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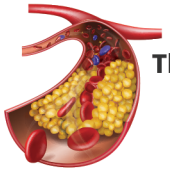

The 28th Annual Meeting of the Israeli Society for Research, Prevention and Treatment of Atherosclersis

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ABSTRACT BOOK

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14.11.2024
DAN HOTEL TEL AVIV

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Untargeted metabolomics reveals biomarkers for the diagnosis of coronary artery plaques as observed by coronary cardiac computed tomography

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Abstract

Background: Atherosclerosis, a major cause of morbidity and mortality in the West, involves stiffening of the arteries due to the accumulation of lipids and oxidized lipids on the blood vessel walls, triggering the development of artery plaque. Coronary artery disease (CAD) is the most common manifestation of atherosclerosis. The prevalence of CAD in the general population remains high, despite efforts to improve the identification of risk factors and preventive treatments. The discovery of new biomarkers is vital to improving the diagnosis of CAD and its risk factors.

Aims: We aimed to identify novel biomarkers that could provide an early diagnosis of coronary artery atherosclerotic plaques, their type, and the percentage of stenosis.

Methods: We used an untargeted metabolomics approach to identify potential biomarkers that could enable highly sensitive and specific CAD detection. The study consisted of 109 patients who underwent cardiac computed tomography angiography at the Cardiology Department of Ziv Medical Center. 54 patients were diagnosed with coronary atherosclerotic plaques (CAD group), and 55 without plaques used control.

Results: Untargeted metabolomics using LC-MS/MS revealed 2560 metabolites in the patients' serum:106 showed statistically significant upregulation in the serum of the CAD group compared to the healthy control group ($p < 0.05$). These metabolites belonged to the following chemical families: acyl-carnitines, cyclodipeptides, lysophosphatidylcholine, and primary bile acids. In contrast, 98 metabolites displayed statistically significant downregulation in the serum of the CAD group compared to the control group, belonging to the following chemical families: amino acids and derivatives (inhibitory neurotransmitters), lipids, secondary bile acids, N-acyl-alpha amino acids.

Conclusions: Our comprehensive untargeted serum metabolomic analysis revealed biomarkers that can be used for the diagnosis of patients with CAD. Further cohort studies with a larger number of participants are needed to validate the detected biomarkers.

Title: The Fluid Mechanics of Vascular Diseases and Localized Therapeutics

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Introduction: The vascular system is a complex and dynamic network where interactions between vascular physiology and fluid transport processes play a crucial role in both health and disease. Many vascular conditions, such as atherosclerosis, aneurysms, stroke, heart valve disease, and arterial thrombosis, have been linked to abnormal local blood flow characteristics, including low or high shear stress and flow disturbances like eddies. Understanding the biophysical aspects of these abnormal flow patterns and their contribution to vascular diseases could provide valuable insights into the causes of these conditions and help inform the development of novel therapeutic and diagnostic strategies.

Methods: To study targeted drug delivery under pathological hemodynamics in various vascular disease conditions including brain aneurysms and stenotic arteries, in vitro perfusion experiments were performed. Human reconstructed blood vessel in vitro models recapitulating vascular diseases, such as arterial thrombosis and brain aneurysms were fabricated, and endothelial cells were cultured in these vessels. Different nanoparticle-based drug carriers were fabricated and their deposition under flow was studied. Computational Fluid dynamic simulation was performed to study the link between flow properties and particle deposition.

Results: Our findings revealed that particle localization is strongly influenced by vessel geometry and local flow characteristics. Moreover, while highly adhesive particles predominantly adhere in high-shear regions linked to athero-thrombosis, increased deposition in vascular areas associated with inflammation and plaque buildup, such as recirculation zones, can be achieved using weakly adhesive particles. The results show that particle adhesion can be tuned to allow selective deposition at different disease sites such as: arterial stenosis sites or aneurysm sites. By engineering particles with defined geometries covered with a targeting motifs improved drug delivery may be achieved offering new opportunities to improve therapeutics.

Conclusion: The link between blood flow dynamic and vascular disease sites can be leveraged to improve localized therapeutics to these disease sites.

A NEW SPRING IN CHOLESTEROL METABOLISM: NEW FUNCTIONAL AND STRUCTURAL INSIGHT

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Introduction: Cellular and whole-body lipid homeostasis is controlled by a multitude of transcriptional and post-transcriptional mechanisms. Herein, the Sterol Regulatory Element Binding Proteins (SREBPs) play a central role as the master transcriptional regulators of cholesterol and fatty acid metabolism. The transcriptional activation of SREBPs involves a series of intracellular trafficking and proteolytic events that have been extensively characterized in the last two decades. Using a genome-wide functional genetic screen we have recently discovered that the uncharacterized gene, SPRING (also known as C12ORF49), is essential for SREBP signaling. Our aim is to characterize the role of SPRING in SREBP-regulated lipid and lipoprotein metabolism.

Methods: To study the physiological role of hepatic SPRING we developed liver-specific Spring knockout mice (LKO). In order to investigate how SPRING governs SREBP activation we generated cells devoid of SPRING and S1P (the protease that performs the first proteolytic cleavage step of SREBP) and used these to reconstitute variants of both proteins to elucidate the role of the SPRING-S1P nexus in control of SREBP signaling. Structural insight on the mechanism of action of SPRING was obtained by determining the structure of the SPRING-S1P complex by cryo-EM.

Results: LKO mice have severely attenuated hepatic SREBP signaling. This is associated with impaired cholesterol and fatty acid synthesis, and as a consequence reduced hepatic levels of these lipids, reduction in VLDL secretion, and a dramatic decrease in circulating cholesterol levels in both male and female mice. accordingly, absence of hepatic Spring renders LKO mice resistant to fructose-induced hepatosteatosis. Mechanistically, we found that SPRING is a critical determinant of S1P-mediated cleavage of SREBP, owning to its ability to promote the auto-proteolytic maturation of S1P into its mature, fully active form in the Golgi. The structural basis for this lies in the ability of SPRING to displace the inhibitory S1P pro-domain in the Golgi, a step required for SREBP cleavage. These physiological, mechanistic, and structural findings will be presented.

Conclusions: SPRING is a core component of the SREBP activation machinery, and has a profound role in governing hepatic lipid and lipoprotein metabolism. Therapeutic modalities that target hepatic SPRING may be an attractive strategy to lower plasma lipid levels and to treat fatty liver disease.

The Genetic link between Depression and Cardiovascular Disease in Premenopausal Women

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Abstract:

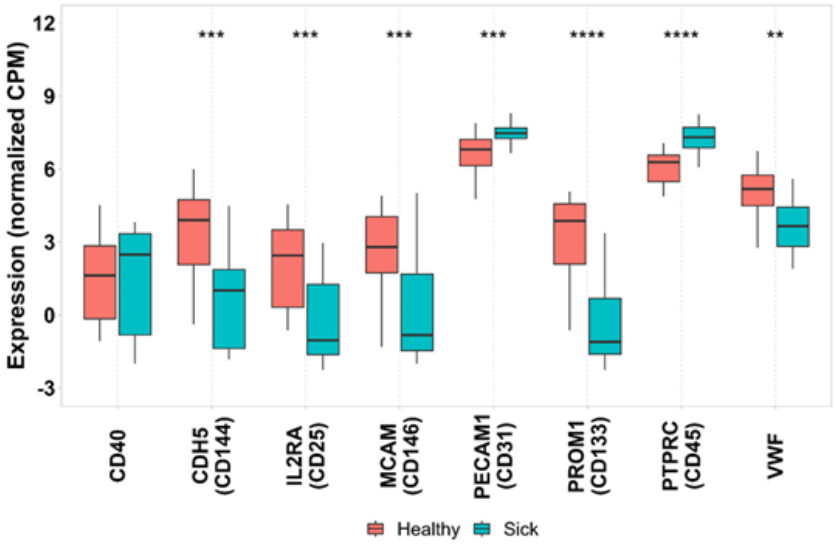
Background: Cardiovascular disease (CVD) events are rare in pre-menopausal women. Still, women with depression have a higher prevalence of CVD. It is known that patients with depression suffer from endothelial dysfunction, and impaired ability to regenerate endothelial progenitor cells. Still, the association between depression and CVD is not well understood, especially in young women.

Methods: We collected pheripheral blood samples from 30 pre-menopausal women diagnosed with major depression and 28 aged-matched healthy women. From these blood samples we extracted RNA and conducted RNA sequencing to obtain comprehensive gene expression profiles. Gene expression analysis was performed to identify differences between the two groups.

Results: We detected 6540 differentially expressed genes between the two groups, of which 5577 were down-regulated and 963 up-regulated. Of these genes, we detected a significant decrease of CD144 (VE-Cadherin) (p=0.0001), CD146 (MCAM) (p=0.0001) and CD133 (PROM1) (p=0.00009), all known to enhance endothelial progenitor cells and regeneration of damaged blood vessels.
A significant increase was found in the expression of CD31 (PECAM1) (p=0.0003) and CD45 (PTPRC) (p=0.00001), both known to promote atherogenesis and thrombogenesis with platelets' and T lymphocytesw activation.

Discussion: In young women with depression, RNA gene expression analysis demonstrated that genes responsible for endothelial cells adherens junction, mature endothelial cells, and endothelial progenitor cells were downregulated. On the other hand, genes for platelets' and lymphocytes' activation were upregulated in this population compared with healthy age-matched women. We have shown previously that pre-menopausal women with depression had an impaired ability to grow colonies of endothelial progenitor cells. Young women with depression are more vulnerable genetically to develop CVD because of the downregulatred genes of stem cells' endothelial vascular regeneration and upregulation of genes coding for platelets' and T lymphocytes' activation, this way accelerating the atherosclerotic and atherothrombotic pathway.

Key words: RNA gene expression, endothelial progenitor cells (EPCs), CD144, CD146, CD133



THE PCSK9 CONTENT IN PLATELETS OF HeFH PATIENTS. ROLE IN PLATELET FUNCTIONALITY AND THE EFFECT OF anti-PCSK9 mAbs

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Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease which binds to the Low-Density Lipoprotein Receptors (LDL-R), leading to their intracellular degradation and subsequently to the increase in plasma LDL-cholesterol levels. PCSK9 is primarily expressed and secreted by the liver. Recent studies have demonstrated the existence of PCSK9 in human platelets, however the role PCSK9 in platelet functionality remains to be established.

Aim: In the present study we determined the levels of PCSK9 in washed platelets (WP) prepared from patients with heterozygous familial hypercholesterolemia (HeFH). The effect of the monoclonal antibodies (mAbs) against PCSK9 administered in these patients in vivo on the PCSK9 content in platelets as well as on platelet aggregatory response in vitro, were investigated.

Methods: 21 non-smoking HeFH patients aged 53±10 years (11 men/10 women), exhibiting LDL-cholesterol levels ≥100 mg/dL, despite receiving the maximum tolerated hypolipidemic treatment (rosuvastatin 20-40 mg or atorvastatin 40-80 mg plus ezetimibe 10 mg), were treated with an anti-PCSK9 mAb (alirocumab or evolocumab). Washed platelets were prepared from peripheral blood samples withdrawn before (baseline) and 2 months after the administration of 4 doses of the anti-PCSK9 mAbs (follow-up). WP were lysed using a lysis buffer and their content in total protein and PCSK9 were determined using the BCA method and a commercially available ELISA kit, respectively. Furthermore, the forms of PCSK9 in WP were determined by western blotting analysis. The platelet aggregatory response to Arachidonic acid (AA) or Thrombin at baseline and at follow-up was also studied.

Results: WP from HeFH patients contain both, the mature and the furin-cleaved forms of PCSK9. The total intracellular PCSK9 levels at baseline were 2.15 ± 0.27 ng / mg cell protein. Importantly, after administration of 4 doses of alirocumab or evolocumab, these levels significantly increased to 3.32 ± 1.02 ng / mg protein ($P<0.04$) in parallel with the expected significant reduction of the LDL-cholesterol levels. Furthermore, the platelet aggregatory response to AA or Thrombin was significantly reduced at follow-up as compared with that determined at baseline.

Conclusions: The present study demonstrates that WP from HeFH patients contain both forms of PCSK9. Administration of the anti-PCSK9 mAbs increase the PCSK9 levels in WP and reduce the platelet aggregatory response, suggesting that the intracellular PCSK9 exhibits an inhibitory effect on platelet aggregation. The underlying mechanism of this effect as well as the possible other effects of PCSK9 on platelet functionality, needs further investigation.

Dynamic life style-induced changes in Asymmetric Dimethylarginine (ADMA) correlate with alteration in lipid profile and fasting insulin in subjects with the metabolic syndrome

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Background: Elevated levels of Asymmetric Dimethylarginine (ADMA) are linked to a higher incidence of Major Adverse Cardiovascular Events (MACE). ADMA is a significant predictor of MACE, independent of other risk factors such as age, sex, blood pressure, smoking history, and diabetes. It is known to inhibit nitric oxide synthase, reducing nitric oxide production and potentially causing endothelial dysfunction. ADMA could be a valuable diagnostic tool for cardiovascular risk assessment, though its integration into current risk scores requires further validation.

Methods: A cohort of 75 participants (33 men and 42 women) diagnosed with Metabolic Syndrome (MS) according to ATPIII criteria, underwent a 1-year intensive multidisciplinary treatment. This included personalized physical training and a low-calorie, high-protein Mediterranean diet. Baseline characteristics were mean±SD: age 53.3±11.2 years, weight 99±17 kg, BMI 34.5±4 kg/m², ADMA 0.5±0.2 µmol/L, L-Arginine 45±15 µmol/L, triglycerides (TG) 193±85 mg/dL, cholesterol 190±35 mg/dL, and insulin 26±18 µIU/mL.

Results: After one year, participants experienced a 9% reduction in BMI ($p<0.0001$), a 10% reduction in cholesterol only in men ($p<0.0001$), and a 27% reduction in TG ($p<0.05$ in women, and $p<0.0001$ in men). ADMA levels decreased by 17% ($p=0.036$ for women, $p=0.0064$ for men). L-Arginine levels increased by 14% but did not reach statistical significance. Significant correlations were observed between changes in ADMA and: insulin ($r=0.51$; $p<0.05$), cholesterol ($r=0.38$; $p<0.05$), TG ($r=0.36$; $p<0.05$).

Conclusion: In the metabolic syndrome, lifestyle modifications, including a Mediterranean diet rich in protein and weight loss achieves reduction in ADMA levels which is linked to changes in classical risk factors such as serum cholesterol, triglycerides and insulin.

IMPLEMENTATION RESEARCH: THE STATE OF CURRENT MANAGEMENT OF THE HEIGHTENED RISK FOR ASCVD EVENTS IN A COHORT OF PATIENTS WITH LUPUS ERYTHEMATOSUS

Introduction/ Background: Patients with lupus erythematosus (LE) are at heightened risk for clinical events, chiefly heart attacks and strokes, from atherosclerotic cardiovascular disease (ASCVD). We recently proposed new guidelines to assess and manage ASCVD event risk specifically in LE.1 Here, we examined current cardiovascular management in light of these new recommendations.

Methods/ Materials: We studied our entire UPenn Longitudinal Lupus Cohort of patients with cutaneous LE, without (CLE-only) or with (CLE+SLE) concurrent systemic LE, for whom we had full access to medical records (n=370, LE-ASCVD Study Cohort). This study was approved by the University of Pennsylvania Institutional Review Board, IRB Protocol number 849182. Participants gave informed consent to participate in the study before taking part.

Results: Of our LE-ASCVD Study Cohort, 336/370 (90.8%) had a designated primary-care physician. By the new guidelines, the most recent LDL levels were above-goal for 249/370 (67.3%). Two-hundred sixty-six (71.9%) had hypertension, which was under- or un-treated in 198/266 (74.4%). Of current smokers, 51/63 (81.0%) had no documented smoking cessation counseling or referrals. Diabetes and triglyceridemia were generally well-managed. Of the Cohort, 278 qualified for two widely used online estimators of ASCVD event risk in primary prevention: the ACC-ASCVD Risk Estimator Plus and QRisk3. We also stratified these 278 patients into our recently defined categories of ASCVD event risk in LE. These three methods for estimating ASCVD event risk showed clinically meaningful discordance for 169/278 (60.8%). The documented rate of ASCVD events in the first 10 years after enrollment was 13.5% (95% CI 8.9%, 17.9%), similar between CLE-only and CLE+SLE, indicating an at-risk population despite the preponderance of women and a median age at enrollment of only 47 years.

Conclusions:
Patients with CLE-only or CLE+SLE are under-treated compared with the new guidelines and, accordingly, they experience a significant burden of ASCVD events. Moreover, it is unclear how to accurately assess their future ASCVD event risk, except that it is substantial. Efforts are underway to improve ASCVD event risk estimation and guideline implementation in lupus patients.
This study was supported by funding from the Lupus Foundation of America. Abstract adapted from reference2 with permission under The BMJ Author Licence.

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