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Combing Genome-Wide Association Studies and Single-Cell Analysis to Elucidate the Mechanisms of Kidney Disease: Proceedings of the Henry Shavelle Professorship

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Abstract
Background: Kidney diseases pose a significant global health burden; there is an urgent need to deepen our understanding of their underlying mechanisms. ***Summary:*** This review focuses on new innovative approaches that merge genome-wide association studies (GWAS) and single-cell omics (including transcriptomics) in kidney disease research. We begin by detailing how GWAS has identified numerous genetic risk factors, offering valuable insight into disease susceptibility. Then, we explore the application of scRNA-seq, highlighting its ability to unravel how genetic variants influence cellular phenotypes. Through a synthesis of recent studies, we illuminate the synergy between these two powerful methodologies, demonstrating their potential in elucidating the complex etiology of kidney diseases. Moreover, we discuss how this integrative approach could pave the way for precise diagnostics and personalized treatments. ***Key Message:*** This review underscores the transformative potential of combining GWAS and scRNA-seq in the journey toward a deeper understanding of kidney diseases.

Introduction

Chronic kidney disease (CKD) and end-stage renal disease pose substantial societal challenges, with over 800 million people worldwide affected by kidney disease [1]. Genetics plays a crucial role in the development of these diseases. The estimated heritability of kidney function in the general population is around 30% [2], but it could be much higher in African Americans and other minority populations [3, 4]. Environmental factors, including hypertension, diabetes, obesity, and aging are significant contributors to kidney disease, particularly in those genetically predisposed to these conditions.

Identification of genes that cause kidney disease will not only improve our understanding of disease development but could extend to the successful development of therapies. Drug development becomes notably effective when targeted toward a causal gene or pathway. This concept has been demonstrated in cardiology, where genetic studies have identified pivotal disease-driving genes such as PCSK9 [5, 6]. This discovery has led to the development of powerful FDA-approved drugs.

Genetic studies in the field of nephrology have made ground-breaking discoveries in the context of rare monogenic forms of CKD. This includes diseases like focal

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segmental glomerulosclerosis (FSGS) and membranous nephropathy [7–9] and has shed light on key causal cell types implicated in these diseases, such as the podocyte in FSGS [3]. These studies have facilitated not only the development of diagnostic and prognostic markers but also contributing to therapeutic advancements.

While rare loss of function variants has been identified in a large number of patients with FSGS and cystic kidney disease, it has been the common noncoding variants that explain most kidney function heritability in the general population [10–12]. Genome-wide association studies (GWAS) are capable of identifying common nucleotide variants associated with kidney function and disease development. More than 90% of the variants identified by GWAS are located in noncoding regions of the genome [11, 12]. Additionally, multiple single nucleotide polymorphisms (SNPs) are often inherited together, which further clouds the identification of the likely causal variant. Consequently, there is an urgent demand to identify genes, cell types, and pathways implicated in kidney disease, particularly those elucidated by GWAS so we can translate GWAS discoveries into better disease understanding and enable therapeutics development.

Our current working model proposes that disease-causing genetic variants, predominantly found in gene regulatory or open chromatin regions, alter the binding strength of transcription factors. This model has recently been excellently summarized by Gaulton et al. [13]. Differences in transcription factor binding cause quantitative changes in target gene expression in a cell type-specific manner. However, pinpointing the causal variants is complicated by the fact that DNA sequences close to each other are often inherited together [14]. Furthermore, due to the secondary chromatin structure, the nearest coding gene is not always the causal one, making it difficult to identify disease-causing genes [15]. Adding to this complexity, the effects of a given genotype can vary between organs and cell types [16], which further complicates our understanding of disease development. Hence, there is an immediate need for innovative research methods capable of deciphering these complexities and fully harnessing genetic information in our fight against kidney diseases.

Common Variant Mapping in GWAS for Kidney Function

GWAS have been instrumental in unraveling the association between common genetic variants and kidney function. Often, these studies use the creatinine-based estimated glomerular filtration rate (eGFR) as a proxy phenotype for kidney function, though other phenotypes, including cystatin-based eGFR, blood urea nitrogen (BUN), proteinuria, serum uric acid, and metabolite levels, have also been studied [17–21].

Initial GWAS studies, conducted with approximately 60,000 participants, already revealed several significant genetic signals, the most prominent being around the *UMOD* gene where genetic variants were different in people with low eGFR [22]. More recent studies, with increased sample sizes and refined methodologies, have identified more than 800 loci in our genome where genetic variants are associated with kidney function [23]. These findings have greatly enriched our understanding of the genetic framework underpinning kidney diseases.

In the early days of eGFR GWASs, the primary focus was on populations of European ancestry, but this has gradually expanded to include various racial and ethnic groups. This diversification has been enlightening, revealing population-specific associations and uncovering loci that were overlooked in earlier studies. Most importantly variants in the *APOL1* gene, discovered in African populations, have been identified that markedly increase the risk of CKD in this population [9].

Several identified loci are situated within or in proximity to genes known to harbor mutations that cause monogenic forms of kidney disease (e.g., UMOD, PKD2) [24, 25]. This potentially highlights the shared genetic foundation between rare and common forms of kidney disease [23]. However, it is important to note that over 90% of the identified genetic variants reside in noncoding regions of the genome and span multiple genes [11]. This makes it challenging to determine which genes are the actual targets of these GWAS-identified genetic variants (Fig. 1a) [11, 16]. The annotation of human GWAS studies necessitates the generation of a large amount of orthogonal omics information, including but not limited to genomic, transcriptomic, and epigenomic data. Moreover, the integration of these data with GWAS findings is crucial to identify likely causal genes, cell types, and pathways for kidney disease development. Unfortunately, obtaining human kidney tissue samples has been challenging, and there remains a critical need for human tissue-derived omics information. Additionally, the development of new bioinformatics tools for data integration and gene prediction is essential.

Quantitative Trait Loci Analysis and Its Role in GWAS Annotation

Quantitative trait loci (QTL) analysis is an important tool to correlate genetic variants with quantitative measures such as gene expression (expression QTL:

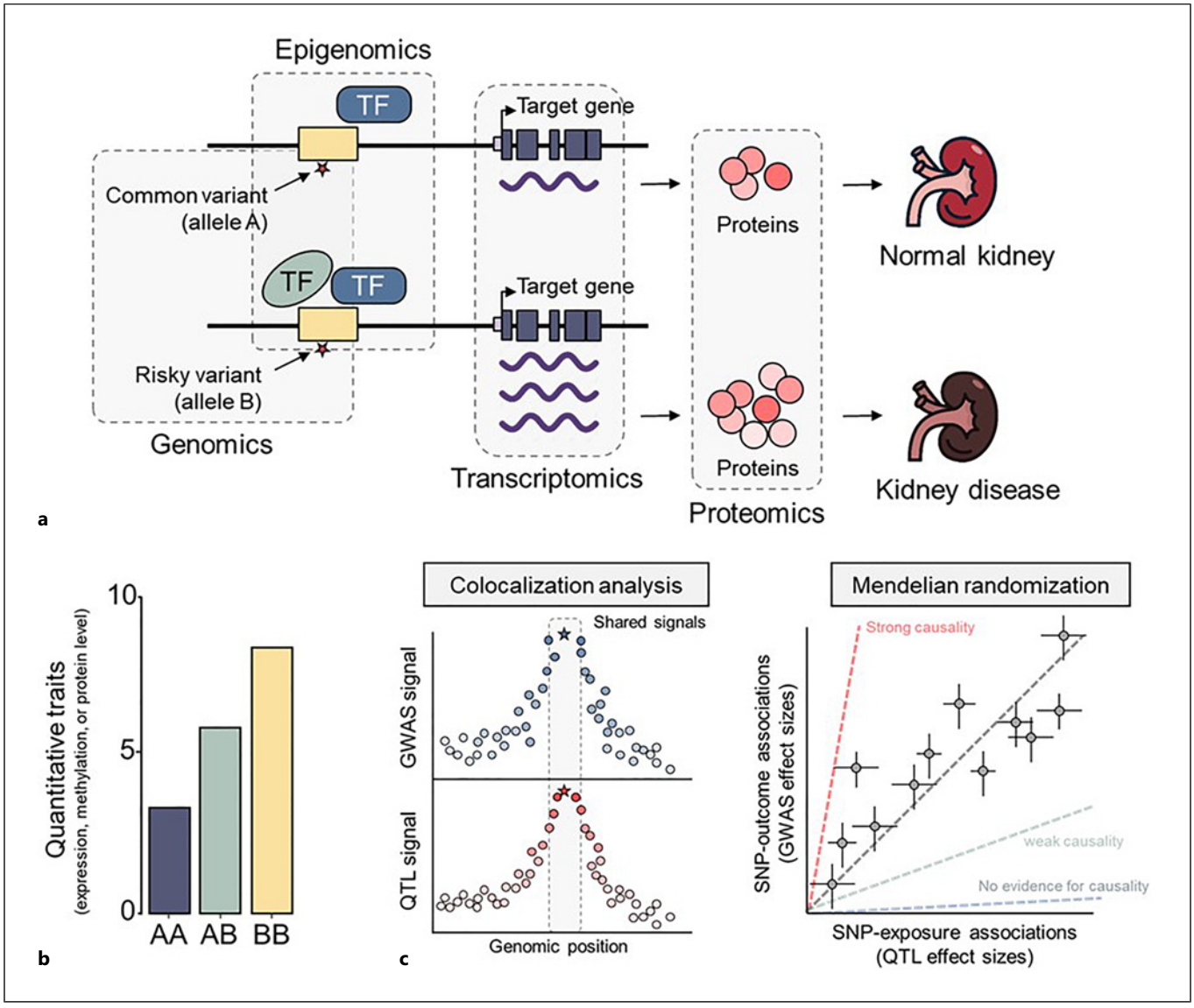

Fig. 1. Multiomics data integration for functional characterization of GWAS variants. **a** Proposed mechanism for noncoding GWAS variants modulation: schematic illustrating how noncoding GWAS variants within regulatory elements may alter gene regulation and cellular functions. Variants can impact transcription factor binding, leading to alterations in the recruitment of transcriptional machinery, gene expression, protein levels, and potentially affecting kidney functions. **b** Overview of quantitative trait loci (QTLs): QTLs are genomic regions associated with the variation of quantitative traits, including but not limited to expression levels, DNA methylation patterns, and protein quantities. **c** Integration of GWAS and eQTL data using statistical approaches: depicts two statistical approaches to link GWAS and eQTL data. On the left, Bayesian colocalization analysis provides a method to identify if the same genetic variant associates with two different traits. On the right, Mendelian randomization uses genetic variants to estimate the causal effect of a modifiable exposure on an outcome, thus providing evidence of causality where standard observational studies cannot.

eQTL), methylation (methylation QTL: mQTL), and protein levels (protein QTL: pQTL) (Fig. 1b) [26–28]. Expression QTL studies probe the association between genetic variants and gene expression levels, offering a list of likely causal genes for the functional effects of variants identified by GWAS. Methylation QTL (meQTL) studies, conversely, explore the connection between genetic variants and alterations in DNA methylation, an essential epigenetic modification regulating gene expression. MeQTL analyses can illuminate the mechanisms through

which these variants may wield their effects [29, 30]. Within the context of GWAS, QTL analyses are indispensable in interpreting the functional implications of identified genetic variants, especially those located in noncoding regions of the genome. They help pinpoint changes in gene expression, methylation, or protein levels associated with genetic variations linked to disease development.

Computational integration of QTL information (eQTL, meQTL, or other molecular QTL) with GWAS results holds potential in bridging the divide between statistical association and biological causation. By linking identified variants to specific molecular traits (like gene expression or DNA methylation levels), researchers can begin to untangle the potential functional effects of these variants, thereby revealing the molecular pathways implicated in disease susceptibility.

Several methods have been developed to facilitate the integration of GWAS and eQTL data for disease causal gene identification (Fig. 1c). These tools are based on the simple principle of finding genes those expressions are regulated by genetic variants identified by GWAS studies therefore likely disease causing. For instance, Bayesian colocalization is a process that estimates if the same variant is linked to both a disease and changes in gene expression. A method known as COLOC has been designed to assess multiple hypotheses and discern between colocalization and distinct associations [31].

Mendelian randomization (MR) analysis is another key tool that can help prioritize causal genes. This method gauges the causal effect of a gene expression (or open chromatin) on disease state using genetic variants associated exclusively with the risk factor as instrumental variables [32]. While MR and Bayesian colocalization provide complementary information, they both have inherent limitations and need cautious interpretation. Genes, pathways, and regulatory mechanisms identified by these methods can help prioritize GWAS mechanisms, but these prioritized pathways require external validation.

Single-Cell Transcriptomics and Kidney Disease

Recent advancements in single-cell omics methods such as single-cell gene expression analysis (scRNA-seq) single nucleus open chromatin analysis (snATAC-seq) have provided unparalleled insights into the complex cell diversity and regulatory networks present in different cell types in the kidney [33]. This has not only given new perspectives on kidney disease pathogenesis but also indicated potential avenues for therapeutic strategies by highlighting key genes, cell types, and pathways for disease development.

For example, one of the first cutting-edge study conducted by Park et al. [34] employed scRNA-seq to construct a comprehensive gene expression atlas for each cell in the mouse kidney. Their work uncovered more than 30 different cell types in the kidney by defining their key marker genes. They identified a variety of differentiated cell types, including a newly discovered transitional cell within the collecting duct that can alter the principal to intercalated cell number of this kidney segment. They further hypothesized that different genetic mutations causing similar phenotypic kidney diseases might originate from the same kidney cell types. In another pioneering study, Miao et al. [35] combined scRNA-seq with regulatory region annotation in snATAC-seq, to outline the open chromatin landscape of the adult and developing mouse kidneys. They pinpointed key cell-type-specific transcription factors and primary gene-regulatory circuits in kidney cells, offering invaluable insights into kidney cell differentiation. Furthermore, they have also mapped and highlighted genetic variants that were located in kidney cell-type-specific gene-regulatory regions and likely contributed to gene expression changes.

Building on these findings, Balzer et al. [36] generated a single-cell resolution rat kidney atlas using scRNA-seq for healthy and diabetic samples. They used machine learning tools like Tensorflow to identify phenotype-relevant cell types associated with kidney fibrosis development, revealing significant parallels between the ZSF1 rat model of diabetic kidney disease (DKD) and human DKD at both the phenotypic and transcriptomic levels.

Meanwhile, Abedini et al. [37] presented a comprehensive, spatially resolved human kidney atlas integrating single-cell omics data from a wide array of kidney tissue samples with varying degrees of disease severity. The researchers identified novel cell types, determined cell-type-specific changes in disease states, and characterized the gene expression program of cells previously only defined by their spatial location. Their study highlighted the cellular and architectural complexity of kidney fibrosis and proposed a comprehensive understanding of the fibrotic microenvironment. This includes not just matrix accumulation but also the diverse cellular interactions. They identified various types of injured tubular (iPT) cells and unique gene expression markers shared among them. They also discovered interactions between immune and stromal cells, implicated in the progression of fibrotic diseases.

Additionally, the team demonstrated the predictive value of the fibrotic microenvironment gene signature (FME-GS) score in identifying patients at risk of end-stage renal disease, even when traditional fibrosis scores were of limited predictive value [37]. A key finding was the differentiation of various stromal cell types involved in fibrotic diseases, which are a significant global health concern. They identified novel markers, new stromal cell types, and defined their spatial locations, offering potential targets for therapeutic intervention in kidney fibrosis.

Linking GWAS and Single-Cell Studies

The combination of GWAS and scRNAseq can shed light on the cell-type-specific impacts of genetic variations and unravel the underlying mechanisms of diseases; therefore, it is extremely powerful tool to translate GWAS studies into disease-causing cell types, pathways, and mechanism (Fig. 2).

GWAS is efficient at identifying genetic variants associated with disease risks but often struggles with singling out the causal genes or cell types. In contrast, scRNA-seq helps decode the transcriptome of individual cells, thereby facilitating a cell-by-cell examination of gene expression. This heightened resolution proves indispensable for dissecting heterogeneous tissues like the kidney and studying their unique transcriptional landscapes at an individual cell level.

When we integrate GWAS and scRNA-seq data, it becomes possible to associate disease-linked variants with specific cell types and gene expression alterations. Such integration can illuminate the cell types impacted by risk variants and the genes whose expression these variants influence [21]. Moreover, it provides a way to characterize the cell-type-specific transcriptomic changes associated with genetic risk variants, thereby deepening our understanding of the cellular context of genetic risk factors.

The study conducted by Liu et al. is a significant stride in precision medicine, leveraging snATAC-seq data from six adult human kidney samples to identify kidney cell types that are causally related to particular traits. Their analysis of open chromatin in over 57,000 cells revealed that the accessible regions specific to collecting duct principal cells and endothelial cells showed enrichment for systolic blood pressure GWAS [23].

The team used the snATAC-seq data also to prioritize target genes for eGFR GWAS variants. They discovered that most of these GWAS variants were situated in PT-specific open chromatin regions. Employing single-cell chromatin co-accessibility analysis, they identified more than 500 target genes associated with nearly 800 eGFR GWAS loci. A striking example is the UMOD locus, where variants exhibited a strong GWAS association, with most showing co-accessibility with the UMOD promoter, indicating that the genetic variants likely regulate UMOD expression [23].

Several new statistical methods being developed to systematically link GWAS with scRNAseq analysis [38–41]. A method called sc-linker, integrated single-cell RNA sequencing data from multiple tissues, epigenomics, and GWAS summary statistics (Fig. 2) [40]. The goal was to identify disease-critical cell types and cellular processes for a variety of diseases and complex traits. This method defines gene programs for a disease state or a cellular process, associates these genes with SNPs that regulate them, and applies a linkage-disequilibrium-aware regression model to connect the SNP annotations to diseases or traits. This technique facilitates a more refined analysis of different cell types, subtypes, diseased cell states, and cellular processes, while still prioritizing specific genes and gene sets for further investigation. Another new method is scGWAS, which effectively leverages scRNA-seq data to infer the cell types in which the disease-associated genes manifest and to construct cellular modules which imply disease-specific activation of different processes. Several other tools are being developed for efficient integration of GWAS and cell type gene regulation or open chromatin information.

The Key Role of Kidney PT Cells and eGFR Regulation

Liu et al. [23] analyzed the genetics of kidney function in humans, utilizing a combination of eGFRcre GWAS, human kidney eQTLs, meQTLs, and human kidney single-cell open chromatin and expression data. The study revealed that DNA methylation can account for a larger fraction of kidney disease GWAS heritability than gene expression, adding to the existing knowledge that tissue eQTL information only explains a modest proportion of GWAS trait heritability.

The incorporation of cell-type epigenome data, such as human kidney snATAC-seq, markedly enhanced the precision in identifying causal cell types, target genes, and variants [42–44]. Researchers observed significant heritability enrichment mediated by kidney methylation in PT-specific accessible regions for kidney function traits [23]. The unique genetic and epigenetic regulation in these cells, unveiled by the integrated analysis, positioned these cells at the center for disease development.

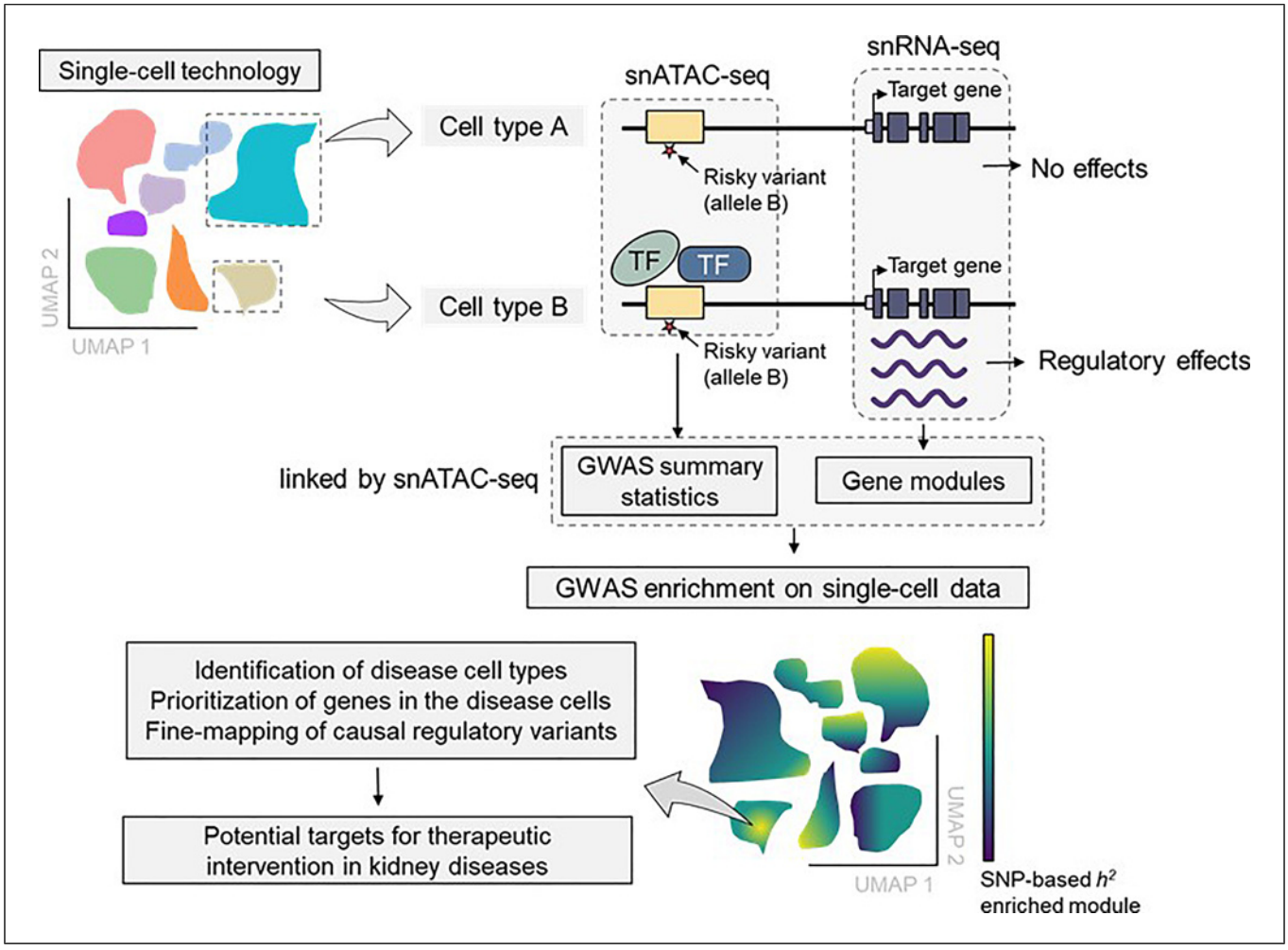

Fig. 2. Utilization of single-cell technologies to decipher cell-type-specific impacts of genetic variations and uncover mechanisms of kidney diseases. This figure presents the potential of single-cell technologies in studying the cell-type-specific effects of genetic variants, especially noncoding ones. Noncoding variants can significantly impact gene regulation in certain cell types while exerting minimal or no effect in others. These differences can be attributed to the alterations in chromatin accessibility at cell-type-specific regulatory elements, reshaping the transcriptional landscape of target genes. Single-cell transcriptomic profiling is highlighted as a crucial tool for examining these variant effects at an unprecedented resolution. The figure further suggests the utility of epigenomic data, such as single-nucleus assay for transposase-accessible chromatin using sequencing (snATAC-seq), for mapping these variants to their respective target genes. The integration of heritability-based analyses with single-cell transcriptomic data is underscored, demonstrating its ability to systematically link single-cell transcriptomes and GWAS associations. This integrative approach facilitates the identification of disease-relevant cell types, causal genes, and potential therapeutic targets, providing a powerful resource for kidney disease research.

The advancement of single-cell epigenomics, crucial for cataloging candidate *cis*-regulatory elements (cCREs); however, they face several challenges [45]. Currently, the under-sampling of rare cell types hampers the comprehensive identification of cCREs. The classification of cell subtypes and states relies heavily on computational methods, necessitating additional molecular validation for accuracy. The interpretation of disease-associated variants is limited by the small sample sizes in current studies and a lack of diverse contextual data across different populations and conditions. Moreover, the primary focus has been on profiling accessible chromatin, missing out on other critical epigenomic layers, e.g., histone modification or methylation. The emerging field of CRISPR-based therapeutics stands to benefit significantly from improved

cCREs annotation, which would enhance the design of interventions targeting specific noncoding regions associated with diseases. Despite the outlined challenges, integrating data across different studies and improving existing methodologies, alongside novel machine learning applications, can progressively bridge these gaps, opening avenues for better understanding and therapeutic targeting of various diseases.

Despite the important limitations, the convergence of various research methodologies highlighted key cellular pathways implicated in kidney dysfunction, notably pyroptosis and ferroptosis [44]. Pyroptosis and ferroptosis, are forms of programmed cell death, are implicated in a host of pathological conditions, including kidney diseases [44, 46]. Through our integrated analysis, we discovered the enrichment of genes in these pathways in PT cells during kidney disease GWAS studies, indicating their potential as appealing therapeutic targets [42]. As PT cells are the most common cell types in the kidney future studies with larger sample sizes will be essential to evaluate the role of other cell types. For example, podocyte specific single-cell multiomics studies are likely to be important for interpretation of genes and variants associated with proteinuria.

Overall, this multidimensional approach not only revealed the crucial role of PT cells and the pyroptosis and ferroptosis pathways in kidney disease, but also underscored the importance of integrating studies to fully understand the pathogenesis of complex diseases. This understanding paves the way for the development of targeted therapies aimed at these key elements, offering hope for more effective treatment strategies for kidney disease.

Conclusion

By leveraging a comprehensive approach that integrates GWAS, quantitative trait loci (QTL) analysis, and single-cell transcriptomic and epigenetic data, we have spotlighted the central role of PT cells in kidney function and kidney disease development [21, 23]. Furthermore, we have identified two pivotal pathways – pyroptosis and ferroptosis – as significant factors in PT cells for eGFR heritability. These insights stem from a finely tuned convergence of genetic, epigenetic, and transcriptional data, unmasking the intricate interplay of these elements in the pathophysiology of kidney disease [44]. Our findings underscore the tremendous potential of integrated omics research in deciphering complex disease mechanisms and illuminate promising new paths for the development of targeted therapeutic strategies.

Conflict of Interest Statement

The Susztak laboratory is supported by Boehringer Ingelheim, Regeneron, Bayer, GSK, ONO Pharma, Gilead, and Novo Nordisk for work that is not related to the current manuscript.

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Author Contributions

J.L., E.H., S.L., and K.S. wrote the manuscript.

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