pentoxifylline was shown to reduce albuminuria and estimated glomerular filtration rate, most likely by improving the local renal microcirculatory fluid dynamics. In addition to above-mentioned pharmacological interventions, the new information provided by Awa *et al.*[3] indicates that genetic ablation of TNF-α also leads to amelioration of diabetic injury. Finally, in view of the above discussion of the vast amount of scientific and clinical work encompassing the past two to three decades, one can make a timely comment at this juncture that the TNF-α/TNF-α receptor system certainly has some added value in serving as a potential therapeutic target besides controlling hyperglycemia and hypertension to improve outcomes in the progression of diabetic nephropathy toward end-stage renal disease.

DISCLOSURE
The authors declared no competing interests.

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Epigenetic regulation in acute kidney injury: new light in a dark area

Chengyuan Tang[1] and Zheng Dong[1,2]

Epigenetic mechanisms have been implicated in the pathogenesis of renal diseases, including acute kidney injury (AKI). Mar *et al.* now unravel the acetylation and methylation at histones that are associated with the transcription of key genes in AKI. Notably, histone modifications display a remarkable heterogeneity in ischemic and endotoxic AKI. Targeting epigenetic programs may offer novel strategies to protect kidneys from AKI and enhance kidney repair and recovery.

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Acute kidney injury (AKI) is manifested by a rapid decline of renal function that is associated with high morbidity and mortality. It may also lead to end-stage renal disease and contribute to the initiation and progression of chronic kidney disease. Clinically, the main causes of AKI include sepsis, ischemia/reperfusion (I/R), and nephrotoxicity. Pathologically, AKI is characterized by the damage of renal tubules, vascular dysfunction, and a robust inflammatory response.[1] Despite the pathological characterization, the underlying molecular basis of AKI remains poorly understood. Recent studies have suggested an emerging role of epigenetic regulation in AKI.[2] However, systematic analysis of epigenetic response in AKI was lacking. Mar and colleagues[3] (this issue) have now unveiled heterogeneous patterns of epigenetic regulation at several relevant genes in AKI induced by I/R, the endotoxin lipopolysaccharide (LPS), and I/R in conjunction with LPS.

Epigenetics refers to heritable changes in gene expression that do not involve changes in the nucleotide sequence. DNA methylation and histone modifications are two important epigenetic mechanisms. DNA methylation refers to the addition of a methyl group to the 5 position of a cytosine ring in the CpG dinucleotides catalyzed by DNA methyltransferases, which in general represses gene transcription. In contrast, post-translational modifications of histone proteins may alter chromatin structure and the docking sites for transcription regulators, leading to transcriptionally permissive or repressive states. There are several types of histone modification, such as methylation, acetylation, phosphorylation, and ubiquitination. The acetylation of histones at specific lysine residues is catalyzed by histone acetyltransferases and, in general, favors gene transcription, whereas histone methylation may promote or suppress gene transcription depending on the gene and sites of modification. In addition to DNA methylation and histone modifications,

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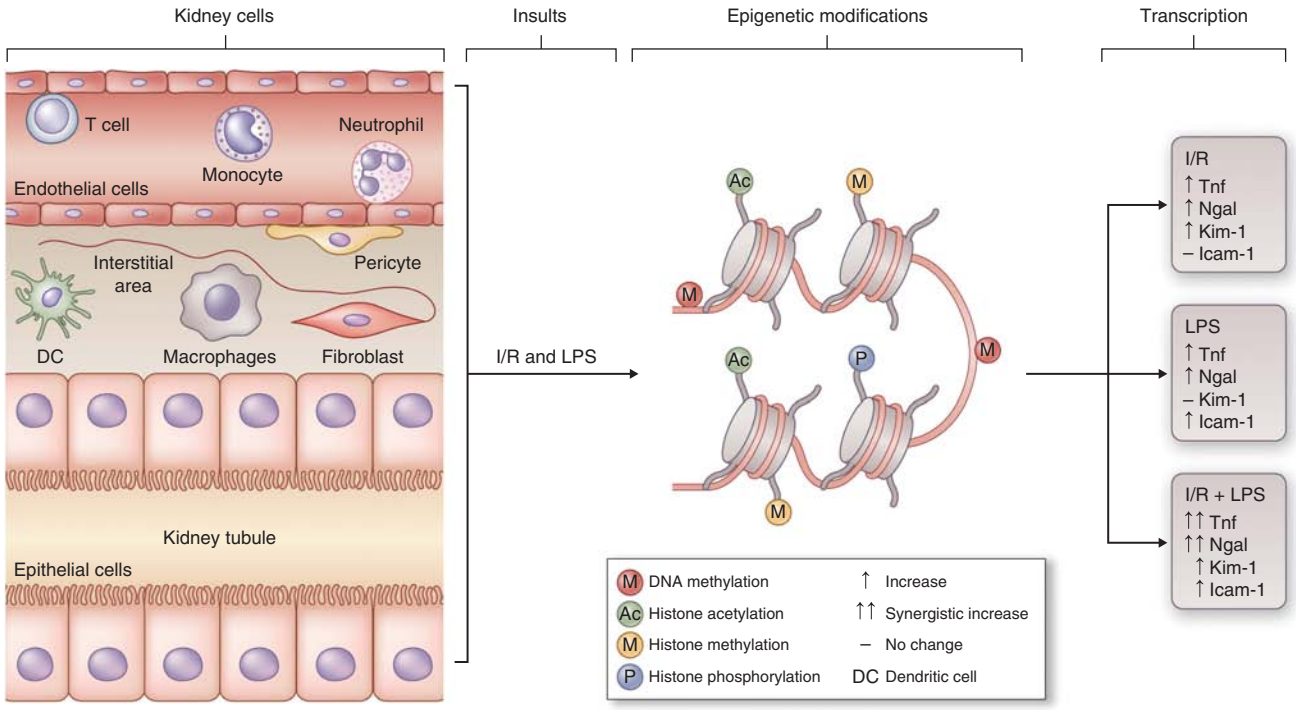

Figure 1 | Epigenetic regulation of AKI-associated gene transcription.

non-coding RNAs, such as long non-coding RNAs and microRNAs, are also considered important epigenetic modulators. In kidneys, epigenetic mechanisms have been implicated in renal development, and emerging studies have further suggested an important role of epigenetic regulation in the pathogenesis of renal diseases.[4]

In their study,[3] Mar and colleagues profiled the transcription of 56 AKI-associated genes in kidney tissues during I/R, LPS, or LPS plus I/R treatment. mRNA expression of these genes was highly different across various types of injury and also at different time points of the same injury. Among them, *Tnf* and *Ngal* were induced by LPS and I/R and synergistically by I/R plus LPS, whereas *Kim-1* and *Icam-1* were induced only by I/R and LPS, respectively. On the basis of their well-documented roles in AKI and the distinct temporal and injury-specific transcription patterns, *Tnf*, *Kim-1*, *Ngal*, and *Icam-1* were chosen as representative genes for further analysis. Binding of RNA polymerase II to these genes correlated well with their mRNA expression, supporting a critical role of transcriptional induction of these genes during AKI. What is responsible for transcriptional activation in these genes? Classically, one would focus on specific transcription factors, including both activators and repressors. However, as alluded above, epigenetic mechanisms may play a significant role as well. By reshaping the chromatin structure, epigenetic modifications may expose the key docking sites for transcription factors on specific genes, resulting in the assembly of efficacious transcription complexes and ensuing gene transcription. Mar and colleagues have now shed significant light in this novel area by revealing the regulation of AKI-associated genes via histone modifications.[3]

To analyze histone modifications relating to a specific gene, Mar and colleagues[3] used a microplate-based chromatin immunoprecipitation assay, called Matrix ChIP. In this assay, the antibody against a specific histone modification is immobilized in a well of the microplate and then incubated with samples for immunoprecipitation and chromatin binding, followed by real-time PCR analysis of specific genes. Matrix CHIP is a powerful technique as it can simultaneously detect the association of various histone modifications with multiple genes. By Matrix CHIP, Mar and colleagues examined and compared histone modification patterns at the *Tnf*, *Ngal*, *Kim-1*, and *Icam-1* genes in AKI. Although histone modifications at these genes showed some similarities, remarkable heterogeneities were detected among the modifications in different genes and AKI models, and at different time points or stages of AKI.[3] For example, repressive histone methylation marks were attenuated at all four genes within 26–74 h after I/R, whereas permissive histone acetylation was induced by I/R only at the *Tnf* gene. Epigenetic response at histones was also profoundly different for I/R and LPS. As such, I/R increased permissive histone methylation and histone phosphorylation at the locus of the *Tnf*, *Ngal*, and *Kim-1* genes, but LPS had no effects; instead, LPS reduced repressive histone methylation only at the *Icam-1* gene.[3] Histone modifications at these four genes also exhibited distinct time-dependent changes in response to I/R and LPS. For example, the repressive histone phosphorylation mark H4pSer1 at all four genes increased at 3 hours and decreased at 74 h after I/R.[3] Together, these findings demonstrate a highly dynamic