Epigenetic changes may explain chronic kidney disease

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The research of physician-scientist Katalin Susztak, MD, PhD, associate professor of Medicine in the Renal Electrolyte and Hypertension Division, at the Perelman School of Medicine, University of Pennsylvania, strives to understand the molecular roots and genetic predisposition of chronic kidney disease. In a recent *Genome Biology* paper, Susztak, and her co-corresponding author John Greally from the Albert Einstein College of Medicine, Bronx, NY, found, in a genome-wide survey, significant differences in the pattern of chemical modifications on DNA that affect gene expression in kidney cells from patients with chronic kidney disease versus healthy controls. This is the first study to show that changes in these modifications – the cornerstone of the field of epigenetics – might explain chronic kidney disease.

Epigenetics is the science of how gene activity can be altered without actual changes in the DNA sequence. DNA can be modified by different chemical groups. In the case of this study, these are methyl groups that, like using sticky notes as reminders, open or close up regions of the genome to make these areas more or less available to be "read" as a gene.

Chronic kidney disease is a condition in which the kidneys are damaged and cannot adequately filter blood. This damage can cause wastes to build up, which leads to other health problems, including cardiovascular disease, anemia, and bone disease. More than 10% of people, or more than 20 million, aged 20 years or older in the United States have chronic kidney disease, according to the Centers for Disease Control.

Past epidemiological studies have shown that adverse intrauterine and postnatal conditions have a long-lasting, over-a-lifetime role in the development of chronic kidney disease. Adverse intrauterine factors include small size of babies for gestational age due to a lack of nutrients, or conversely, a large size for gestational age, for example if mom had pregnancy-related diabetes.

Studies from the Diabetes Control and Complications trial also indicate that patients with diabetes who had poor diabetes control 25 years earlier still have an increased risk of kidney disease despite having a decade of excellent glucose control. "This is called the metabolic memory effect," says Susztak. "Kidney cells remember the past bad metabolic environment."

Comparing Two Cell Types

Susztak's lab used human kidney cells that looked almost the same under a microscope, but the way each cell type is affected by the methyl groups was very different. In general, an increase in the number of methyl groups on a gene turns off expression, and a decrease of methyl groups turns on a gene's expression.

Specifically, they found that the differences in the methyl groups were not on promoter regions in the diseased kidney cells, but mostly on enhancer regions, and were also near sequences for important kidney transcription factors. "This all speaks to the importance of these regions in regulating gene expression," says Susztak.

Promoter regions are in front of genes and near the gene they influence. Enhancer regions are farther away from the gene of influence. This difference indicates that the two cell types would likely respond differently to stress.

"The difference in methylation related to kidney fibrosis—genes encoding collagen and growth factors—at core kidney development sites in the genome raises the possibility that these differences are established early on in a person's development because the genes Pax2 and Pax8 are active in the developing kidney in the fetus," explains Susztak.

"Most of the research on kidney epigenetics so far has been on promoter regions on kidney cancer cells," says Susztak. "The difference we found in dysregulation between the two cell populations may indicate that dysregulation in cancer is different from dysregulation in chronic kidney disease. Five years ago there was no epigenetic information outside of cancer," says Susztak.

Overall, the findings raise the possibility that dysregulation of epigenetic marks plays a role in chronic kidney disease by affecting pathways that lead to more fibrosis. Identifying the genes and proteins associated with this system gone awry may help identify new biomarkers and targets for new drugs.

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