MOLECULAR CYTOGENETICS

POSTER PRESENTATION Open Access

Role of IL-6/JAK/STAT pathway in inducing vascular insulin resistance

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From International Conference on Human Genetics and 39th Annual Meeting of the Indian Society of Human Genetics (ISHG)
Ahmadabad, India. 23-25 January 2013

Introduction

Insulin resistance is a hall mark of metabolic disorders. Studies have demonstrated that inflammatory regulator interleukin-6 (IL-6) plays an important role in disruption of IR/Akt/eNOS signaling pathway resulting vascular insulin resistance. Accumulating evidences suggests a significant role of epigenetic mechanisms such as DNA methylation in progression of metabolic disorders. Hence the present study aimed to understand the role of epigenetic mechanisms involved during IL-6 induced vascular insulin resistance and its consequences in cardiovascular diseases.

Materials and methods

Human umbilical vein endothelial cells (HUVEC) and Human dermal microvascular endothelial cells (HDMEC) were used for this study. Endothelial cells were treated in presence or absence IL-6 (20ng/ml) for 36 hours and followed by insulin (100nM) stimulation for 15 minutes. Levels of phosphorylated- and total Akt served as readout for insulin resistance. To investigate changes in DNA methylation, cells were treated with or without neutrophil conditioned medium (NCM) as a physiological source of inflammation or IL-6 for 36 hours. Genomic DNA was processed for HPLC analysis for methyl cytosine content and cell lysates were analyzed for DNMT1 (DNA (cytosine-5)-methyltransferase 1) and DNMT3A (DNA (cytosine-5)-methyltransferase 3A) levels using immunoblotting.

Results

Endothelial cells stimulated with insulin exhibited an increase in phosphorylation of Akt $^{ser\ 473}$ in serum free conditions but such insulin response was not observed in cells treated with IL-6, suggesting chronic exposure of endothelial cells to IL-6 leads to insulin resistance. HPLC analysis for global DNA methylation resulted in decreased levels of methyl cytosine in cells treated with pro-inflammatory molecules (both by NCM and IL6) as compared to 3.2% in untreated control to 2% in treated. Kinetic studies depicted a transient increase DNA methylation at 24 hours which was followed by steep decrease at 36 hours. Subsequently, analysis in cells treated with IL-6 showed a significant decrease in DNMT1 levels but not in DNMT3A. Other pro-inflammatory marker such as TNF-α did not exhibit such changes. Interestingly we also observed Akt phsophorylation refelcetd DNMT1 changes suggesting plausible role of PI3K/Akt signaling axis in regulation of DNMT1 expression.

Conclusion

Taken together our study suggests that IL-6 induces vascular insulin resistance and involvement of epigenetic changes.

Published: 21 January 2014

doi:10.1186/1755-8166-7-S1-P96
Cite this article as: Balakrishnan *et al.*: Role of IL-6/JAK/STAT pathway in inducing vascular insulin resistance. *Molecular Cytogenetics* 2014 7(Suppl 1):P96.

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