

Decoding cardio-kidney-metabolic disease networks: A proteogenomic roadmap to precision therapeutics



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The emerging paradigm of cardio-kidney-metabolic (CKM) diseases as interconnected pathophysiological entities has been revolutionized by this comprehensive multi-omics investigation by Hirohama et al.,¹ which demonstrates that tissue-specific proteomics provides unique mechanistic insights beyond conventional genomic and transcriptomic approaches.² By integrating whole-genome sequencing, RNA sequencing, and proteomics analysis of 337 human kidney samples with Bayesian co-localization and Mendelian randomization analyses across 36 CKM genome-wide association studies, this study identifies 89 prioritized proteins that illuminate previously unrecognized molecular bridges connecting cardiovascular, renal, and metabolic dysfunction. The discovery of kidney-specific roles for proteins such as angiopoietin-like protein 3 in lipid metabolism and renal function, alongside charged multivesicular body protein 1A in hypertension and kidney disease, exemplifies how tissue proteomics can unveil organ-specific contributions to systemic disease networks that are invisible to blood-based biomarker studies. This proteogenomic approach represents a critical methodological advancement in precision medicine, as it provides a systematic framework for identifying targetable therapeutic mechanisms by triangulating evidence from genetic susceptibility loci, tissue-specific gene expression patterns, and protein abundance levels—thereby offering a more complete molecular portrait of CKM disease interconnectivity that could inform the development of multi-target therapeutic strategies for the one-third of the global population affected by these devastating and economically burdensome conditions.

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