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Histone Methylation in CKD

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Epigenetic regulations mainly include DNA methylation, histone modifications, and regulation by non-coding RNAs. Histone modification, a more flexible posttranslational modification beyond the DNA sequence, has been under intensive investigation and plays a pivotal role in the expression of genes in maintaining normal biological function. DNA is wrapped around histone proteins and modification of histone proteins controls the chromatin condensation, resulting in the change of accessibility of DNA to transcription. Histone modifications involve a dynamic process, carried by epigenetic writers, such as histone acetyltransferases and histone methyltransferases (HMTs), epigenetic readers, such as bromodomains, chromodomains and tudor domains, and epigenetic erasers, such as histone deacetylases (HDAC), recognizing and inducing various epigenetic marks on amino acid residues on histone tails. Addition or removal of these modifications of histone tails leads to gene activation or repression.

Histone acetylation leads to opened chromatin conformation, thereby more accessible to RNA polymerase II and facilitating transcription of genes. HDAC makes a more compact chromatin structure to be unable to bind RNA polymerase II, decreasing the gene expression. HDAC inhibitors (HDACi) are new epigenetic therapy for hematological malignancies, such as lymphoma and multiple myeloma. Many studies found that the abnormal expression of HDAC in animal model of kidney fibrosis which is considered to be involved in the signal transduction during fibrotic process. Indeed, some studies indicated that HDACi can effectively slow the progression of kidney injury in mouse model of unilateral ureteral obstruction (UUO). However, not all of HDAC have been well-studied.

Histone methylation may result in the nearby gene repression or activation, depending on the location and degree of methylation. H3K9 trimethylation (H3K9me3) leads to gene silencing. Animal studies have also shown that inhibition of H3K9me3 may ameliorate high fat diet-induced nonalcoholic steatohepatitis and also myocardial infarction and the following cardiac fibrosis in mice. Our studies showed that SUV39H2, a HMT, and H3K9me3 increased in UUO kidney. When mice were injected intraperitoneally with chaetocin, an inhibitor of SUV39H2, the increase of fibrotic gene expression and fibrosis in UUO kidney were reversed. We sorted COL1α1-GFP positive myofibroblasts and the expression of fibrotic gene also can be reduced by chaetocin. In the CKD model of 8-week 0.2% adenine diet, chaetocin group demonstrated an improvement in renal function compared with vehicle group. Therefore, it is possible that the level of H3K9me3 in kidney myofibroblasts can be reversed by chaetocin, therefore redifferentiating myofibroblasts back into pericytes.