Asia Pacific Science Press

Asia Pacific Journal of Clinical Medical Research
ISSN(O):3079-8345
ISSN(P):3079-8337
Vol. 1 No.2 (2025)

Metabolite-Chromatin Interaction Network Drives Kidney Regeneration: The Coordinated Regulation of Succinate/H3K9ac and α-KG/TET Demethylation

Peng Lu[1]*, Lei Zhang[1], Jingjing Fan[2], Jin Xing[3], Li Xu[1], Yan Sun[1]

1.Department of Clinical Laboratory, Cangzhou Central Hospital, Cangzhou, 061000, China;
2.Department of Emergency ICU, Cangzhou Central Hospital, Cangzhou, 061000, China;
3.Department of Nephrology, Cangzhou Central Hospital, Cangzhou, 061000, China

Corresponding author: Peng Lu

Abstract: As the "fourth messenger" of epigenetic regulation, metabolites playa spatiotemporally specific regulatory role in kidney regeneration by dynamically reshaping the state of chromatin modifications. This review systematically expounds the coordinated mechanism of the dual axes of succinate/H3K9ac and α-ketoglutarate (α-KG)/TET enzymes: Succinate activates regeneration-related genes by regulating histone acetylation (H3K9ac), while α-KG relieves the epigenetic repression of the Wnt pathway through TET-mediated DNA demethylation. The dynamic balance between the two maintains epigenetic plasticity. Multi-omics integration strategies (such as Gaussian graphical models and deep learning frameworks) and single-cell epigenetic tracking technologies (such as spatial metabolomics) have revealed the regulation of metabolite gradients on cellular heterogeneity and the immune microenvironment. The coordinated application of metabolite precursor supplementation (such as NAD precursors) and dynamic monitoring systems (such as isotope tracing and artificial intelligence models) has promoted the shift of metabolic medicine from the "static replacement" paradigm to the "dynamic reshaping" paradigm. However, technical bottlenecks (such as insufficient multimodal integration) and clinical translation pitfalls (such as challenges in standardized production) still need to be overcome. In the future, through the development of "metabolism-immunity" co-regulatory strategies and intelligent closed-loop systems, it is expected to achieve precise interventions for kidney regeneration and disease treatment.

Keywords: Metabolite-Epigenetic Interaction; Succinate/H3K9ac; α-KG/TET Enzymes; Renal Stem Cells
Published: May 15, 2025
DOI: https://doi.org/10.62177/apjcmr.v1i2.316

Background Reconstruction: Breakthrough in the Traditional Understanding of Metabolic-Epigenetic Cross-Regulation

New Understanding of the Dilemma in Kidney Regeneration

The traditional view holds that the limited regenerative capacity of the kidney is mainly attributed to the irreversible damage of terminally differentiated cells or the exhaustion of the stem cell pool. However, recent studies have revealed the central role of the dynamic interaction between metabolic reprogramming and epigenetic regulation in kidney regeneration. Kidney cells undergo significant metabolic adaptive changes after injury. For example, proximal tubule epithelial cells shift from fatty acid

oxidation to glycolysis. This metabolic reprogramming not only affects energy supply but also directly regulates epigenetic modifications through the accumulation or depletion of metabolic intermediates, forming a "metabolic memory" effect [1]. Single-cell multi-omics analysis shows that the metabolic heterogeneity of different cell subsets (such as fibroblasts, immune cells, and epithelial cells) during kidney repair significantly affects their epigenetic remodeling trajectories, leading some cells to enter a profibrotic or senescent state [2]. Notably, persistent mitochondrial dysfunction (such as a decrease in NAD+ levels) in chronic kidney disease (CKD) can inhibit the activity of histone deacetylases (HDACs), induce a persistent open chromatin state of pro-inflammatory genes, and ultimately form the molecular basis of "irreversible repair" [3].

Metabolites as the Fourth Messenger of Epigenetic Regulation

The classical signal transduction paradigms (such as hormones and cytokines) can no longer fully explain the dynamic regulation of the genome by the metabolic environment. Emerging evidence indicates that metabolic intermediates act as the "fourth messenger" of epigenetic regulation through multiple mechanisms and play a key role in spatiotemporally specific regulation of chromatin modifications and gene expression.

Metabolites can directly serve as substrates or regulatory factors of chromatin-modifying enzymes, dynamically affecting the state of epigenetic modifications. For example, α-ketoglutarate (α-KG) is an essential cofactor for TET dioxygenases and JmjC demethylases. Changes in its concentration gradient can regulate the processes of DNA hydroxymethylation and histone demethylation, thereby regulating the expression of genes related to kidney development (such as Pax2 and Six2) [4]. In contrast, succinate and fumarate competitively inhibit the activity of TET enzymes, induce DNA hypermethylation, and inhibit the expression of regeneration-related genes (such as Klotho), suggesting the importance of metabolite concentration balance for epigenetic plasticity [5]. In addition, the spatiotemporal specificity of nuclear metabolic pathways provides a precise regulatory basis for local epigenetic modifications. The newly discovered nuclear tricarboxylic acid cycle (nTCA) can directly support the chromatin modification activities of histone acetyltransferases (such as p300) and the PARP family by locally generating acetyl-CoA and NAD+. This "metabolic compartmentalization" mechanism enables kidney cells to quickly respond to microenvironmental changes. For example, after ischemia-reperfusion injury, the rapid recruitment of nuclear citrate synthase (CS) can enhance H3K27ac modification, activate regeneration-related enhancers (such as Hippo pathway regulatory elements), and promote tissue repair [6].

Metabolites can also drive non-classical epigenetic modification mechanisms, expanding the diversity of epigenetic regulation. Gut microbiota metabolites short-chain fatty acids (SCFAs) regulate the epigenetic immune memory of kidney macrophages through the dual effects of inhibiting histone deacetylases (HDACs) and activating G protein-coupled receptors (GPCRs), affecting the resolution of inflammation and the fibrotic process [7]. On the other hand, the urea cycle intermediate arginine promotes the transcription of genes related to the proliferation of renal tubular epithelial cells through H4R3me2 modification mediated by arginine methyltransferases (PRMTs), revealing a new mechanism of the coordinated regulation of cell fate by metabolic reprogramming and epigenetics [8]. These findings together indicate that metabolites, as the fourth messenger, tightly couple microenvironmental signals with genomic responses through a multi-dimensional and dynamic epigenetic regulatory network, providing a new perspective for understanding the role of metabolic-epigenetic interactions in physiological and pathological processes.

Breakthrough Discoveries

In diabetic nephropathy, abnormal adenine metabolism has been found to disrupt epigenetic homeostasis through a dual mechanism - on the one hand, by consuming S-adenosylmethionine (SAM) to limit the activity of DNA methyltransferases (DNMTs), and on the other hand, by activating the AMPK/mTORC1 signaling axis to reshape chromatin accessibility, ultimately leading to podocyte dedifferentiation and thickening of the basement membrane [9]. This discovery provides direct pathological evidence for metabolic-epigenetic cross-regulation [10]. In summary, metabolites, as the "fourth messenger" of epigenetic regulation, play the role of a spatiotemporally specific regulatory hub in kidney regeneration by integrating microenvironmental signals and genomic responses. Dual-target intervention strategies targeting metabolic enzymes (such as IDH1/2, ACLY) or epigenetic modifiers (such as HDAC inhibitors, BET protein inhibitors) are expected to break through the

dilemma of kidney regeneration [11].

Core Mechanism: The Coordination of Dual Pathways in Metabolite-Driven Chromatin Remodeling

The Succinate/H3K9ac Axis: Turning on the Epigenetic Switch of Regeneration

As a key intermediate metabolite of the tricarboxylic acid cycle (TCA), succinate directly participates in chromatin remodeling by regulating histone acetylation modification (H3K9ac). Studies have shown that the enrichment of H3K9ac is closely related to chromatin openness and gene transcription activation. For example, during the determination of cell fate, succinate affects the activity of histone acetyltransferases (such as GCN5) by regulating the production of acetyl-CoA, thus promoting the deposition of H3K9ac in the promoter or enhancer regions of specific genes [12,13]. This "switch" function of epigenetic modification is particularly important in regenerative medicine. For instance, when pluripotent stem cells differentiate into specific lineages, the dynamic changes of H3K9ac can activate regeneration-related genes (such as genes in the Wnt pathway), providing an epigenetic basis for tissue repair [14,15]. In addition, succinate also indirectly enhances the stability of H3K9ac by inhibiting the activity of α-KG-dependent demethylases (such as TET), forming a positive regulatory loop [16,17].

The α-KG/TET Axis: Unlocking the Epigenetic Repression of the Wnt Pathway

As an essential cofactor for TET dioxygenases, α-ketoglutarate (α-KG) relieves the epigenetic repression of key genes in the Wnt pathway by regulating the processes of DNA hydroxymethylation (5hmC) and demethylation. TET enzymes generate 5hmC by oxidizing 5-methylcytosine (5mC), promoting the relaxation of the chromatin structure and the binding of transcription factors (such as RUNX2) [18,19]. In tumor and developmental models, the depletion of α-KG leads to the inhibition of TET activity, which in turn causes the DNA hypermethylation and silencing of genes in the Wnt pathway (such as β-catenin target genes) [20,21]. Conversely, exogenous α-KG supplementation can restore TET function, unlock the "epigenetic repression" of Wnt signaling, and drive cell proliferation and differentiation [22,23]. It is worth noting that α-KG also forms an antagonistic effect with the H3K9ac axis by regulating the activity of histone deacetylases (HDACs), jointly maintaining epigenetic homeostasis [24,25].

The Spatiotemporal Kinetics of the Coordination of the Dual Axes

The coordinated action of the dual axes of succinate and α-KG exhibits dynamic balance and complementary characteristics in the spatiotemporal dimension. During early embryonic development or tissue regeneration, the succinate-driven H3K9ac axis preferentially activates the transcription of regeneration-related genes, while the α-KG/TET axis maintains chromatin plasticity through demethylation, ensuring the continuous activation of developmental pathways such as Wnt [26,27]. For example, in the differentiation of neural stem cells, the rapid deposition of H3K9ac and TET-mediated DNA demethylation occur at different time peaks, corresponding to the gene initiation and expression maintenance stages respectively [28,29]. Spatially, the compartmentalized distribution of nuclear metabolites (such as the enrichment of α-KG in heterochromatin regions) further enhances the specific regulation of the dual axes [30,31]. In addition, metabolic stress (such as hypoxia or nutrient deficiency) will disrupt the balance of the dual axes, leading to epigenetic disorders: the accumulation of succinate inhibits TET activity, and at the same time, excessive acetylation of H3K9ac triggers abnormal gene activation, and this phenomenon is particularly significant in tumorigenesis and aging [32,33].

The coordinated mechanism of the dual axes driven by metabolites (succinate/H3K9ac and α-KG/TET) closely couples the cellular metabolic state with epigenetic remodeling through spatiotemporal dynamic regulation. This coupling not only provides potential targets for regenerative medicine (such as reprogramming epigenetic switches through metabolic interventions), but also lays a theoretical foundation for understanding the epigenetic-metabolic interaction network in developmental abnormalities and disease progression (such as neurodegenerative diseases and cancers) [34,35,36,37].

Technological Breakthrough: Dynamic Analysis of the Metabolic-Epigenetic Interaction Network

The interaction between metabolism and epigenetics is a core mechanism for regulating cell fate, but its dynamic analysis

still faces technical bottlenecks. In recent years, breakthroughs in multi-omics integration strategies and single-cell epigenetic tracking technologies have brought revolutionary progress to this field.

Multi-omics Integration Strategies

Multi-omics integration strategies systematically analyze the hierarchical relationships of the network of interactions between metabolism and epigenetics by jointly analyzing multi-dimensional data such as genomics, transcriptomics, epigenomics, and metabolomics, providing important tools for revealing dynamic regulatory mechanisms. The current mainstream strategies mainly include the following three types of methods:

1.The integration of knowledge-driven and data-driven approaches is one of the core paths for constructing the metabolic-epigenetic interaction network. By introducing prior knowledge of biological networks to guide data integration and combining unsupervised dimensionality reduction methods (such as joint low-dimensional embedding) to mine cross-omics associations, the specificity of the analysis can be significantly improved [38]. For example, the network analysis method based on the Gaussian graphical model (GGM) can jointly analyze methylation and transcriptome data, and accurately identify gene modules regulated by metabolites. An example is the coordinated regulatory nodes between the glycolytic pathway and DNA methylation modifications in renal fibrosis [39].

2.The combination of machine learning and metabolic network models has further promoted the construction of cross-scale dynamic models. By using deep learning frameworks to integrate single-cell multi-omics data, the epigenetic remodeling trajectories under metabolic perturbations can be simulated. For example, the integration method based on the variational autoencoder (VAE) can analyze the nonlinear associations between fluctuations in metabolite concentrations and changes in chromatin accessibility, and predict the epigenetic repair pathways driven by α-ketoglutarate after renal ischemia injury [40]. In addition, the construction of hybrid networks by fusing known metabolic-epigenetic interaction relationships with inferred cross-omics associations forms multi-level functional modules. Studies have shown that such hybrid networks can break through the limitations of traditional single omics, discover the synergistic effects between metabolic enzymes (such as IDH1) and chromatin modifiers (such as TET2), and reveal their dual regulatory functions in the occurrence of renal cancer [41,42].

3. Although significant progress has been made in multi-omics integration, data heterogeneity (such as differences in sequencing depth) and nonlinear associations remain major challenges. For example, the differences in the dynamic ranges of metabolomics and epigenomics data may lead to false associations, and more robust standardization and joint modeling algorithms need to be developed to improve the biological interpretability of the results [43]. In the future, combining spatio-temporal resolution technologies with multi-omics dynamic modeling will further improve the quantitative analysis ability of the metabolic-epigenetic interaction network. Single-cell Epigenetic Tracking

The rapid development of single-cell technologies has provided unprecedented spatio-temporal resolution for analyzing the cellular heterogeneity of the interactions between metabolism and epigenetics, enabling researchers to reveal the dynamic regulatory mechanisms of the metabolic microenvironment on epigenetic states at the single-cell level.

Multimodal single-cell sequencing is one of the core tools in current research. New single-cell multi-omics technologies (such as scATAC-seq combined with scRNA-seq) can simultaneously capture chromatin accessibility, DNA methylation, and transcriptome information, and accurately analyze the epigenetic heterogeneity driven by metabolic states [44]. For example, in the study of atherosclerosis, the combined analysis of single-cell epigenetics and transcriptomics revealed the association between macrophage metabolic reprogramming (such as glycolysis activation) and inflammatory epigenetic memory (such as the persistence of H3K4me3 modification), clarifying the molecular basis of metabolites maintaining inflammatory polarization by regulating chromatin states [45]. In addition, the progress of dynamic network inference tools has further promoted the construction of the metabolic-epigenetic interaction network. Algorithms based on generative adversarial networks (GAN) and mutual nearest neighbors (MNN) (such as scCross, DeepMAPS) can integrate cross-modal data, construct cell type-specific metabolic-epigenetic regulatory networks, and simulate the spatio-temporal effects of changes in metabolite concentrations on the activities of chromatin-modifying enzymes [46,47]. These tools have successfully predicted the dynamic trajectory of DNA hypermethylation induced by the succinate gradient through the inhibition of TET enzyme activity in a renal fibrosis model [48,49].

The breakthrough in spatial epigenomics has added a spatial dimension to the study of metabolic-epigenetic interactions. Spatial multi-omics technologies (such as MERFISH combined with epigenetic analysis) can locate the spatial distribution of metabolites in the tissue microenvironment and analyze their interactions with local epigenetic states [50,51]. For example, in the tumor microenvironment, the spatial gradient distribution of lactic acid drives the epigenetic silencing of key genes (such as IFN-γ) in immune cells (such as T cells) by inhibiting the activity of histone deacetylases (HDAC), revealing the regulatory mechanism of the spatial heterogeneity of metabolites on immune escape [52].

Despite the significant progress made in single-cell epigenetic tracking technologies, their limitations cannot be ignored. Data sparsity (such as insufficient detection sensitivity for low-abundance metabolites) and biases in cross-batch integration may mask the true metabolic-epigenetic associations [53,54]. In the future, combining metabolic fluorescent probes (such as NADH sensors) with single-cell metabolomics technologies is expected to achieve real-time dynamic monitoring of metabolite concentrations and epigenetic modification states, providing more accurate tools for analyzing the spatio-temporal specificity of metabolic-epigenetic interactions [55,56].

New Therapeutic Paradigm: Precise Intervention Targeting Metabolite Homeostasis

The dynamic imbalance of metabolic homeostasis is a core pathological feature of various diseases, including metabolic syndrome, cancer, neurodegenerative diseases, etc. In recent years, precise intervention strategies targeting metabolite homeostasis have gradually become a research hotspot. The core of these strategies lies in reconstructing metabolic balance through the supplementation of metabolic precursors, and achieving real-time regulation with the help of dynamic monitoring technologies, thus forming a closed-loop treatment model of “intervention-feedback-optimization”. Metabolic Precursor Supplementation Strategy

The metabolic precursor supplementation strategy provides a new idea for restoring metabolic homeostasis and intervening in the pathological process by exogenously inputting key metabolic intermediates to reshape the disrupted metabolic network in the diseased state. The core of this strategy is to target the “bottleneck nodes” in the metabolic pathway, and reverse metabolic imbalance and activate the repair mechanism by supplementing specific precursor molecules.

NAD precursors (such as nicotinamide riboside NR) are one of the current research hotspots. Supplementing NAD precursors can maintain the inhibitory state of mitochondrial oxidative phosphorylation in hematopoietic stem cells (HSCs) by activating the GCN2 signaling pathway, thereby protecting their long-term self-renewal ability [57]. Clinical studies further show that NAD precursors can improve aging-related metabolic disorders (such as mitochondrial dysfunction) and enhance the ability of DNA damage repair, providing a potential therapeutic strategy for delaying aging-related diseases (such as neurodegenerative diseases) [58]. In addition, as a hub molecule between glycolysis and lipid metabolism, citric acid supplementation can inhibit the abnormal proliferation of tumor cells and restore the homeostasis of energy metabolism. For example, in a renal cancer model, exogenous citric acid inhibits the activity of ATP citrate lyase (ACLY), blocks the lipid synthesis pathway of tumor cells, and at the same time enhances oxidative metabolism to inhibit metastasis [59].

The regulation of amino acid precursors demonstrates the pleiotropy of metabolic intervention. For example, L-arginine (L-arg) affects host protein synthesis and energy supply by regulating immune metabolism (such as nitric oxide synthesis) and the interaction with gut microbiota, and plays a dual regulatory role in metabolic diseases (such as obesity) and immune disorders (such as autoimmune nephritis) [60]. Similarly, serine metabolism is reprogrammed during the aging process, and the supplementation of its precursor can reverse the shift of glycolytic flux and restore the homeostasis of purine metabolism, thereby alleviating aging-related mitochondrial dysfunction [61].

The targeted supplementation of microbial metabolites also provides a unique perspective for the metabolic precursor strategy. Gut microbiota metabolites such as short-chain fatty acids (SCFAs) regulate the host immune-metabolic axis (such as GPR43 receptor signaling), inhibit the release of pro-inflammatory factors and enhance the intestinal barrier function, showing significant curative effects in inflammatory bowel disease and chronic kidney disease [62].

In the future, the metabolic precursor supplementation strategy needs to combine multi-omics technologies to accurately identify disease-specific metabolic nodes and optimize the delivery system to improve targeting. By integrating metabolomics

and epigenetic analysis, the reprogramming effect of precursor supplementation on the metabolic-epigenetic interaction network can be dynamically evaluated, providing a theoretical basis for personalized treatment.

Construction of the Dynamic Monitoring System

The spatiotemporal heterogeneity of metabolic homeostasis requires the deep integration of intervention strategies and real-time monitoring technologies to achieve accurate capture and regulatory optimization of the dynamic changes in the metabolic network.

Stable isotope tracing technology provides a high-resolution tool for analyzing the dynamics of metabolic flux. Through isotope-labeled metabolomics at the whole organism level (such as the fruit fly model), researchers can systematically track the dynamic shifts of metabolic flux during the aging process and reveal key events such as the imbalance of the glycolysis-serine metabolism axis [63]. For example, in aging research, this technology has found that the increased mitochondrial serine efflux leads to the blockage of purine synthesis, which is an important driving factor for aging-related metabolic decline [64]. The breakthrough of non-invasive biosensing technology has promoted the simultaneous monitoring of metabolic-physiological signals. For example, an in-ear multimodal sensor can detect the dynamic association between metabolic markers (such as glucose and ketone bodies) and electroencephalogram signals in real time, capturing the regulatory effect of metabolic fluctuations on neural activities, and providing a new method for the early warning of neurodegenerative diseases such as Alzheimer's disease [65].

Artificial intelligence-driven metabolic prediction models further expand the predictive ability of dynamic monitoring. By integrating GWAS data and multi-omics association analysis (such as the Gene-Metabolite Association Atlas), these models can identify the physiological substrates of uncharacterized metabolites and predict the systems biology effects of intervention targets [66,67]. For example, a deep learning-based metabolic network model has successfully predicted the cascade regulation of host bile acid metabolism by gut microbiota metabolites, providing new targets for the precise intervention of metabolic liver diseases [68,69].

However, the core challenge of the dynamic monitoring system lies in the cascade feedback mechanism of the metabolic network. For example, mitochondrial glutathione (GSH) regulates the expression of its own synthase through a thiol redox sensor, forming a homeostatic loop, and such dynamic systems are difficult to analyze through traditional linear models [70]. To address this problem, it is necessary to develop "metabolic cybernetics" algorithms to integrate and model metabolite concentrations, enzyme activities, and gene regulatory networks to achieve real-time optimization of intervention parameters. For example, a dynamic regulation framework based on reinforcement learning can reverse aging-related metabolic remodeling by feedback regulating the NAD+/NADH ratio [71,72]. In the future, combining multimodal dynamic data (such as single-cell metabolomics and real-time imaging) with adaptive control algorithms will promote the development of the metabolic monitoring system towards the integration of "perception-analysis-intervention", providing a closed-loop regulation solution for disease treatment.

Collaborative Innovation and Future Directions

The collaborative application of the metabolic precursor supplementation strategy and the dynamic monitoring system has shown significant clinical potential, marking the paradigm shift of metabolic medicine from "static replacement" to "dynamic remodeling". For example, in the treatment of non-alcoholic steatohepatitis (MASH), by real-time tracking the cell-specific distribution of metabolic precursors (such as NAD) through a liver organoid model and combining with dynamic data of metabolic flux, the design of the targeted delivery system can be optimized, significantly improving the intervention efficiency [73]. This "monitoring-intervention" linkage strategy provides a new idea for the precise regulation of metabolic diseases.

Future development directions will focus on multi-dimensional technological innovation and interdisciplinary integration: 1. Multi-omics integration monitoring platform: Combining single-cell metabolomics with spatial metabolic imaging technology to analyze the dynamic evolution of metabolic heterogeneity in the tissue microenvironment. For example, spatial resolution metabolomics can reveal the spatiotemporal association between lactic acid and epigenetic silencing of immune cells in the tumor microenvironment, providing a basis for targeted metabolic reprogramming [74,75]. 2. Metabolic-

immune interaction regulation: Exploring the regulatory role of immune-metabolic hub molecules such as STING protein in the delivery of metabolic precursors, and developing dual intervention strategies that target both metabolic pathways and immune checkpoints. Studies have shown that STING activation can enhance the repair effect of NAD precursors on mitochondrial function, providing a new target for metabolic-immune co-regulation [76,77]. 3. Intelligent closed-loop system: Using wearable devices and implantable biosensors to establish an automated intervention system based on real-time feedback of metabolic flux. For example, a closed-loop system based on the linkage of continuous glucose monitoring and an insulin pump has initially achieved personalized metabolic management for diabetic patients [78,79]. This new paradigm not only promotes the theoretical innovation of metabolic medicine but also provides new technical tools for precision medicine. By integrating multi-omics dynamic data, artificial intelligence prediction models, and real-time regulation systems, future metabolic interventions will achieve a leap from "passive correction" to "active remodeling", opening up a broader path for the treatment of complex diseases [80,81].

Challenges and Future Directions

Key Scientific Questions

The core scientific challenges faced by current research mainly focus on two aspects: the analysis of basic mechanisms and the integration of interdisciplinary theories. Firstly, many studies have pointed out that the mechanisms of action of biomedical intervention methods (such as gene therapy and nanodrug delivery systems) have not been fully elucidated. For example, there are still theoretical gaps in the response characteristics of neurons to light stimuli in optogenetic hearing restoration technology [82]. Secondly, there is a lack of the ability to comprehensively analyze biological phenomena across scales. For instance, a unified theoretical framework for the dynamic regulatory mechanism of the extracellular matrix (ECM) in tissue regeneration has not been formed, which directly hinders the development of new biomaterials [83]. In addition, precise regulatory strategies for disease heterogeneity still lack theoretical support at the molecular level. For example, a complete dose-response model has not been established for immunotherapy based on the cGAS-STING pathway [84]. In the future, it is necessary to break through the existing theoretical bottlenecks through multi-omics data integration and computational modeling [85].

Demand for Technological Innovation

Technological iteration is the core driving force for breaking through the transformation bottleneck of metabolic medicine. Currently, key innovations are urgently needed in the following three major fields:

1.The integration of multimodal technologies is an important direction for improving detection capabilities. Traditional unimodal technologies (such as ultrasound or photoacoustic imaging) are difficult to analyze the spatiotemporal dynamics of metabolic networks due to limitations in resolution and functional coverage. Developing new cross-scale detection systems (such as molecular-level coding systems based on DNA self-assembly technology) can significantly improve detection sensitivity and the ability to analyze multiple parameters simultaneously. For example, this technology realizes the single-cell co-localization analysis of metabolite concentrations and epigenetic modification states through the spatial positioning coding of nucleic acid probes, providing a new tool for analyzing metabolic-epigenetic interactions [86].

2.Standardization of the manufacturing process is the key to promoting the clinical transformation of tissue engineering. Although advanced technologies such as 3D bioprinting can construct a biomimetic metabolic microenvironment, there is still a contradiction between printing accuracy and biocompatibility. Establishing a database of dynamic cross-linking parameters (such as the correlation map between the elastic modulus of photosensitive hydrogels and cell viability) can optimize the bioink formula and printing parameters, and achieve the reproducible production of tissue engineering products (such as artificial kidney organoids) [87]. In addition, the integration of intelligent technologies urgently needs to break through the algorithm bottleneck. Although artificial intelligence is widely used in drug screening, it is limited by data quality and complexity (such as the heterogeneity of nanoparticles). Therefore, it is necessary to develop an algorithm framework based on active learning. Such a framework can improve the delivery efficiency by iteratively optimizing the size, surface charge, and metabolic targeting of nanoparticles (NPs) [88].

3. The combination of microfluidic technology and organ-on-a-chip may become a key innovation point for breaking through the limitations of in vitro models. For example, a liver chip integrated with a metabolic sensing unit can simulate pharmacokinetics and monitor the uptake and transformation of metabolic precursors by hepatocytes in real time [89]. In the future, technological innovation needs to take into account interdisciplinary collaboration and clinical applicability. By integrating molecular engineering, artificial intelligence, and biomanufacturing technologies, and constructing a closed-loop system of "design-validation-optimization", the leap of metabolic medicine from basic research to clinical application will be accelerated. Traps in Clinical Transformation

In the process of transformation from the laboratory to the clinic, metabolic medicine faces multiple systemic obstacles, and these challenges run through the entire chain of technology development, verification, and regulation.

The challenge of standardized production is the primary problem restricting the clinical transformation of biomaterials. More than 60% of extracellular matrix (ECM) biomaterials failed to pass preclinical verification due to differences in components between batches, revealing the lack of standardization in raw material purification processes (such as the control of collagen cross-linking degree) and sterilization processes (such as the optimization of γ-ray dosage), resulting in unstable material performance and safety [90].

The limitations of clinical verification are reflected in the disconnection between the model system and the real human environment. For example, the efficacy-toxicity ratio (ETR) of nanodrugs in animal models often significantly differs from the results of human trials. This is mainly due to the insufficient simulation of the immune microenvironment (such as the polarization state of tumor-associated macrophages) in existing disease models (such as mouse tumor xenografts) [91,92].

The complexity of the regulatory path further exacerbates the transformation resistance. Innovative therapies (such as sonodynamic therapy) often face the problem of ambiguous classification due to their novel mechanisms of action, and the traditional regulatory framework is difficult to assess their risk-benefit ratio. Establishing a dynamic regulatory sandbox mechanism (such as conditional marketing authorization) can accelerate the approval process while ensuring safety tracking [93,94]. It is worth noting that the dilemma of clinical trial design caused by patient heterogeneity is becoming increasingly prominent. For example, the efficacy of metabolic precursor intervention may fluctuate due to differences in the composition of the individual gut microbiota. It is necessary to develop dynamic enrollment criteria based on real-world data (such as electronic health records and multi-omics integration) to balance the speed of innovation and safety [95,96].

Future breakthrough directions need to focus on systematic solutions:

1.Construct a "technology-clinic-industry" tripartite collaborative platform: Through the pre-verification database sharing mechanism (such as the organ-on-a-chip verification platform), integrate organoid models and clinical data to reduce transformation risks. For example, a kidney chip can simulate pharmacokinetics and predict the distribution and clearance efficiency of nanoparticles in the human body [97,98].

2. Strengthen the closed-loop feedback between computational medicine and experimental medicine: Use digital twin technology to construct patient-specific metabolic models and dynamically optimize treatment plans. For example, a digital twin system based on individual metabolic flux data can predict the remodeling effect of NAD precursor supplementation on mitochondrial function and guide precise dosage adjustment [99,100]. These strategies will promote the evolution of metabolic medicine from an "experience-driven" to a "data-driven" transformation mode, providing systematic support for breaking through the traps in clinical transformation.

Design of the Combination Points for the Review

The deepening of metabolic medicine research requires directly addressing the contradictions within the existing theoretical and technical systems, and integrating innovative research paradigms from a multi-dimensional perspective. Analyzing contradictory evidence is the starting point for theoretical breakthroughs. For example, the Wnt signaling pathway exhibits dual roles in tissue repair and fibrosis: its repair-promoting function depends on β-catenin-mediated cell proliferation, while the pro-fibrotic effect is associated with the abnormal activation of the DKK3 protein [101]. The latest research shows that the dynamic regulation of metabolite gradients can reconcile this contradiction—α-ketoglutarate (α-KG) inhibits the DNA methylation modification of the DKK3 gene by activating the TET2 enzyme, thus spatially limiting the fibrotic tendency

of the Wnt pathway [102]. Based on such findings, this paper proposes a theoretical model of the "metabolite buffer pool", emphasizing that succinate and α-KG regulate the epigenetic modification thresholds (such as histone acetylation/DNA methylation) through dynamic balance, forming a buffer system that maintains epigenetic plasticity. For instance, in renal ischemia-reperfusion injury, the increase in succinate concentration competitively inhibits the α-KG/TET2 axis, reducing the rate of DNA demethylation. At the same time, it promotes histone deacetylation mediated by HDACs, forming a pro-fibrotic epigenetic memory.

Criticizing technical limitations points the way for methodological innovation. Although existing chromatin analysis technologies (such as CUT&Tag) can locate stably bound chromatin-modifying enzymes, they are unable to capture transient metabolite-chromatin interaction events. Developing in-situ metabolite labeling technologies based on click chemistry (such as metabolite-PROTAC probes), combined with single-molecule imaging, is expected to elucidate the dynamic regulatory mechanism of metabolite fluctuations on the three-dimensional structure of chromatin.

Reconstructing the clinical pathway requires driving the upgrading of treatment strategies with mechanism innovation. Traditional broad-spectrum HDAC inhibitors often lead to severe side effects due to the lack of tissue specificity. However, designs based on the regulatory patterns of metabolites (such as succinate analogs) can achieve specific inhibition of local HDACs. For example, a succinate prodrug targeting the proximal tubules of the kidney can selectively inhibit the fibrosis-related HDAC4/5 subtypes while preserving the physiological functions of HDACs in other tissues [103]. This "metabolic-epigenetic targeting" strategy will promote the transformation of clinical treatment from extensive intervention to precise regulation.

Summary and Prospect

Metabolites dynamically couple the cellular metabolic state with the genomic response by regulating the epigenetic network (such as H3K9ac and DNA methylation), providing a new perspective for kidney regeneration. The coordinated mechanism of the dual axes of succinate and α-KG reveals the molecular basis of metabolite gradients balancing repair and fibrosis in the spatiotemporal dimension [104,105]. Breakthroughs in multi-omics technologies and single-cell tracking have provided high-resolution tools for analyzing the heterogeneity of the metabolic-epigenetic interaction network [106,107]. The combination of metabolic precursor supplementation (such as NAD and citric acid) and real-time monitoring systems marks the evolution of metabolic intervention towards a closed-loop regulation mode [108,109].

However, current research still faces multiple challenges: at the technical level, the dynamic analysis of transient metabolite-chromatin interactions requires the development of new in-situ labeling technologies (such as click chemistry probes); in clinical translation, the lack of standardization of biomaterials and the insufficient biomimesis of disease models limit the reliability of treatment strategies [110,111]; the refinement of the metabolic-immune interaction mechanism and the dose-response model still needs to be further explored [112,113]. Future directions should focus on: the integration of multimodal technologies (such as the combination of organ-on-a-chip and metabolic sensing units) to improve the spatiotemporal resolution of dynamic monitoring of the metabolic network [114,115]; the development of "metabolic-epigenetic-immune" triple-targeting strategies, such as coordinated interventions based on the STING pathway [116]; the construction of a "digital twin-real-time feedback" system to achieve personalized metabolic remodeling [117,118]. Through interdisciplinary collaboration and technological innovation, metabolic medicine is expected to break through the regeneration dilemma and open up new paths for the precise treatment of chronic kidney disease and aging-related diseases [119,120].

Funding

This study was funded by Medical Science Research Project of Hebei (No.20220364).

Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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