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Epigenetic Dynamics of Kidney Development: Chromatin Accessibility and miRNA Expression

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Description

The kidney's functional unit is the nephron, responsible for filtering waste and maintaining water, acid-base balance and electrolyte levels in the body. Human nephron numbers vary widely (typically from around two hundred thousand to over one million nephrons) and are established before birth (around post-natal day 2–3 in mice). Nephrons do not regenerate after birth and a lower nephron count is linked to higher risks of chronic kidney disease and hypertension. Nephron quantity largely depends on a cell population known as nephron progenitor cells. As kidney development progresses, nephron progenitors shift towards differentiation, leading to their gradual depletion and the eventual halt of nephrogenesis. Understanding the mechanisms behind nephrogenesis cessation is crucial for determining nephron count and kidney disease risk. During kidney development, self-renewing Cited1+/Six2+ nephron progenitor's transition to primed Cited1-/Six2+ progenitors, then differentiate into Wnt4-expressing renal vesicles in response to Wnt9b/β-catenin signaling. Intrinsic transcriptional changes between early and late nephron progenitors involve genes and pathways influencing stem cell aging, notably mTor and its inhibitor hamartin. Hamartin is believed to reduce nephron progenitor sensitivity to self-renewal signals, contributing to nephrogenesis cessation. Early nephron progenitors show a higher tendency for self-renewal, reflected in enriched chromatin accessibility at binding sites for core nephron progenitor transcription factors like Six2 and Wt1, which target enhancer sequences in key genome regions.

Nephron progenitors

Nephron progenitors are initiated by increased β-catenin levels, leading to the activation of Lef1/Tcf7 complexes at genes poised for nephrogenesis program activation. These complexes are suggested to interact with Tcf7l1 and Tcf7l2, forming regulatory chromatin loops that facilitate gene activation. Recent research has highlighted the role of microRNAs (miRNAs) in regulating nephrogenesis cessation, miRNAs are short, non-coding RNA molecules that target mRNA transcripts for reduced translation or enhanced degradation *via* the RNA-Induced Silencing Complex (RISC). Lin28b protein represses the let-7 miRNA family; as nephrogenesis progresses, Lin28b expression decreases, while let-7 miRNA family expression increases in nephron progenitors. Inducing Lin28b expression in the Wt1-lineage suppresses let-7 miRNA, extending nephrogenesis. Whether other miRNAs control nephrogenesis timing remains unknown. Additionally, while enhancers that regulate long non-coding RNA expression during nephrogenesis are identified, none have been proven to regulate miRNA expression in nephron progenitors.

Genomic analyses

In this investigation, our aim was to concurrently pinpoint novel miRNAs that contribute to the cessation of nephrogenesis, alongside potential cis-regulatory characteristics. To achieve this, we conducted matched smRNA-seq and ATAC-seq analyses on primary, un-passaged nephron progenitor cells at embryonic day 14.5 (E14.5) and Post-natal day zero (P0), with the objective of observing alterations in miRNA expression and chromatin accessibility across these two temporal stages. Through this approach, we successfully identified 114 miRNAs exhibiting differential expression in nephron progenitor cells between these time points, alongside the delineation of 2103 regions of changing chromatin accessibility termed Differentially Accessible Regions (DARs). Enrichment analyses targeting the predicted gene targets of significantly altering miRNAs, as well as the genomic locations of DARs, implicated pathways influencing epithelial cell differentiation, cell migration, extracellular matrix interactions and crucial developmental signaling pathways including Wnt, Notch and TGF-β signaling. Our analysis revealed significant modifications in chromatin accessibility and provided compelling evidence pinpointing two genomic regions as potential enhancers for the genes Eya1 and Pax8 within nephron progenitor cells. Moreover, we identified consistent patterns of chromatin accessibility and miRNA expression alterations involving 33 pairs of miRNAs and DARs, notably including let-7-5p, miR-125b-5p, miR-181a-2-3p and miR-9-3p and delineated putative genes. Nephron progenitor cells were obtained through positive selection for Itgα8 at embryonic day 14.5 (E14.5) or at Post-natal day zero (P0) and each sample was subsequently divided to undergo smRNA-seq, ATAC-seq and quality assurance procedures.