similar cholesterol, triglyceride and basal glucose levels after 6 hours of starving. However, the uric acid levels were increased in iPLA2γ-KOmice. Following the intraperitoneal injection of Intralipid, iPLA2γ-KO mice exhibited a prolonged hyperglycemic state compared to wt mice. Glucose-stimulated insulin release in isolated pancreatic islets (PI) was moderately decreased in iPLA2γ-KO PI. Physiologically relevant concentrations of palmitic acid stimulated insulin secretion in PI from wt mice, and this stimulation was absent in iPLA2γ-KO PI. In conclusion, the data are consistent with iPLA2γ ablation causing impairment of GPR40-dependent insulin secretion, resulting in prolonged glycemia. Thus, our results support the role of iPLA2γ in regulating insulin secretion in vivo.

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Regulation of β-TrCP Mediated Nrf2 Degradation by GSK3β during Hyperglycemic Renal Toxicity

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Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is a master regulator of cellular homeostasis that regulates more than 1% human genes including the ones related to glucose metabolism. Type 2 diabetes mellitus is associated with reduced Nrf2 mediated responses due to its compromised protein stability. The molecular mechanism behind Nrf2 degradation during hyperglycemia remains incompletely understood. Present study demonstrates that phosphorylation of Nrf2 by GSK3β at Neh6 domain causes its nuclear destabilization and ubiquitination by an E3 ligase β-TrCP, resulting in its loss of action in a keap1 independent manner. Co-immuno-precipitation studies and dual staining microscopy showed higher β-TrCP –Nrf2 interaction leading to its ubiquitination and degradation in the diabetic rats. Down-regulation of GSK3β by lithium chloride *in vivo* significantly decreased β-TrCP levels and enhanced Nrf2 nuclear stability compared to diabetic rats. In addition, nuclear Nrf2 retention upon GSK3β inhibition enhanced antioxidant levels and increased p-mdm2 (Ser 166) protein expression which suppressed p53 activation by its ubiquitination thereby preventing cell death. Renal tubular cells transfected with Nrf2 si-RNA and post treated with high glucose (HG) showed higher expression of Mst1, Bax and Bim pro-apoptotic proteins compared to normoglycemic (NG) cells suggesting that Nrf2 play a major role in precipitating diabetic kidney disease. Overall, the study confirms that hyperglycemia activates GSK3β (RNA/Protein) which in turn degrades Nrf2 via β-TrCP and limits cell survival. The data also shows potential role of GSK3β/ β-TrCP axis in Nrf2 instability during diabetes. Thus, targeted inhibition of GSK3β may be exploited to prevent the patho-complications evolved during hyperglycemic renal toxicity.

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Lycopene Shows Anti-protein Carbonylation and Anti-inflammatory Properties in Liver of Rats Treated with a Hypercaloric Refined-Carbohydrate Rich Diet

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Purpose: High-sugar intake and obesity are strinctly related to oxidative and inflammatory damages which underlie developments of many severe clinical conditions. This study aimed to investigate the effects of a lycopene supplementation (Lyc-suppl) on protein carbonylation, lipid content and inflammatory marker in liver of obese rats treated with a hypercaloric refined-carbohydrate rich diet.
Methods: Animals were randomized in four groups: control (Co), control with Lyc-suppl (Co + Lyc), obese (Ob) and obese with Lyc-suppl (Ob + Lyc). Obese was induced by a hypercaloric refined-carbohydrate (75% energy) plus saturated fat based diet. Control diet consisted of a normocaloric oil-rich diet. Animals were treated during 30-wk. During the last 10wk animals were treated by intragastric gavage with lycopene (10mg/kg) or placebo. After 30-wk animals were sacrificed for obtaining liver and adipose tissues. Epididimal, retroperitoneal and visceral fat depots were weighted and used for the calculation of adiposity index (AI). Triglycerides (TG), tumor necrosis factor alpha (TNF-α) and protein carbonyl (PC) levels were assayed in liver tissues. Statistical analyses used ANOVA two-way and significance level of 5% ($p < 0.05$).
Results: All obese rats showed higher AI in comparison to Co rats and Lyc-suppl was not able to prevent obese development. PC levels in liver of Co was increased as well as in Ob (Co = Ob). Possible explanation for this unexpected finding was that Co diet was rich in vegetable oils which are prone to be oxidized and thus forming higher amounts of reactive carbonyl species. But, both Co + Lyc and Ob + Lyc groups showed lower PC levels in comparison to Co and Ob groups. In addition, liver tissues of Ob showed increased TG and TNF-α levels in comparison to Co and Co + Lyc. Liver tissues of Ob + Lyc showed lower levels of TG and TNF-α than Ob but still higher than Co or Co + Lyc levels.
Conclusion: Lyc-suppl shows anti-protein carbonylation in both high-oil and high-carbohydrate rich diets and induces lower lipid deposition and anti-inflammatory process in rat liver.

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Morin Prevents ER Stress Mediated Hepatotoxicity by Modulating PERK-eIF2α-ATF4 Axis in Diabetic Male Wistar Rats

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Hyperglycemia provokes ROS mediated oxidation of macromolecules resulting in their malfunction. Proteins being one of the abundant cellular macromolecules are prone to oxidation leading to conformational changes, loss of activity and accumulation in ER. Accumulation of misfolded proteins results in ER stress and activates the unfolded protein response (UPR) sensors i.e. PERK, ATF-6 and IRE-1α to enhance the proper protein folding activity. Activation of PERK arrests global protein synthesis by phosphorylating eIF2α at Ser51 which in turn, transcribes ATF4 and CHOP that inhibits anti-apoptotic protein Bcl2 thereby inducing apoptosis (proteotoxic apoptosis) via caspase-3 pathway during sustained ER stress. This study was aimed to assess the effect of a bioflavonoid, morin, to reduce ER stress provoked hepatotoxicity in diabetic male Wistar rats. Earlier we showed that Morin reduces hepatotoxicity by modulating PHLPP2/GSK3β/Nrf2 axis resulting into enhanced antioxidant response. ER stress inhibitory potential of Morin was compared with a known ER stress chemical inhibitor, ISRIB in diabetic rats. Protein disulfide isomerase assay, microsomal GSH/GSSG ratio and total thiol levels indicated that Morin reduced ER stress significantly. Pull down assay established that Morin inhibits PERK activation by interacting with its luminal domain which was further confirmed by molecular docking studies. Further, immunoblotting and immunofluorescence studies showed that Morin reduced UPR sensor activation and down-regulated their target proteins such as IRE-1, ATF6, p-eIF2α, XBP1, Bip, PDI, ATF-4, and CHOP, thereby preventing ER stress significantly. Moreover, histopathological studies confirmed prevention of hepatic injury by Morin. Thus, the study shows that Morin may