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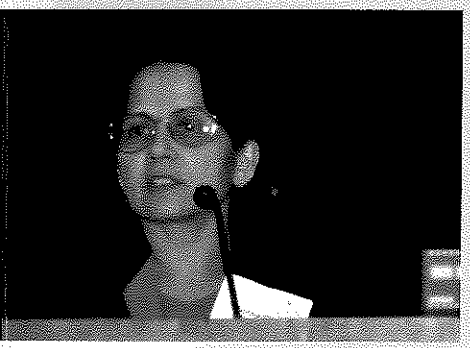

Arteriosclerosis, Thrombosis and Vascular Biology

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Abstracts

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verify miR targeting Suv39h1. Effects of Suv39h1 targeting on inflammatory gene promoter histone methylation (by chromatin immunoprecipitation) and gene expression were analyzed by quantitative real-time PCR. We observed significant and sustained upregulation of miR-125b, and a parallel downregulation of Suv39h1 protein (predicted miR-125b target) in MVSMC derived from diabetic *db/db* mice relative to control *db/+* mice even after culturing ex vivo in non-diabetic conditions. miR-125b mimics inhibited both Suv39h1 3'UTR luciferase reporter activity and endogenous Suv39h1 protein levels relative to control oligos. Conversely, miR-125b inhibitors showed opposite effects. In HeLa cells, miR-125b mimics decreased SUV39H1 protein levels and this was accompanied by increased expression of inflammatory genes interleukin-6 (IL-6) and monocyte chemoattractant protein 1 (MCP-1) and reduced H3K9me3 at their promoters. Interestingly, miR-125b mimics increased monocyte binding to *db/+* MVSMC towards that seen in *db/db* MVSMC, mimicking the inflammatory phenotype of diabetic cells and demonstrating functional relevance. Thus diabetic conditions in VSMC may augment inflammatory genes by decreasing the repressive epigenetic H3K9me3 mark due to miR125b-mediated knockdown of Suv39h1. miR-125b might be a novel target for the prevention or treatment of vascular complications in type 2 diabetes.
L.M. Villeneuve, None; **M. Kato**, None; **M. Wang**, None; **M.A. Reddy**, None; **L. Lanting**, None; **R. Natarajan**, None.

76
Plaque Angiogenesis Is Induced by Diabetes and Accelerates Atherosclerosis Beyond Metabolic Factors
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Background and Hypothesis: Atherosclerosis is a serious complication of diabetes, however, it is not known whether plaque angiogenesis (PA) is induced by diabetes and accelerates atherosclerosis in diabetes. We hypothesized that diabetes-induced plaque angiogenesis (PA) augments atherosclerosis beyond the effects of hyperglycemia and dyslipidemia alone. We previously reported a highly angiogenic strain of ApoE-null mice (ApoE-HA) that developed more PA due to the absence of collagen XVIII, an endogenous inhibitor of angiogenesis that is abundant in the aorta. Our rationale proposed that ApoE-HA and ApoE-null mice would develop similar metabolic changes in response to type 1-diabetes (T1D), but would have different susceptibilities to form vascularized plaques, which would enable us to discern a relative contribution of PA. **Methods**: Male 8-wk old ApoE-null and ApoE-HA mice were treated with or without streptozotocin. T1D and non-diabetic (ND) mice of both strains (N=13 per group) were fed a chow diet and aortas were collected after 12 weeks of T1D to compare atherosclerosis development between all 4 groups. Random blood glucose was checked weekly. Insulin given 3 times/wk as needed to prevent weight loss. **Results**: T1D increased total cholesterol (TC) and mean blood glucose (Glu) compared to ND, however, both risk factors were similar between T1D cohorts of high and low angiogenesis strains (ApoE-HA: TC=806 mg/dl ± 75; Glu=590 mg/dl ± 83; ApoE-/-: TC=775 ± 63; Glu= 565 ± 79). Compared to ND cohorts, T1D increased plaque areas 8.8-fold and 2.1-fold for ApoE-HA and ApoE-/- strains, respectively. T1D aortas contained more CD31+ vasa vasorum; none were detected in ND groups. To determine whether PA was more robust in T1D independent of plaque burden, we normalized PA area for plaque area in each aorta. Adjusted VV areas of T1D ApoE-HA aortas (5.6 ±0.6) were increased relative to T1D ApoE-/- (2.7 ±1, P<0.01) and to ND ApoE-HA (2.1 ±1, P<0.01) raised on 0.15% cholesterol diet for 24 weeks to match plaque areas. **Conclusions**: Together this data shows: i) PA is temporally accelerated and induced by T1D compared to ND mice with a similar burden of atherosclerosis; and ii) T1D-enhanced PA has an additive effect on the acceleration of atherosclerosis beyond metabolic changes.
I.B. McKittrick, None; **G.R. Romeo**, None; **K.S. Moulton**, None.

77
Extended Release Niacin/Laropiprant Lowers Serum Phosphorus Concentrations In Patients with Type 2 Diabetes and Mild Hyperphosphatemia
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In type 2 diabetics (T2D) with normal renal function, serum phosphorus (P) concentrations have been reported as a strong, independent predictor of cardiovascular disease mortality. Calcium salts, despite their efficacy as a phosphate lowering treatment in advanced chronic kidney disease (CKD), can enhance vascular calcification, which may be particularly problematic in T2D. Uncontrolled studies and two small, limited duration placebo-controlled trials indicate that niacin compounds lower serum P concentrations in patients with end-stage renal disease (i.e., stage 5 CKD, an estimated glomerular filtration rate [eGFR] < 15 ml/min/1.73 m2). Such data are complemented by mechanistic studies indicating that niacin causes direct inhibition of sodium-dependent, active intestinal phosphate transport. We expanded upon these observations by evaluating the impact of extended-release niacin [ERN], given in fixed-dose combination with laropiprant [L], a specific inhibitor of prostaglandin-mediated, niacin-induced flushing, versus placebo [PBO], on serum P concentration in a randomized, 36 week trial of dyslipidemic patients with T2D (baseline creatinine <2mg/dL). Serum P was analyzed in a subset of the total patients ((N=446 ERN-L; N=339 PBO) whose baseline serum P was > 3.5 mg/dl (n=224 ERN-L; n=169 PBO), at weeks 0,4,8,12,18,24,30, and 36. Their eGFR ranged from 36-184, with n=62 (15.8%) having an eGFR < 60 (i.e. CKD ≥ Stage 3; 30-59). Patients received 1 tablet daily of ERN-L (ERN 1g/ L 20 mg) for 4-weeks, and 2 tablets once daily, thereafter, or matched PBO. Post-hoc repeated measures analysis in this subgroup demonstrated ERN-L lowered serum P concentrations by 0.39 mg/dl (95% CI: -0.46, -0.31; p <0.001), relative to PBO, expressed as the treatment difference between the Week 12-36 average changes from baseline (baseline means of 3.98 and 3.97 mg/dl for ERN-L and PBO, respectively). These data confirm that niacin's P-lowering effects---which may have therapeutic implications for the management of hyperphosphatemia in renal disease---extend across a broad spectrum of renal function (eGFR) in T2D without stage 4 or 5 CKD (an eGFR ≥ 30).
A.G. Bostom, None; **A.A. MacLean**, Employee of Merck and Co, Significant, A. Employment; **D. Maccubbin**, Employee of Merck and Co., Significant, A. Employment; **D. Tipping**, Employee of Merck and Co, Significant, A. Employment; **H. Gizek**, Employee of Merck and Co, Significant, A. Employment; **W. Hanlon**, Employee of Merck and Co, Significant, A. Employment.

78
Interadventitia Common Carotid Artery Diameter Improves Carotid IMT Ability to Predict Coronary Events: Data from the IMPROVE Study: Carotid Intima Media Thickness (IMT) and IMT Progression as Predictors of Vascular Events in a High-Risk European Population
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Background: The "IMPROVE study" was designed to investigate whether cross-sectional carotid artery intima media thickness (IMT) and overall IMT progression are predictors of new vascular events in European individuals at high risk of cardiovascular diseases. **Aim**: In this report we investigated whether the combination of C-IMTs with the inter-adventitial common carotid artery diameter (CCAD) improves the predictability of cardiovascular events. **Methods**: IMPROVE is a prospective, multicenter, longitudinal, observational study. A total of 3711 subjects (median age 64.4 years; 48% men) with at least three vascular risk factors (VRFs) were recruited in 7 centers in Finland, France, Italy, the Netherlands and Sweden. Collected variables included clinical, biochemical, genetic, socio-economic, psychological, nutritional, and educational data, personal and family history of diseases, drug intake and physical activity. 3703 patients were monitored for a median (IQR) follow-up of 36.2 (35.8-37.4) months. 215 of these patients suffered a first cardiovascular event with an incidence of 19.9 per 1000 person-years. **Results**: In Cox proportional-hazards regression, all the measures of C-IMT were significantly associated with the risk of the combined endpoint even after adjustment for VRFs (age, gender, HDL-C, LDL-C, systolic blood pressure, diabetes, hypertension and pack-years) (P_{trend} <0.005 for all). CCAD was associated with the risk of events independently of vascular risk factors and C-IMT_{max} (adjusted HR for 1 SD increase: 1.26, 95% confidence interval: 1.08-1.48, p=0.004). The results for cardio and cerebro-vascular events were in line with those observed with the combined end point. By time-dependent ROC analysis, CCAD alone had about the same predictive ability of the best predictor among C-IMT variables (IMT_{mean}). Together, IMT_{mean} and CCAD provided a better predictive ability than conventional VRFs (+10.4%). The combination of IMT_{mean}, CCAD and VRFs further improved the total predictive capacity (+22.1% *vs* VRFs alone). **Conclusions**: CCAD and C-IMT are independent predictors of cardiovascular events in European high-risk patients and together they enhance the predictive capacity of VRFs.
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