31. Changes in Portal Mileau during Sleeve Gastroectomy: A Potential Novel Anti-Diabetic Mechanism of Action

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Bariatric surgery can lead to resolution of diabetes among obese patients, although the underlying mechanism remains unknown. We test the hypothesis that changes in portal milieu and nutrient sensing are important for achieving the metabolic improvement after sleeve gastroectomy (SG). Methods: A stapled SG was performed in Sprague-Dawley rats (n=4). A control group underwent laparotomy without gastroectomy (n=4). Daily weight and food intake were recorded. After 4 weeks, rats were euthanized, jejunal and portal catheters were placed for blood sampling, and proximal duodenal cannula to infuse glucose. Systemic and portal venous blood samples were taken before and after 120 minutes after glucose infusion. Portal-sympathetic glucose gradients were determined to assess intestinal glucose utilization. Intestinal glucose absorption was also calculated. Groups were compared using t-tests. Results: SG led to reduced food intake and weight loss compared to controls. Small intestine weight was unchanged after SG, suggesting absence of the intestinal hypertrophy. SG did not change the Portal-sympathetic glucose gradient, suggesting no changes in intestinal glucose utilization. Intestinal glucose absorption capacity, reflected in area under the curve after glucose infusion, also remained unchanged. All these results were in contrast to changes seen after gastric bypass surgery.

Clinical Implications: Early changes in the portal milieu seen after gastric bypass surgery are not seen after SG. Therefore, the metabolic benefits of SG and gastric bypass may be mediated by distinct mechanisms and should be further investigated in future.

32. Respiratory-gated Auricular Vagal Nerve Stimulation (RAVANS) Modulates Brainstem Activity and Cardiac Autonomic Tone

Ronald Garcia, MD, PhD

Objective: To evaluate the effects of Respiratory-gated auricular vagal nerve stimulation (RAVANS), an optimized version of transcutaneous vagus nerve stimulation, on the modulation of neural and cardiac autonomic regulation. Methods: Forty subjects (34.8±12.8 years, 36 females) included in previous pilot studies evaluating RAVANS on migraine and depression were randomized to receive RAVANS gated to exhalation or sham stimulation during a 6-minute HRMI scan, and after a 30-min period were crossed over to the alternative stimulation. Functional MRI scans were collected using a 3.0 Tesla Siemens 3 T Trio MRI System (Siemens Medical, Erlangen, Germany) and a region-of-interest analysis was performed with a brainstem mask and permutation-based nonparametric tests. An EEG signal was collected during RAVANS and heart rate variability analysis (HRV) was performed. Results: The contrast between RAVANS and sham stimulation revealed significantly increased activation of the brainstem, including the nucleus ambiguus. In addition, a significant decrease in the low-frequency (LF) component of HRV was observed. Conclusion: Auricular vagus nerve stimulation synchronizes activity in brainstem and central neural components involved in cardiac autonomic regulation. These results support further evaluation of RAVANS for the treatment of cardiovascular diseases involving autonomic dysfunction.

Clinical Implications: An increased understanding of the autonomic dysfunction is associated with the development and progression of several cardiovascular diseases. If proven effective, this therapy could have significant beneficial effects in the prognosis and the reduction of heart care costs associated with these disorders.

33. Lysine Specific Demethylase-1 Deficiency Accelerates the Development of Renal Damage and Hypertension During Long Term Exposure to Sodium

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Lifespan exposure to salt increases hypertension and cardiovascular/renal (CVR) risk. We recently proposed the Lysine Specific Demethylase-1 (LSD1) as a novel contributor to the etiology of salt hypertension and as a therapeutic target in hypertension. Here we (1) evaluate the timing of onset for CVR changes during long-term sodium loading and (2) assess the preventive value of sodium restriction, in WT and LSD1-deficient (HET) mice. Mice randomized to high (HS) or low salt (LS) were fed longitudinally for 7 months. BP and albumin/creatinine ratios (A/C) were assessed monthly. SBP increased progressively, reaching significance in month 7 for HS. LS/HS and HS/LH differences in SBP effects were driven by a significant interaction between genotype and age on HS. Similar trends were obtained for DIP, suggesting a volume mediated effect. A/C was progressively increased in both HS groups: this change preceded the BP effect. The LS diet prevented/delayed changes in both BP and A/C. Our novel study provides a timeline for CVR development, emphasizing the role of LSD1 in the development of systolic pressure. Moreover, long-term sodium restriction prevented the development of target-organ damage and delayed BP increases in this model.

Clinical Implications: Our study performed in a clinically relevant animal model, suggest that LSD1 deficiency is a risk factor for cardiovascular health, particularly during long-term sodium loading. Sodium restriction may be an efficient prevention strategy for human carriers of LSD1 gene variants.

34. Improving the Total Pancreatectomy with Islet Auto-Transplantation Procedure with a Comprehensive Multi-Disciplinary Team Approach

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Chronic pancreatitis is a disabling condition associated with recurrent abdominal pain, poor nutrition, and worsening glucose tolerance. Total pancreatectomy can lead to pain relief but results in a need for lifelong insulin replacement. Many centers have developed protocols to assess how well the islet cells are working after the development of diabetes, other centers have developed a technique of isolating the islets (clusters of cells that control glucose levels) from the removed pancreases, and re-infusing them into the patient’s liver. BWH is seeking to improve on the experience of total pancreatectomy with islet auto-transplantation (TPIAT) by forming a multi-speciality working group to coordinate care of these patients. In conjunction with colleagues at MGH, we have also developed protocols to assess the function of the islets over time. To date, our first three patients have evidence of islet transplant function after TPIAT; though they remain on varying amounts of insulin. A comprehensive and multidisciplinary approach has been essential for optimal care. Surgical complications and psychological problems have been diagnosed and are being resolved in a coordinated fashion. In conjunction with endocrinologists at MGH, we have also developed protocols to assess how well the islet cells are working after surgery. To date, our first three patients all have milder diabetes than they would have had without the transplant procedure. We have found that a comprehensive and multidisciplinary approach is essential for optimal care. Surgical complications and psychological problems have been diagnosed and are being resolved in a coordinated fashion. In conjunction with endocrinologists at MGH, we have also developed protocols to assess how well the islet cells are working after surgery. To date, our first three patients all have milder diabetes than they would have had without the transplant procedure. We have found that a comprehensive and multidisciplinary approach is essential for optimal care.
Natural killer (NK) cells are so-called due to their natural cytotoxicity against tumors. Obesity is a risk factor for several cancers. We have previously shown that obesity is associated with reduced NK cell cytotoxicity, and obese mice are unable to kill tumors. Transcriptional analysis revealed that obesity induced >1500 gene expression changes in NK cells. Chief among these was the up-regulation of lipid uptake and metabolism genes and down-regulation of genes encoding the cytotoxic machinery. This correlated with in vivo accumulation of lipids, and reduced cytotoxic genes in NK cells from obese individuals compared to lean healthy controls. Increased cellular lipids correlated reduced glycolysis, which is required for NK cell effector functions. In vitro culture of ‘lean’ NK cells with lipids confirms these defects. Further mechanistic analysis revealed that obese NK cells form a synapse with tumors but cannot kill them. Imaging revealed that these NK cells couldn’t polarize their cytotoxic machinery at the tumor interface. These data suggest that an enriched lipid environment modifies the transcriptional program and the metabolic behavior of the NK cells that results in their incapacity to establish a functional synapse and to kill tumor cells.

Clinical implications: Our research seeks to understand the increased risk of cancer during obesity. Our work may provide new therapeutic strategies to decrease and prevent cancer associated with obesity.

36. NK Cell Lipid Accumulation During Obesity Impairs Killing Activity Linked To A Metabolic And Transcriptional Defect

Xavier Micheleet, PhD
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Obesity is associated with an increase risk of cancer. Natural Killer (NK) cells are white blood cells that serve as the body’s first line of defense against cancer. They kill by attaching to tumors and releasing toxic granules. We found that obese individuals have fewer NK cells compared to lean people. Furthermore, the remaining NK cells have lost their ability to kill. Under the microscope, we see that NK cells from obese people can recognize and attach onto the tumor cell but they do not kill them. We therefore looked inside the NK cells and found that the cytotoxic machinery was lost in obesity, instead the NK cells were full of lipids. Genetic screening revealed that ‘obese’ NK-cells gained many genes that induce lipid uptake, and they lost their signature killing genes. When we took ‘lean’ NK-cells and fed them lipids, they lost their killing machinery. This suggests that obesity changes the genes and functions of NK cells, making them incapable of killing tumors, which may be why obesity is associated with a higher cancer risk. We believe that metabolic modification of NK cells may restore their killing function in obesity.

Clinical implications: Our research seeks to understand the increased risk of cancer during obesity. Our work may provide new therapeutic strategies to decrease and prevent cancer associated with obesity.

38. The Deficiency of C59 Accelerates The Development of Diabetic Atherosclerosis in Mice

Rupam Sahoo, PhD
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Diabetes and pre-diabetes are major risk factor for cardiovascular disease (CVD). Individuals with diabetes are a much higher risk of heart attacks, stroke and vascular disease caused by an accumulation of atherosclerotic plaques that can rupture and cause massive blood clots. These clots can block blood flow to the heart or brain leading to heart attack or stroke. Atheromatous plaques are usually composed of a core of necrotic cells, cholesterol, and immune cells encased in a matrix of extracellular matrix proteins.

Extensive experimental and clinical evidence supports a strong link between the complement system, membrane attack complex (MAC), complement regulatory proteins and the pathogenesis of cardiovascular disease. We previously reported that human CD59, an 18–20 kDa GPI-linked glycoprotein that inhibits formation and function of the MAC, is inactivated by glycation of amino acid residue Arg110 that together with H44 forms a unique glycation motif adjacent to its active site. To assess experimentally how the functional deficiency of C59 impacts the development of diabetes complications, we generated mCD59 sufficient and deficient diabetic Apoe-/ mice into the Apoe-/ background (to overcome the highly resistant nature of mice to develop atherosclerosis) and induced diabetes by multiple low doses of streptozotocin. The functional deficiency of C59 accelerates the development of diabetic atherosclerosis in mice, as evidenced by significantly larger atherosclerotic lesion areas in the carotid arteries of diabetic C59-deficient Apoe-/- mice compared to diabetic C59-sufficient Apoe-/- mice (p<0.005). The aortic roots of diabetic mCD59+/Apoe-/- mice also exhibited significantly increased lipid deposition. MAC deposition and macrophage infiltration are also increased in diabetic C59-deficient Apoe-/- mice compared to diabetic C59-sufficient Apoe-/- mice (p<0.05). These results provide experimental support to the hypothesis that inactivation of CD59 in humans with diabetes contributes to their higher risk of CVD.

Clinical implications: We have shown that C59 deficiency accelerates the development of diabetic atherosclerosis in molecular engineered mice. As evidences suggest role of complement system in the development of diabetic atherosclerosis, this study has huge implication in studies diabetic macrovascular complications in human.
It was reported that miR-181b inhibits TNF-a-activated downstream NF-kB signaling. Herein, we reveal that miR-181b inhibits upstream NF-kB signaling uniquely activated by thrombin. MiR-181b inhibited thrombin-induced activation of NF-kB signaling demonstrated by the reduction of phospho-IKK-b, -IkB-a, and p65 nuclear translocation in ECs, and NF-kB target genes including VCAM-1, ICAM-1, E-selectin, PAI-1, and TF. MiR-181b targets Card10, an adaptor protein that participates in IKK complex activation by signals transduced from GPCRs such as PAR-1. MiR-181b reduced the expression of Card10, but not PAR-1. In addition, miR-181b inhibited Card10 3’-UTR luciferase reporter activity, and Argonaute-2 miRNP-IP studies revealed 4-fold enrichment of Card10 mRNA in the RISC by miR-181b, indicating that Card10 is a bona fide direct target. Knockdown of Card10 expression phenocopied miR-181b’s effects on thrombin- but not TNF-a-activated NF-kB signaling and targets, suggesting stimulus-specific regulation of NF-kB signaling and endothelial responses by miR-181b in ECs. Finally, miR-181b reduced thrombus formation by 73%, and prolonged the time to occlusion by 1.6-fold in photochemical injury-induced arterial thrombosis. These studies highlight the relevance of miRNA-dependent targets in response to ligand-specific signaling in ECs. Delivery of miR-181b or Card10 inhibition may represent a new therapeutic approach to reduce arterial thrombosis by improving EC function.

Clinical Implications: Results from this study will advance our understanding on macro-vascular thrombosis, a known predisposition in obese and diabetic subjects. Endothelial miR-181b may represent a key regulator linking obesity and diabetic vascular thrombosis by controlling inflammation that could be exploited for therapeutic intervention in patients with diabetic vascular disease.