Balakrishnan et al. (2017) Can J Biotech, Volume 1, Special Issue, Page 104
https://doi.org/10.24870/cjb.2017-a90

Canadian Journal of Biotechnology

ISSN 2560-8304

Poster Presentation **OPEN ACCESS**

Category: Functional Genomics

Inflammation induced insulin resistance is associated with DNA methylation changes in vascular endothelial cells

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Abstract

Vascular insulin resistance manifests in decreased production of nitric oxide subsequently leading to vasoconstriction and atherosclerosis. Inflammatory molecules such as IL-6 are known to induce insulin resistance in vascular endothelial cells. Epigenetic mechanisms including promoter DNA methylation have been demonstrated in development and progression of metabolic disorders and atherosclerosis. However, precise and underlying epigenetic mechanisms governing vascular insulin resistance are not known. Human endothelial cells treated with a) IL-6 and insulin together, b) pretreated with IL-6 and c) hyperinsulinemic conditions induced vascular insulin resistance leading to decreased Akt/eNOS activation and subsequently stabilized STAT3 phosphorylation. In 3D spheroid and matrigel assays, IL-6 abrogated insulin effects on angiogenesis. IL-6 induced insulin resistance was associated with down regulation of DNMT1 and DNMT3B, but not DNMT3A and resulted in decreased enzyme activity leading to global DNA hypomethylation. Protein levels of DNMT1 and DNMT3B were inversely correlated with S-phase of cell cycle. CpG microarray analysis revealed hypomethylation of promoters associated with 199 genes and promoter hypermethylation of 98 genes. Further, methylation status of promoters of genes associated with insulin signaling and angiogenesis such as *RPS6KA2*, *PI3KR2*, *FoxD3*, *Exoc7*, *MAP3K8*, *ITPKB*, *EPHA6*, *IGF1R* and *FOXC2* were validated by bisulfite sequencing. Differentially methylated CpG sites of four out of five hypomethylated genes harboured putative binding site for HMGB1, a potent inflammatory mediator, suggesting HMGB1 might serve as epigenetic switch facilitating a pro-inflammatory milieu in response to IL-6 in endothelial cells. Our data indicates causal link between IL-6 induced DNMT1 changes and altered gene expression involved in insulin signaling and angiogenesis.

Citation: Balakrishnan, A., Satyamoorthy, K. and Joshi, M.B. Inflammation induced insulin resistance is associated with DNA methylation changes in vascular endothelial cells [Abstract]. In: Abstracts of the NGBT conference; Oct 02-04, 2017; Bhubaneswar, Odisha, India: Can J biotech, Volume 1, Special Issue, Page 104. https://doi.org/10.24870/cjb.2017-a90