Role of Epigenetics in Diabetic Nephropathy and Diabetic Vascular Inflammation

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Type 1 and Type 2 diabetes are complex diseases associated with accelerated inflammation and multiple complications including Diabetic Nephropathy. Increasing evidence suggests that epigenetic factors may regulate the complex interplay between genes and the environment and affect human diseases such as diabetes and its complications. Abnormal activation of vascular cells, circulating monocytes and renal cells triggered by inflammatory genes has been implicated in diabetic complications, but the underlying molecular mechanisms are not fully understood. We evaluated the hypothesis that key nuclear epigenetic chromatin remodeling mechanisms are involved in the expression of these inflammatory chemokines and cytokines in vascular smooth muscle cells and monocytes under diabetic conditions in vitro and ex vivo from diabetic mice, as well as in peripheral blood cells isolated from diabetic patients. We have also examined the role of epigenetic mechanisms in the regulation of fibrotic genes in mesangial cells related to the pathogenesis of diabetic nephropathy. Furthermore, we are testing the hypothesis that epigenetic changes may be responsible for the phenomenon of metabolic memory noted in clinical trials where diabetic patients previously on conventional glycemic control continue to develop persistent complications like diabetic nephropathy despite subsequent intensive control.

Covalent modifications on nucleosomal histones, such as acetylation and methylation of lysine residues, play epigenetic roles in the regulation of gene transcription. Histone lysine methylation can lead to either gene activation or repression depending upon the specific lysines methylated. Using chromatin immunoprecipitation (ChIP) assays, we observed that a dysregulation of specific epigenetic activating and silencing histone methylated lysine marks and the corresponding methyltransferases at gene promoters play key roles in the regulation of inflammatory and fibrotic genes and metabolic memory under diabetic conditions in cell and animal models. We also indentified mechanisms involving cross-talk with microRNAs. In order to identify diabetes-specific epigenetic signatures, we developed a systems biology approach to profile and compare histone lysine methylation patterns in cells cultured under high glucose conditions versus normal glucose, and also in blood cells obtained from normal volunteers versus patients with diabetes (including patients displaying metabolic memory). For this, we utilized the ChIP-chip (ChIP linked to microarrays) and related approaches to examine the genome-wide profile of key histone marks usually associated with active or repressed genes. Our results revealed that specific sets of genes depict differential histone lysine methylation under diabetic conditions. By applying bioinformatics pathway analyses software, we identified high scoring biological and diabetes-relevant networks amongst these genes. These epigenomics approaches provide evidence that the altered histone methylation of certain genes may be a key mechanism underlying the persistent micro- and macro-vascular complications seen in the diabetic population. The results could lead to the development of new therapeutic targets for the treatment and/or prevention of sustained diabetic renal complications.