DNA Methylation of Skeletal Muscle Tissue in Patients with Hypertension and Diabetes Undergoing Cardiopulmonary Bypass

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Abstract

Background & Aim: Epigenomic changes may affect the condition of patients before and after surgery. The epigenome−wide DNA methylation profiling of human skeletal muscle (SKM) specimens obtained from patients undergoing cardiac surgery utilizing cardiopulmonary bypass (CPB) was examined.

Methods: SKM was obtained from the internal mammary artery bed before and after termination of cardiopulmonary bypass. Specimens of patients without hypertension or diabetes (control), those with hypertension alone (BP = 130), those with hypertension combined with either controlled (HbA1C <=7) or poorly controlled (HbA1C > 7) diabetes were examined. SKM DNA methylation was profiled via Illumina MethylationEpic arrays and analyzed by principal component analysis, cluster analysis and analysis of variance followed by network and pathway analysis.

Results: DNA methylation in samples from patients with hypertension and diabetes was significantly different in 5822 loci for controlled diabetes and in 7177 loci for uncontrolled diabetes; hypertension alone produced minimal effect. These loci produced a tightly interacting network with 560 hubs and 7055 edges. These loci were associated with genes involved in pathways of IL−1, IL−12, IL−18, TNFa; IFN.. and VEGF signaling, in NF−..B and Wnt pathways, apoptosis and DNA damage response. SKM at the end of CPB revealed 282 highly significant loci or 193,567 loci with lower significance and the magnitude of the effect not exceeding 10−20%.

Conclusion: Preoperatively, patients with diabetes show substantial change in SKM DNA methylation epigenome wide. Compared to diabetes, hypertension did not as substantially influence the methylome in the SKM. During surgery multiple low−grade methylation changes occur that may mask the effects of the disease; moreover in a few loci more prominent changes occur that may be part of a compensatory/regulatory response to surgery utilizing CPB.

Clinical Implications: A combination of diabetes and hypertension is associated with epigenomic changes in the skeletal muscle which are more pronounced than those with hypertension alone. A heart surgery with cardiopulmonary bypass induces epigenomic change sin skeletal muscle. Here we show that even in the short time taken for a cardiopulmonary bypass operation, multiple genome−wide DNA methylation changes occur in skeletal muscle. The effects of surgery on epigenetic regulation have been largely neglected. This may be a target for postoperative evaluation and therapeutic correction.