AKI and Genetics: Evolving Concepts in the Genetics of Acute Kidney Injury: Implications for Pediatric AKI

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Abstract

Keywords

- ▶ acute kidney injury
- ▶ genetics
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In spite of recent advances in the field of acute kidney injury (AKI) research, morbidity and mortality remain high for AKI sufferers. The study of genetic influences in AKI pathways is an evolving field with potential for improving outcomes through the identification of risk and protective factors at the individual level that may in turn allow for the development of rational therapeutic interventions. Studies of single nucleotide polymorphisms, individual susceptibility to nephrotoxic medications, and epigenetic factors comprise a growing body of research in this area. While promising, this field is still only emerging, with a small number of studies in humans and very little data in pediatric patients.

Introduction

Acute kidney injury (AKI) is a complex condition that is defined by rapid deterioration of kidney function. AKI is highly prevalent, occurring in one of three hospital admissions for children, associated with a mortality rate of 13.8%.¹ Critically ill patients who suffer AKI episodes have increased morbidity, with prolonged hospital stay and ventilation time.^{2,3} Furthermore, AKI survivors are at risk for progression to chronic kidney disease (CKD) and end-stage renal disease (ESRD).^{4,5} We need to better understand modifiable risk factors to develop prevention strategies and improve outcomes.

There have been major advances in the field of AKI. Using standardized diagnostic criteria (AKIN,⁶ RIFLE,⁷ KDIGO⁸) has allowed for comparisons between and across studies. Urine and plasma biomarkers (NGAL, IL-18, KIM-1, LFABP) are being studied to enhance real-time diagnosis of renal tubular injury and overcome the limitations of serum creatinine. Renal replacement therapy is increasingly utilized for management of fluid overload and renal failure. In spite of all these advances, however, there is no definitive treatment for AKI other than avoidance of further renal injury by

maintaining renal perfusion and limiting exposure to nephrotoxins.

The natural history of AKI is difficult to anticipate at the individual patient level owing to clinical heterogeneity and interacting risk factors such as nephrotoxic medications and preexisting comorbidities. Presented with the same clinical risk factors, patients can have divergent AKI paths.

These patient-level variabilities have prompted interest in genetic variations that may impact individual susceptibility. Advancements in the understanding of AKI pathophysiology in ischemia–reperfusion, sepsis, cardiac surgery, and drug toxicity have led to the study of genetics in AKI. Techniques for studying candidate genes include targeted studies of specific single nucleotide polymorphisms (SNPs) and genome-wide association studies (GWAS). Recently, epigenetic studies in animal models have shown that chromatin biology (chromatin organization, DNA methylation, and histone modification) may also play a role in AKI.⁹

Emerging evidence from genetic studies in AKI comes primarily from animal models, with a subset of clinical studies of mostly adult patients, with limited involvement of pediatric patients. Extrapolating adult-based studies in

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genetics for the pediatric population is not well described, thus limiting our understanding of genetic contributions to pediatric AKI development. Our objective is to review the current knowledge of genetic and epigenetic factors that influence AKI focusing on the implications of this complex syndrome in children.

Candidate Genes Associated with AKI in Critically Ill Patients

Advancements in the understanding of the cellular and molecular pathophysiology of AKI pathways have propagated targeted studies of candidate genes. There are two recent systematic reviews of genetic determinants of AKI.^{10,11} A small number of studies have identified SNPs that confer protective or increased risk for AKI in critically ill adult patients. Genes of interest include angiotensin-converting enzyme insertion/deletion (ACE I/D), tumor necrosis factor- α (TNF- α), and interleukin-10 (IL-10). See **Table 1** for summary of these genes and their functions. However, the function of these SNPs is not easily replicated, yielding conflicting results. Variations in sample population, AKI definitions, or outcome measures create challenges for comparing results across studies. Here, we summarize the small body of research on genetic polymorphisms in the pediatric population, all of which arises from one European center in very low-birth-weight (VLBW) neonates. We mention other AKI genetic research based on adults that may be relevant to children.

Critically Ill Neonates

Perinatal hypoxic ischemic injury and vasomotor nephropathy are important causes of AKI in the neonatal population.^{12,13} Fekete et al¹⁴ examined the association between genetic polymorphisms of heat shock protein 70 (HSP73 and HSP72) and AKI in VLBW infants. HSP plays an important role in renal recovery following ischemic injury by folding, repairing, and degrading proteins.¹⁵ The authors identified 37 of 130 VLBW infants who developed AKI (serum creatinine > 1.36 mg/dL and/or serum urea > 25 mg/dL and/or urine output < 1 mL/kg/hour). Infants carrying the HSP72 (1267) GG genotype, a variant with low gene expression, had an increased risk of AKI (odds ratio [OR]: 3.17; 95% confidence interval [CI]: 1.34–7.45; $p < 0.01$), adjusting for sepsis, patent ductus arteriosus, necrotizing enterocolitis, severe hypotension, and respiratory distress.

This group also studied role of vascular endothelial growth factor (VEGF) polymorphisms in the same population.¹⁶ VEGF is upregulated during ischemia and is important for angiogenesis and endothelial cell survival¹⁷ among others. Reduced VEGF expression following ischemic injury has been associated with endothelial cell transformation into fibroblasts rather than repair.¹⁸ Carriers of the VEGF-2578AA genotype, predisposing to low VEGF production, were underrepresented in the LBW infants with AKI compared with healthy controls ($p = 0.021$, adjusted OR [95% CI]: 0.2 [0.05–0.78]) after controlling for gestational age, sepsis, and other AKI risk factors. However, this genotype was also associated with increased risk for NEC.

Finally, Nobilis et al¹⁹ evaluated the impact of ACE and angiotensin type 1 receptor (AT1) gene variants on neonatal AKI. The renin–angiotensin–aldosterone system (RAAS) plays a primary role regulating renal blood flow and glomerular filtration rate in both the fetus and newborn.²⁰ The ACE I allele is associated with lower ACE activity, and the AT1RC¹¹⁶⁶ variant is associated with impairment of vasoconstriction, findings that suggest these polymorphisms might confer additional AKI risk. Thirty-eight percent (42/110) of their patients developed AKI (same criteria as in the previous studies). Although there is a plausible association between ACE I/D variants and AKI, there was no allelic frequency difference between those with or without AKI. Traditional AKI risk factors such as sepsis, hypoxemia, and APGAR scores were different between the two groups. Furthermore, there were many severely ill neonates who died before their blood could be collected. This study highlights the potential challenges in studying AKI genetics in a clinical sample.

Based on these limited studies from one center with considerable overlap in sample population, there is inconclusive evidence to determine associations between genetic polymorphisms and AKI in VLBW infants.

Sepsis-Associated Acute Kidney Injury

Sepsis is a major risk factor for AKI and mortality in both adult²¹ and pediatric^{22,23} populations. The pathophysiology in sepsis-associated AKI is recognized to be different from that of ischemia–reperfusion,²⁴ and likely involving a different gene cluster. One neonatal study evaluated the impact of polymorphisms of proinflammatory cytokines on AKI in a sample of VLBW infants with infection.²⁵ Out of 92 infants, 38 (41%) infants developed AKI; 25% had culture-proven sepsis, with no differential proportions between the AKI and no AKI groups. The AKI group had on average one more traditional AKI risk factor than the non-AKI group (2.97 vs. 1.96; $p < 0.05$). There was no difference in allelic frequencies between the two groups nor between study patients and healthy reference population. The authors identified that having polymorphic alleles in *both* TNF- α and IL-6 (TNF- α /IL-6 AG/GC or AG/CC haplotype) was more common in the AKI versus non-AKI infants (26 vs. 6%, $p < 0.01$) and this was associated with an increased risk for AKI (OR: 8.6, 95% CI: 1.2–63.5), even after adjusting for other traditional AKI risk factors. The authors conclude that carriage of several alleles together instead of any one single allele confers higher risk for AKI. This concept that multiple genes across multiple pathways are likely involved is well recognized and will be discussed further below.

Two studies have evaluated genes of interest in samples of adult patients with sepsis. Henao-Martínez et al²⁶ evaluated SNPs for genes in the Hedgehog pathway in a sample of 250 adults with *Enterobacteriaceae* bacteremia. The Hedgehog pathway is important for organ injury repair and is associated with protection from bacterial sepsis. SNPs in the suppressor of fused homolog (SUFU) gene, a negative regulator of the Hedgehog pathway, correlated with improved renal function (rs10786691, rs12414407, rs10748825, rs7078511) in multivariate analysis.

Table 1 Representative targets for genetic study in acute kidney injury pathways

<i>Candidate gene/factor</i>	<i>Function</i>
Single nucleotide polymorphism studies	
Apolipoprotein E (APO E)	Important role in lipoprotein metabolism; role in acute kidney injury may be related to modulation of the inflammatory cascade ^{62–64}
Angiotensin-converting enzyme (ACE I/D)	Key regulator of renal blood flow and maintenance of glomerular filtration rate, especially in newborn infants. ACE I/D polymorphism influences level of expression of ACE ^{19,27,64,65}
Angiotensin type 1 receptor (AT ₁ R)	Mediates the vasoconstrictor effect of ACE ¹⁹
B cell CLL/lymphoma 2 (BCL2)	Antiapoptosis protein active in acute kidney injury pathway ²⁸
Catalase	Enzyme with protective role from reactive oxygen species/oxidative stress ⁶⁶
Catechol-O-methyltransferase (COMT)	Enzyme involved in the deactivation of catecholamines in the proximal tubule and thick ascending limb of loop of Henle ⁶⁷
Endothelial nitric oxide (eNOS)	Vasodilator involved in regulation of renal medullary blood flow ⁶⁸
Erythropoietin (EPO)	Stimulates antiapoptotic pathways, including upregulation of HSP70, and reduction of proinflammatory markers such as TNF- α ³⁰
Heat shock proteins (HSP72 and HSP73)	Role in refolding disrupted proteins, aiding in the folding of newly synthesized proteins, and degrading irreparably damaged proteins and toxins to prevent further accumulation ¹⁴
Hedgehog pathway	Role in organ injury repair; associated with protection from bacterial sepsis ²⁶
Hypoxia-inducible factor-1 α (HIF-1 α)	Transcription factor that activates transcription of a variety of genes as part of the cellular response to hypoxia ⁶⁹
Interleukins 6 and 8	Proinflammatory cytokines with effects on the renal microcirculation ²⁵
Interleukin 10 (IL-10)	Potent anti-inflammatory cytokine; inhibits production of TNF- α , IL-1B, and IL-6 ^{25,70}
Myeloperoxidase (MPO)	Lysosomal enzyme potentially involved in oxidative stress-mediated kidney injury ³⁴
Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase	Regulation of reactive oxygen species and oxidative stress ⁶⁶
Organic anion transporters (OAT)	Renal tubular uptake transporters located on the basolateral membrane of the proximal tubule
Organic cation transporter (OCT2)	Renal tubular uptake transporters located on the basolateral membrane of the S3 segment of the proximal tubule
Phenylethanolamine <i>N</i> -methyltransferase (PNMT)	Catalyzes the conversion of norepinephrine to epinephrine ⁷¹
Pre-B cell colony-enhancing factor (PBEF)	Inflammatory mediator; increases the production of proinflammatory cytokines such as IL-6, IL-8, and TNF α ²⁷
Serpin peptidase inhibitors (SERPINA4)	<i>SERPINA4</i> encodes kallistatin, a molecule with antiapoptotic and anti-inflammatory properties ²⁸
Salt-inducible kinase 3 (SIK3)	Serine/threonine protein kinase (AMP-activated protein kinase) that is important for regulation of mitosis ⁷²
TNF- α	Proinflammatory cytokine involved in the pathogenesis of systemic inflammatory response system ^{27,70}
Vascular endothelial growth factor (VEGF)	Key regulator of vascular permeability and angiogenesis, and multiple endothelial cell functions. Upregulated during ischemic kidney injury and plays an important role in angiogenesis and endothelial cell survival ^{16,27}
Epigenetic pathways	
ATF3	Stress-induced gene that may play a protective role in AKI by downregulating inflammatory cytokine expression via recruitment of histone deacetylases to promoters of inflammatory genes ⁷³
Bone morphogenic protein-7 (BMP7)	Role in nephron formation during kidney development; may be induced via changes in histone acetylation in response to renal ischemia and contribute to repair of tubular cells and cell proliferation ⁷⁴
Heme oxygenase-1 (HO-1)	Anti-inflammatory cytoprotective enzyme induced during AKI, transcriptionally regulated by changes in chromatin structure ⁷⁵
SIRT1	Histone deacetylase with protective role in oxidative stress and apoptosis ^{56,58}

Cardinal-Fernández et al²⁷ evaluated the impact of ACE I/D, TNF- α , VEGF, and pre-B cell colony-enhancing factor polymorphisms on AKI in 139 adult patients with severe sepsis. AKI was defined using the RIFLE criteria.⁷ Only VEGF +936 CC genotype was associated with AKI in multivariate analysis. Fifty-seven (87.7%) of the 65 patients with AKI carried this genotype. In the subgroup of patients with both AKI and septic shock, the polymorphism IL-8 251 AA was significantly associated with AKI (OR: 4.98; 95% CI: 1.04–23.86; $p = 0.045$). However, there was no association between AKI and ACE I/D polymorphism, or with TNF- α -308 A, again highlighting conflicting results across different samples and studies of candidate AKI genes.

The cellular pathophysiology of AKI consists of not only inflammation but also apoptosis. In a cohort of 1,264 adult intensive care patients with septic shock and acute respiratory distress syndrome (ARDS), 49.6% of patients were identified with AKI with the AKIN criteria.²⁸ Using the Human-CVD BeadChip (a genotyping panel), SNP analysis was performed on 887 patients and compared between those with and without AKI by splitting the cohort into discovery (60%) and validation (40%) subsets. In the discovery set, multivariate analysis adjusting for age, gender, and APACHE III score identified 142 SNPs associated with AKI that were then verified in the validation set. Four SNPs were identified to be protective against AKI in both subsets ($p < 0.05$): two within the B-cell CLL/lymphoma 2 (*BCL2*) gene: rs8094315 (OR: 0.62 per additional copy of the minor G allele, $p = 0.0032$) and rs12457893 (OR: 0.68 per additional copy of the minor C allele, $p = 0.0034$); serpin peptidase inhibitor, clade A, member 4 gene (*SERPINA4*) which encodes kallistatin, rs2093266 (OR: 0.53 per additional copy of minor A allele, $p = 0.0042$); and serpin peptidase inhibitor, clade A, member 5 gene (*SERPINA5*), which encodes protein C inhibitor, rs1955656 (OR: 0.54, $p = 0.0003$). One SNP, salt-inducible kinase 3 (*SIK3*) was associated with increased AKI risk (OR: 1.64 per additional copy of the minor T allele). Having both minor alleles of *BCL2* SNPs (haplotype GC) was associated with decreased AKI (OR: 0.61, $p = 0.000137$). Multivariate regression analysis results were significant after adjusting for clinical factors including BMI, APACHE III score, and need for vasopressors. This study suggests that quiescent apoptotic pathways (*BCL2*, *SERPINA4*) may be protective against AKI development.

Cardiac Surgery–Associated Acute Kidney Injury

AKI following surgical repair for congenital heart disease is also a major risk factor for morbidity and mortality in both infants and children.²⁹ Recognition of individual genetic risk factors may improve risk stratification and perioperative management. While cardiac surgery–associated AKI has been studied in infants and children, current understanding of genetic risk factors comes from adult and animal studies.

In adult cardiac surgery patients requiring cardiopulmonary bypass, Popov et al³⁰ studied SNPs of the promoter region in the erythropoietin gene (*EPO*). Animal studies have shown that EPO receptor binding stimulates antiapoptotic

pathways, including upregulation of HSP70, and reduces expression of proinflammatory markers such as TNF- α .³¹ TT genotype of the SNP rs1617640 promoter region was associated with need for renal replacement therapy ($p = 0.03$); however, there was no difference in RIFLE score or mortality rate between the TG and GG genotypes. In a pilot RCT of 71 adult patients requiring coronary artery bypass graft, those randomized to receive EPO 300 IU/kg or saline bolus preoperatively developed AKI incidence of 8 versus 29%, respectively.³² However, a follow-up EARLYARF trial did not demonstrate similar effects of EPO in ICU patients who were at risk of developing AKI.³³

The myeloperoxidase (*MPO*) gene encodes for an oxidative response enzyme (MPO) that is a mediator in ischemia-reperfusion and nephrotoxic injury. Perianayagam et al³⁴ investigated the association of *MPO* gene polymorphism with clinical outcomes of dialysis and death in a primary cohort of adults with known AKI as well as a secondary cohort of adults who were at risk for cardiac surgery–associated AKI. In the AKI cohort, a multivariate regression analysis adjusting for age, sex, and APACHE II scores identified that each copy of the *MPO* rs2243828 C-allele, rs7208693 T-allele, and rs2071409 C-allele and rs2759 was associated with two- to threefold higher odds for dialysis requirement or in-hospital death. In the cardiac surgery cohort, each copy of the *MPO* rs2071409 C-allele was associated with 1.91-fold higher adjusted odds (95% CI: 1.04, 3.51) for the composite outcome of stage 2 AKI, dialysis requirement, prolonged ventilation, or in-hospital death. *MPO* gene polymorphisms contribute to the understanding of genetic influence of AKI pathophysiology and the ability to correlate this effect with important clinical outcomes.

Several other genetic polymorphisms evaluated in cardiac surgery–associated AKI include endothelial nitric oxide (eNOS), apolipoprotein E (APO E), catechol-O-methyltransferase (COMT), ACE I/D, angiotensin (AGT), and interleukin 6 (IL-6). Only APO E has shown a positive association across several studies; however, one large study showed no association.

As mentioned earlier, the complex clinical syndrome of AKI is unlikely to be explained by a single allelic variant. Based on this concept, Basile et al³⁵ used a chromosome substitution animal model to evaluate the impact of multiple alleles simultaneously. Brown Norway (BN) rats are profoundly resistant to AKI following ischemia-reperfusion.³⁶ Individual chromosomes from the BN rats were substituted into the genetic background of Dahl SS rats. None of the consomic rats showed resistance to AKI equal to that of the parental strain, suggesting that multiple alleles on different chromosomes are likely influential on the pathogenesis of AKI. These authors, as have others, noted that GWAS, capable of examining thousands of candidate genes simultaneously, will expedite identification of individual candidate genes as well as interacting clusters of genes. Gene–gene interactions and gene clusters are undoubtedly critical to determining the genetic contributions to a complex trait like AKI.

Nephrotoxic Medications

Nephrotoxic medications are important causes of AKI in both neonates^{37,38} and the general pediatric population.^{39–42} The burden of nephrotoxic medication-associated AKI in terms of morbidity and hospital costs is high. Nephrotoxic medication-associated AKI events are commonly diagnosed in noncritically ill hospitalized children, with a mean rate of 25.5%.⁴¹ AKI rates appear to increase from 16 to 45% with exposure to more than three nephrotoxins.⁴⁰ Minimizing the burden of drug-associated AKI could positively impact the overall morbidity and health care costs for hospitalized children.

Nephrotoxic medications commonly affect the proximal renal tubule, even when used at nontoxic concentrations. Although some pediatric populations are at higher risk of AKI (e.g., critically ill, oncology patients), predicting individual patient risk of nephrotoxin-associated AKI remains challenging. Antibiotics such as aminoglycosides utilize the multi-ligand endocytic receptor megalin at the apical membrane for intracellular uptake, accumulate within lysosomes, and inhibit lysosomal enzymes. In megalin knock out mouse models, aminoglycosides are not associated with nephrotoxicity⁴³; however, human deficiency of megalin is associated with facio-ocular-acoustico-renal syndrome, suggesting that though protective against AKI, megalin is essential for embryological development.

Tubular basolateral transport mechanism with organic cation transporter (OCT2) is found in the S3 segment of the proximal tubule. Cisplatin, a common chemotherapeutic drug, can induce nephrotoxicity due to proximal tubular cell apoptosis and necrosis. In a mouse model, A270S (rs316019) variant for OCT2 displayed protection from cisplatin-induced nephrotoxicity caused by the G > A substitution at the 808 position of the *SLC22A2* gene.⁴⁴ 808G > T SNP in OCT2 ameliorated cisplatin-induced nephrotoxicity.⁴⁵

Another family of basolateral renal tubular uptake transporters is organic anion transporters (OAT). OAT1/*SLC22A6* and OAT3/*SLC22A8* are recognized as the mechanism of cellular uptake for medications such as cidofovir, salicylates, and methotrexate. In mouse models, Kikuchi et al⁴⁵ have identified hepatocyte nuclear factor (HNF1- α , HNF1- β) binding motifs in the promotor region of human organic anion transporter (hOAT3)/*SLC22A8*. Expression of hOAT3 is repressed by DNA methylation, inactivated by mutation in HNF1- α , and basally activated in the presence of either HNF1- α or HNF1- β .⁴⁵ HNF1- α null mice manifest renal Fanconi syndrome with glucosuria, phosphaturia, urate urine excretion, and amino aciduria.⁴⁶ Tissue expression of hOAT3 is likely regulated in concert between genetic (HNF1) and epigenetic (DNA methylation) factors.⁴⁵ Complementing OAT and OCT are drug extrusion transporters at the brush-border membrane of renal proximal tubules. In multidrug and toxin extrusion 1 (Mate1/*SLC47A1*) knockout (KO) mouse model, cisplatin use was associated with more severe AKI with higher increase in serum creatinine and blood urea nitrogen in comparison to wild-type mouse.⁴⁷

It is estimated that genetic variations are responsible for 20 to 90% of the variability of therapeutic response and toxicity.

The “Genetic Contribution to Drug-induced Renal Injury: The Drug Induced Renal Consortium” (NCT02159209) is an international multicenter collaborative enrolling both pediatric and adult patients, applying GWAS study to investigate genetic signals associated with nephrotoxic medications in AKI. Results from this consortium may provide important data about genetic signals pertaining to AKI in pediatrics.

Epigenetics

The role of epigenetics is an emerging field in the study of AKI. The impact of gene–environment interactions over time as well as the role of heritability in environmentally induced modifications may be of particular importance when considering the genetic susceptibility to AKI across different age groups. Age-related changes in AKI risk has been described in both animal models⁴⁸ and from a clinical perspective,⁴⁹ though the age-related risk increase have been examined primarily in the elderly. Epigenetic contributions in this evolving process is worthy of exploration, especially as it relates to evaluating AKI risk over an individual's lifetime. Epigenetic patterns appear to have plasticity, as evidenced by alterations in DNA methylation in cancer biology, cardiovascular disease, and diabetes.^{50–53} Identical twin studies have demonstrated epigenetic discordance over time.^{54,55} Although GWAS studies may detect genomic signal variations in cohort studies, these studies are typically cross-sectional analyses and as such can denote association but not causation. Individual epigenetic profiles are modified with time by repeated cellular mitoses, exposure to oxidative stress and disease pathologies, and epigenetic dysregulation. Prospective studies sampling epigenetic changes over time using large consortium data may be required to study the association between epigenetics and disease states.

Currently, there are few studies evaluating the role of epigenetic factors in AKI. A recent review by Bomsztyk and Denisenko⁹ describes this body of work that comes exclusively from animal models. Of potential interest for pediatric AKI is a study by Fan et al⁵⁶ that showed, in younger mice, higher level of the histone deacetylase SIRT1 was associated with decreased AKI. Histone deacetylases enzymatically condense chromatin structure and repress gene expression.⁹ SIRT1 seems to be an age- and metabolism-dependent histone deacetylase that confers protection in stress response pathways,⁵⁷ which may also be present in kidney tissue.^{58,59} Using an ischemia/reperfusion (I/R) model of 45 minutes, this study compared AKI rates and levels of SIRT1 expression between 2 and 4 months old mice. The younger mice had a significantly attenuated AKI response when compared with the older mice (BUN 38.6 ± 6.8 vs. BUN 190.9 ± 20) and sham-operated mice. Younger mice with AKI also had milder changes on histology. Furthermore, younger mice expressed significantly higher levels of SIRT1 in the kidney than both the same-age sham-operated mice and the older mice. Mice with a missing SIRT1 allele (*SIRT1*^{+/-}, *Het*) had lower SIRT1 expression, higher degree of I/R injury, and more significant AKI. The authors conclude that SIRT1 may be novel therapeutic target for I/R kidney injury. However, Hasegawa et al⁵⁸ found that despite overexpression of SIRT1, 2-month-old mice exposed

to I/R injury for 60 minutes incurred extensive evidence of AKI by measuring BUN. Yet, overexpression of SIRT1 also conferred protection against cisplatin-induced proximal tubular injury by maintaining peroxisome number and mitigating reactive oxygen species-related stress.

Bomsztyk and Denisenko⁹ note several aspects of histone acetylation biology that make this area particularly attractive for the study of AKI. Histone acetylation is a dynamic process, and differences seen in acetylation levels may reflect different forms of kidney injury or different time points of collection. In addition, some changes persist and may play a role in the progression to CKD.

Conclusion

There is a dearth of studies on the impact of genetic variants on AKI in children, with many unanswered questions. Different genes may be triggered at key developmental periods (preterm, term infants, and older children). And certainly epigenetic patterns, influenced by variable environmental exposures as well as intergenerational epigenetic inheritance in mammals with genetic imprinting,⁶⁰ are likely to be important modifying factors. Children do not have the comorbidities that typically confound adult studies (smoking history, diabetes, coronary artery disease). However, children with underlying nonrenal, primary disease (e.g., congenital heart disease, malignancy, cystic fibrosis) comprise the largest groups of AKI sufferers in the pediatric population.⁶¹ These comorbid conditions create challenges for the study of genetic susceptibility as well.

Future genetic studies that encompass cross-talk communication between inflammatory cascades (IL-8, TNF- α), ischemia-reperfusion pathways (VEGF, ACE I/D), apoptotic pathways (*BCL2*, *SERPINA4*, *SERPINA5*, *EPO*), cellular transport for drug toxicity (megalin, OAT, OCT2), and epigenetics (histone deacetylation) may be what is required to appreciate the implications of multifactorial AKI pathophysiology across different pediatric populations where numerous clinical risk factors precede the presentation of AKI phenotype.

In spite of the many unanswered questions, the application of the field of genetics in the study of AKI has the potential to improve outcomes for both children and adults through several different mechanisms. Decreasing the rates of nephrotoxic medication-associated AKI would make a major impact on the burden of AKI in hospitalized children. Understanding genetic factors that are protective in children may aid in the development of therapeutic targets to prevent AKI in adults. And recognizing and targeting pathways in the AKI-to-CKD progression may reduce the burden of renal disease later in life.

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