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Abstract Title: - Role of EGR1 in diabetes, obesity and cancer – An in-silico perspective

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Aims: - Early Growth Response factor 1 (EGR1), belongs to zinc-finger protein family and is a transcription factor, involved in EGFR signalling pathways pivotal for cellular growth, survival, proliferation, and differentiation. It is suggested that EGR1 contributes to the development of metabolic disorders such as Type 2 Diabetes (T2D) and Obesity. Dysregulation of EGR1 expression is associated with co-occurrence of T2D and obesity-related cancers due to its oncogenic promoter activities. It also exhibits loss of DNA damage response due to silencing thus contributing to replicative senescence. Nevertheless, the specific mechanism whereby EGR1 modulates these processes remains to be elucidated. Using in silico approach, we establish the role of EGR1 and its interacting repair proteins in metabolic disorders leading to cancer.

Methods: - A protein interactome of EGR1 and various DNA repair proteins was constructed. For all of these genes, we predicted the relevant signalling pathways by enrichment analysis. Non-synonymous SNPs in EGR1 was retrieved for mutational studies. Detailed mutational profiling of EGR1 gene using structural and functional tools was carried out. Further, analysis on each of the mutations were done to study their impact at the site of mutation. Docking studies of mutant EGR1 with the wild type repair proteins was done. Investigations on the mRNA expression of EGR1 under normal and malignant conditions and its co-expression patterns with the interacting repair proteins were also performed. Drug sensitivity analysis was carried out to study the impacts of EGR1 on drugs used for the concurrent management of T2D and obesity-related cancers.

Results: - Protein-protein interactions of EGR1 with DNA repair proteins suggested its experimental crosstalk with BRCA1, TP53BP1 and TP53. Detailed mutational profiling of EGR1 gene suggested that 3 out of 244 mutations were detrimental for protein functions. Docking of mutant EGR1 with wild type repair proteins showed modified dynamics which may cause long term adverse impact on genome integrity. Analysis of TNMplot revealed that EGR1 was significantly overexpressed in tumour tissues of large intestine. Using GSCA database, we found that BRCA1 and TP53 overexpression were sensitive to most small molecule drugs, while the same cell lines overexpressing EGR1 were resistant to most of the drugs.

Conclusions: - Our study highlights the putative roles of EGR1 in T2D and Obesity and subsequent progression of cancer. We try to elucidate the irregularities in DNA repair pathways due to a mutant EGR1. Further investigation on EGR1 regulation will help us in identifying novel mechanisms underlying the relationship between T2D, obesity and cancer.

Keywords: - Protein-protein interactions of EGR1 with DNA repair proteins suggested its experimental crosstalk with BRCA1, TP53BP1 and TP53. Detailed mutational profiling of EGR1 gene suggested that 3 out of 244 mutations were detrimental for protein functions. Docking of mutant EGR1 with wild type repair proteins showed modified dynamics which may cause long term adverse impact on genome integrity. Analysis of TNMplot revealed that EGR1 was significantly overexpressed in tumour tissues of large intestine. Using GSCA database, we found that BRCA1 and TP53 overexpression were sensitive to most small molecule drugs, while the same cell lines overexpressing EGR1 were resistant to most of the drugs.