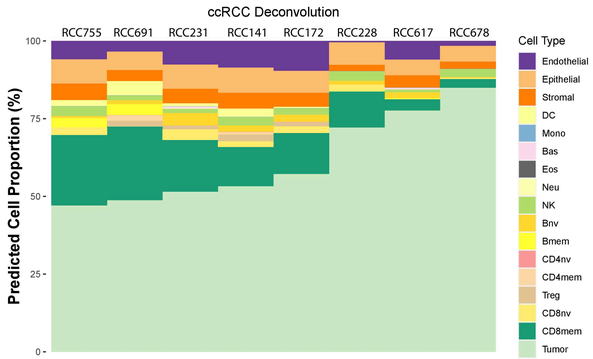
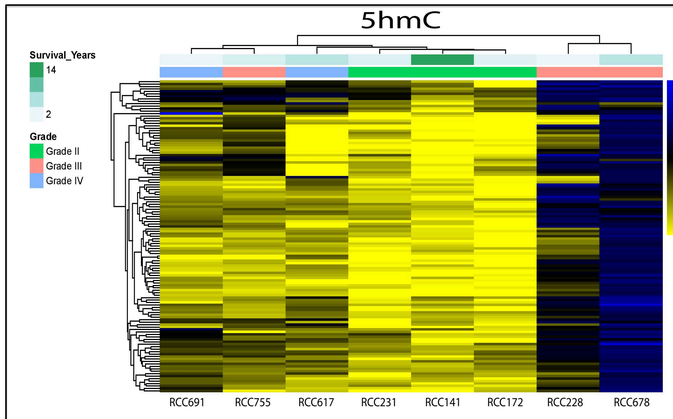
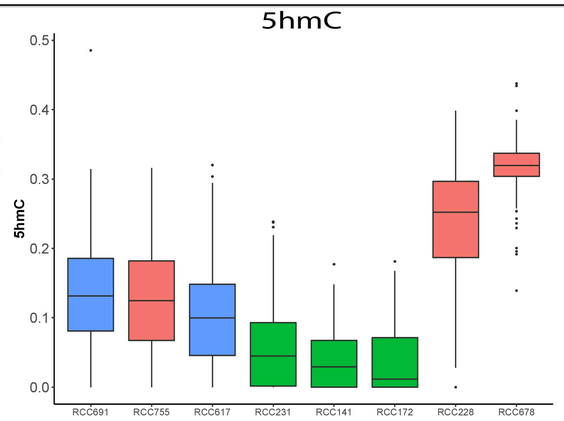
Background

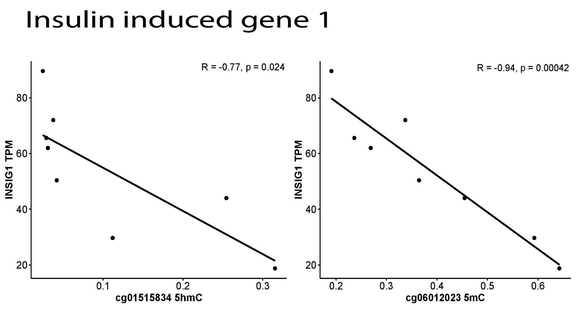
- Clear cell renal cell carcinoma (ccRCC) is the most common type of kidney cancer, representing 70% of all renal cell carcinoma cases.
- 5hmC has been proved to be a promising biomarker for early diagnosis and prognostic evaluation for cancers[1].
- Recent studies found the mutual regulatory correspondence between miRNA expression and 5mC in multiple cancers[2].
- However, critical gaps remain in understanding the underlying genetic and epigenetic regulatory mechanisms in ccRCC.
- We aim to investigate the associations of 5mC and 5hmC with mRNA and miRNA expression in ccRCC.

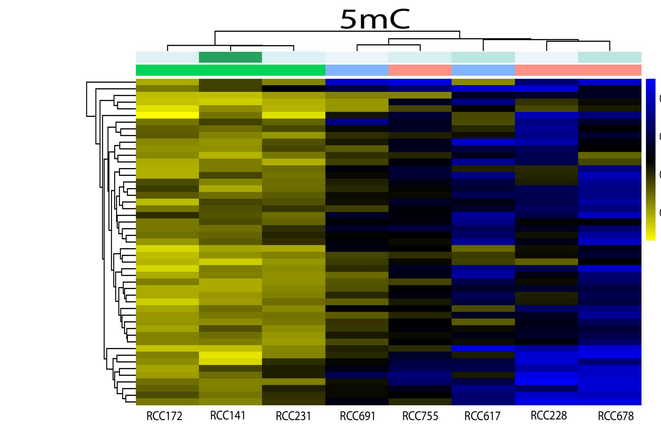
Findings

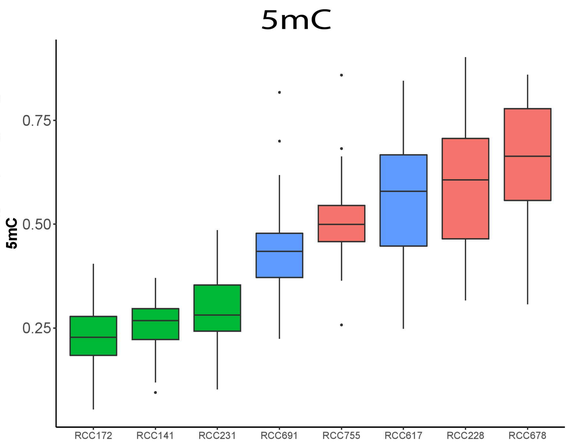


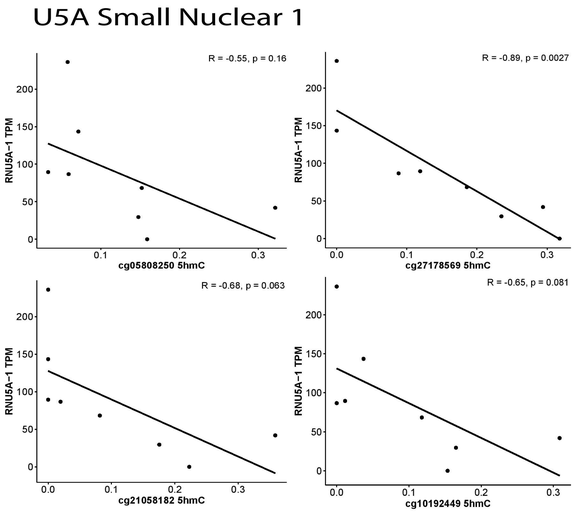








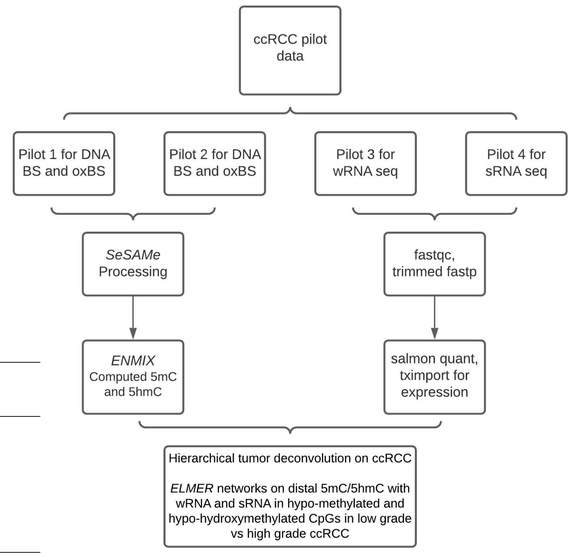




Data and Methods

- This pilot study selected eight ccRCC samples from the Dartmouth Renal Tumor Biobank based on tumor grade (Grades 1-2: n = 3; Grades 3-4: n = 5), towards a full study target of 224 samples.
- Infinium EPIC beadchips were used to measure 5mC and 5hmC. mRNA and miRNA expression were measured using whole RNA-seq and small RNA-seq technologies.
- The Enhancer Linking by Methylation/Expression Relationships (ELMER) package was used to construct the genetic-epigenetic regulatory networks from epigenome and transcriptome profiles.
- 5mC based hierarchical tumor deconvolution was used to infer ccRCC cell composition.

	Tumor	Adjacent Normal	p
N	174	50	
Age mean (SD)	60.91 (12.02)	62.65 (13.24)	0.41
Female N (%)	66 (37.9)	17 (34)	0.73
Survival years mean (SD)	2.40 (2.55)	3.15 (3.36)	0.14



Summary of Findings

- 49 differentially hypo-methylated and 129 differentially hypo-hydroxymethylated CpGs were identified in low grade ccRCC vs high grade ccRCC.
- Genetic and epigenetic regulatory networks revealed interested associations between distal CpGs and mRNA and sRNA expression. For example, INSUG1 can be negatively regulated by distal 5mC and 5hmC while RNU5A-1 is majorly negatively regulated by distal 5hmC.
- Tumor cell deconvolution revealed relatively high levels of CD8T memory cells, dendritic cells, NK cells, and B cells in the ccRCC immune microenvironment.

Discussion and Future Directions

- Gene regulatory networks differ by cytosine modification type 5hmC/5mC in ccRCC progression.
- More extensive mapping of 5mC, 5hmC, mRNA, and miRNA regulatory networks in ccRCC promises a better understanding of the tumor progression and potential discoveries of enhanced biological targets.
- The pilot study promised more effort to explore genetic and epigenetic regulatory mechanisms in ccRCC tumorigenesis and progression. Additional analyses will also include mutation detection, fusion transcript identification, lncRNA classification, and foreign transcript detection (viruses, microbes). More samples are undergoing the experimental procedure to complete the full study.

References

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