P3263 | BENCH Cardiac-specific overexpression of LXR-alpha attenuates left ventricular hypertrophy by modulating glucose uptake and metabolism

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Purpose: Liver X receptors (LXRs) are key transcriptional regulators of lipid and carbohydrate metabolism. Moreover, LXR activation with synthetic agonists was shown to reduce left ventricular (LV) hypertrophy and prevent cardiac dysfunction, albeit at the expense of eliciting adverse systemic side effects such as hypertriglyceridemia and liver steatosis. To circumvent these confounding effects, we generated a murine model whereby LXR signaling is selectively increased in the heart. Thus, the aim of this study was to determine whether cardiac-specific LXR activation reduces pathological cardiac hypertrophy, and furthermore, explore the relevance of LXRs in regulating glucose and lipid metabolism in the heart.

Methods: Murine LXRα was cloned behind the αMHC promoter to create transgenic (TG) mice and transgene-negative littermates (CON). TG and CON mice were subjected to transverse aortic constriction (TAC), or sham surgery, for 5 weeks to induce LV hypertrophy. In vivo cardiac function was assessed with echocardiography.

Results: In TG mice, basal myocardial LXRα protein levels were increased 10-fold. TAC significantly increased LV weight in both CON and TG, while LV weight increase was 24% less in TG (P < 0.001). CON mice exhibited a greater decline in fractional shortening after TAC (-11% vs -6%, P < 0.001). Following TAC, typical changes in fetal gene expression were observed in CON, but to a lesser extent in TG mice. Further investigation into the molecular basis of LXR-mediated cardioprotection with microarray analysis revealed alterations in both glucose and lipid homeostasis. TAC suppressed fatty acid oxidation genes in both CON and TG. However, only in TG mice, basal myocardial Glut1 and Glut4 expression were significantly induced in TG hearts (P < 0.05 vs CON). To this end, myocardial glucose uptake was assessed using 18F-FDG imaging. Basal cardiac FDG-glucose uptake was enhanced in TG mice (P < 0.05 vs CON). Following TAC, FDG-glucose uptake increased in both CON and TG, but to a larger extent in TG (P < 0.05). This adaptation coincided with a more lean phenotype as intracardiac lipid levels were significantly lower in TG mice (P < 0.05 vs CON).

Conclusion: Our gain-of-function studies indicate that constitutive LXR activation in the heart is beneficial in reducing cardiac pressure overload-induced LV hypertrophy and dysfunction. Furthermore, LXR-mediated increases in glucose utilization constitute these cardioprotective effects, and we therefore postulate that LXR activation could be a potential therapeutic target.

P3264 | BENCH Fatty acid catalytic enzymes in vascular smooth muscle cells play a crucial role in the pathogenesis of atherosclerosis

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Purpose: In mice, hypercholesterolemia and fatty acid metabolism and composition in VSMC showed that both SCD1 and Elovl6 knockdown markedly diminished DNA synthesis and induced p21 or p-AMPK expressions. Of importance, analysis of FFA metabolism and composition in VSMC showed that both SCD1 and Elovl6 knockdown markedly suppressed DNA synthesis and induced p21 or p-AMPK expressions. Conclusions: Collectively, our results suggest that perturbation of fatty acid de-saturation or elongation in VSMC causes the shift of fatty acid composition and the inhibition of cell proliferation. Therefore, fatty acid metabolism and composition is crucial for SMC proliferation and progression of atherosclerosis.

P3265 | BEDSIDE MicroRNA-100 regulates a cluster of adipocytokine expression: A human biopsy study in subcutaneous and visceral adipose tissue


Purpose: Recently, our group has identified a cluster of adipocytokines, adiponectin, visfatin, and leptin, that are regulated by several microRNAs (miRNA). These adipocytokines are known to modulate lipid and glucose metabolism, and are associated with obesity and metabolic diseases. In this study, we aimed to determine whether miRNA-100 regulates the expression of adipocytokines, adiponectin, visfatin, and leptin in human adipose tissue.

Methods: We first examined SCD1 and Elovl6 expressions in neonatal rat adipose tissue. We then performed microarray analysis to identify changes in gene expression. We validated these findings by quantitative PCR.

Results: In TG mice, basal myocardial LXRα protein levels were increased 10-fold. TAC significantly increased LV weight in both CON and TG, while LV weight increase was 24% less in TG (P < 0.001). CON mice exhibited a greater decline in fractional shortening after TAC (-11% vs -6%, P < 0.001). Following TAC, typical changes in fetal gene expression were observed in CON, but to a lesser extent in TG mice. Further investigation into the molecular basis of LXR-mediated cardioprotection with microarray analysis revealed alterations in both glucose and lipid homeostasis. TAC suppressed fatty acid oxidation genes in both CON and TG. However, only in TG mice, basal myocardial Glut1 and Glut4 expression were significantly induced in TG hearts (P < 0.05 vs CON). To this end, myocardial glucose uptake was assessed using 18F-FDG imaging. Basal cardiac FDG-glucose uptake was enhanced in TG mice (P < 0.05 vs CON). Following TAC, FDG-glucose uptake increased in both CON and TG, but to a larger extent in TG (P < 0.05). This adaptation coincided with a more lean phenotype as intracardiac lipid levels were significantly lower in TG mice (P < 0.05 vs CON).

Conclusion: Our gain-of-function studies indicate that constitutive LXR activation in the heart is beneficial in reducing cardiac pressure overload-induced LV hypertrophy and dysfunction. Furthermore, LXR-mediated increases in glucose utilization constitute these cardioprotective effects, and we therefore postulate that LXR activation could be a potential therapeutic target.

Conclusions: Collectively, our results suggest that perturbation of fatty acid de-saturation or elongation in VSMC causes the shift of fatty acid composition and the inhibition of cell proliferation. Therefore, fatty acid metabolism and composition is crucial for SMC proliferation and progression of atherosclerosis.

Purpose: MicroRNAs (miRNA), single-stranded non-protein coding gene products, regulate gene expression through post-transcriptional inhibition, and known to be involved in essential biological processes including obesity and insulin resistance. This study was conducted to elucidate the role of miR100 expression in human adiposity and insulin resistance.

Methods: Pair samples were obtained from subcutaneous (SAT) and visceral adipose tissue (VAT) during elective operation in 71 men and 42 women. Mature miRNA levels were determined by miRTCP R and Normalized using U6 small nuclear ribonucleoprotein. Subcutaneous (SAT) and visceral fat area (VFA) was determined by abdominal multidetector CT scanning. Adipocyte sizing was performed using a Coulter counter.

Results: Study 1 (clinical study): In men and women, SAT was larger than VAT, and the mean size of adipocytes was greater in SAT than in VAT. Level of log(miR100) was significantly decreased in VAT in men (p=0.025), but comparable between SAT and VAT in women. Level of log(miR100) in SAT was positively correlated with HOMA-IR, and tended to be positively correlated with expression level of macrophage marker, CD68. Level of log(miR100) in SAT was positively correlated with expression level of IL-1β. NLRP3 and TLR4 in men but not in women. Study 2 (in vitro study): When stimulated with lipopolysaccharide (LPS, 1-10ng/mL), expression of miR100 was not changed in mouse macrophage-like RAW264.7 cells, but enhanced in adipocyte-like 3T3-L1 cells. A repressor molecule family of NADPH oxidases NOX4, which has a possible MR100 target at 3′-UTR, was up-regulated in 3T3-L1 cells by LPS, but not changed in RAW264.7 cells. Another type of NADPH oxidase, was not detected in 3T3-L1 cells but was in RAW264.7 cells.

Conclusion: Adipose tissue miR100 is derived mostly from adipocytes and may play a direct or indirect role in regulating expressions of adipocytokine inflammatory cytokines, adipocyte-specific NADPH oxidase, and insulin sensitivity in human.