

PP-WE-817

The effect of leptin on vascular calcification in apolipoprotein E – deficient miceZeadin MG¹, Butcher M², Werstuck GH³, Khan MI⁴, Yee CK¹, Shaughnessy SG⁵¹Pathology and Molecular Medicine, McMaster University;²Pathology and Molecular Medicine, Henderson Research Centre; ³Biochemistry and Biomedical Sciences, McMaster University and Henderson Research Centre; ⁴Biochemistry and Biomedical Sciences, Henderson Research Centre; ⁵Pathology and Molecular Medicine, McMaster University and Henderson Research Centre, Hamilton, Canada

Recent studies suggest that factors secreted by adipose tissue may be playing a role in promoting cardiovascular disease (CVD). One such factor, the adipocytokine leptin, has been proposed to increase cardiovascular risk in both obese and diabetic individuals. In the current study, therefore, we used apoE-deficient mice to examine leptin's effect on both lesion development and calcification *in vivo*. Briefly, mice were treated with once daily intraperitoneal injections of leptin (125 mug/mouse/day) for a period of two months. The mice were then sacrificed, their hearts removed, and sections of the aortic root analyzed histomorphometrically. Measurements of lesion size, in the region of the aortic valves, did not reveal any differences between leptin-treated and non-treated animals. However, von Kossa staining of the lesions demonstrated an 8.3 ± 2.0 -fold increase in lesion calcification, as well as a 2.5 ± 0.6 -fold increase in valvular calcification in leptin-treated animals as compared to non-treated animals. In addition, the percent total lesion area demonstrating alkaline phosphatase (ALP) positive staining was 5.4 ± 2.1 -fold greater in leptin-treated mice when compared to non-treated, age-matched control mice. This increase in ALP staining was also accompanied by an increase in the expression of the osteoblast-specific markers, osteocalcin and osteopontin. Based on these observations, we conclude that leptin may increase cardiovascular risk by promoting osteogenic differentiation and vascular calcification within atherosclerotic lesions.

Disclosure of interest: none declared.

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Platelet-dependent lymphocyte adhesion under arterial flow conditions: evidence from *in vitro* and *in vivo* studiesZhu L¹, Hu H², Ji Q³ and Li N¹¹Department of Medicine, Clinical Pharmacology Unit, Karolinska Institute, Stockholm, Sweden; ²Department of Pathology and Pathophysiology, Zhejiang University School of Medicine, Hangzhou; ³Department of Cardiology, Qilu Hospital of Shandong University, Jinan, China

Background: Platelets and lymphocytes play pivotal roles in atherosclerosis, but little is known about platelet-lymphocyte interaction during atherogenesis. We therefore studied if platelets support lymphocyte infiltration into the arterial wall.

Methods and Results: Reconstituted human blood with fluorescence labeled platelets and lymphocytes was perfused at different shear rates through a parallel-plate flow chamber equipped with a fluorescent intravital microscope. Platelets readily adhered on collagen-coated surface, and the number and size of adhered platelets/platelet aggregates decreased as the shear rate elevated. Adhered platelets markedly enhanced lymphocyte adhesion, seen as the increases of adhered lymphocytes/mm² from 102 ± 39 in platelet-depleted blood to 274 ± 79 in platelet-containing blood at 200 s (-1) (venous), from 66 ± 26 to 203 ± 51 at 500 s (-1) (arterial), and from 27 ± 10 to 114 ± 27 ($P < 0.01$ for all; $n=6$) at 1000 s (-1) (narrowed arterial). Deposition of lymphocyte subsets after whole blood perfusion was monitored by flow cytometry. Lymphocyte deposition was mostly seen in T cells and was minimal in B and NK cells. T cell adhesion

was preferable in large/activated cells, especially in platelet-conjugated T cells, as platelet-conjugated large CD4 cells were reduced from $30 \pm 9/\mu\text{L}$ before to $18 \pm 4/\mu\text{L}$ ($P < 0.05$; $n = 5$) after perfusion over collagen-coated surface at 500 s(-1). Using a mouse model of photochemically induced arterial thrombosis, we have confirmed the infiltration of fluorescence labeled lymphocytes into platelet thrombi in the mesenteric arteries.

Conclusions: Platelets support lymphocyte adhesion under arterial flow conditions, which is selective among large, platelet-conjugated T cells. Our data suggest that platelets may exacerbate atherogenesis via facilitating T cell adherence and migration into the arterial wall.

Disclosure of interest: none declared.

PP-WE-819

Association of blood cellular markers with carotid plaque size and compositionMatijevic N¹, Wu KK¹, Howard AG², Wasserman B³, Wang W¹, Folsom AR⁴ and Sharrett R⁵¹Internal Medicine-Hematology, University of Texas Health Science Center, Houston; ²Biostatistics, University of North Carolina, Chapel Hill; ³Radiology, Johns Hopkins University, Baltimore; ⁴Epidemiology and Community Health, University of Minnesota, Minneapolis; ⁵Epidemiology, Johns Hopkins University, Baltimore, USA

Background: Atherosclerosis is characterized by infiltration of inflammatory cells derived from circulating blood. Blood cell activation may therefore play an important role in contributing to plaque formation. We postulated that plaque size and composition, measured by magnetic resonance imaging (MRI) of the carotid artery, are associated with proinflammatory conditions of circulating blood cells. To address this, we analyzed blood cellular markers in 1547 participants from the ARIC (Atherosclerosis Risk in Communities) Carotid MRI Study.

Methods: For the thickest area of the carotid wall, we assessed plaque size, expressed as total wall thickness and volume, and plaque composition, assessed as lipid core quantity and fibrous cap thickness, in this large sample of men and women. Cellular phenotyping was performed by flow cytometry (FC) using antibodies against platelets (CD41, CD61, CD62P, and CD154), and monocytes (CD14, CD162, TLR2, TLR4, and MPO). After multivariable adjustments for risk factors, data are presented as standardized beta (beta) coefficients for a number of standard deviations (SD) differences in MRI variables associated with one SD increment in FC measures.

Results: Monocyte TLR-2 was associated with greater plaque size (beta = 0.11, $P = 0.03$), while CD14 (beta = -0.14, $P < 0.01$), MPO (beta = -0.10, $P = 0.03$), and TLR-4 (beta = -0.13, $P < 0.01$) were associated with smaller plaque size. Platelet activation marker CD40L was associated with smaller plaque size (beta = -0.10, $P = 0.03$) and thinner caps ($b = -0.03$, $P = 0.04$), and P-selectin with smaller core size (beta = -0.08, $P = 0.03$).

Conclusions: Blood cell activation is significantly associated with atherosclerotic changes of the carotid arterial wall. Monocyte markers are predominantly associated with plaque size, while platelet markers are associated with plaque size, fibrous cap, and plaque lipid core, supporting their involvement with plaque formation.

Disclosure of interest: none declared.

PP-WE-820

High-risk atherosclerosis of mogilev schoolchildrenAkulich NV¹ and Kruchinsky NG²¹Ecological physiology; ²A.A Kuleshov Mogilev State University, Mogilev, Belarus

The researches have covered 300 10–14 aged schoolchildren living in the city of Mogilev. The frequency of popularity of major atherosclero-

sis risk factors and the cytogenetic status were studied and general and biochemical blood tests were performed using a developed protocol. The protocol application has displayed that a 17% decrease in a number of erythrocytes, the increase in levels of cutaneous cholesterolin and β -lipoproteins by 45% and 67%, respectively, and a fivefold increase in concentration of substances with average molecular mass (SMM) are typical for Mogilev children and teenagers. As a result, the dependence between parameters of the lipid interchange and a function of the blood circulation system was found to be directly proportional. The diastolic pressure of the children under investigation depended directly and inversely proportional on the concentration of substances with average molecular mass and the number of erythrocytes, respectively. It should be noted that there was genomic instability in the group of Mogilev children and teenagers, in particular a higher level of dicentric and ring chromosomes (0.55 ± 0.11 , $P < 0.05$) and polyploid cells (0.36 ± 0.10 , $P < 0.05$). The latter indicates activation of reparation systems. We also detected increases in a rate of radiation damage markers and a general rate of chromosome aberration (6.10 ± 0.43) and aberrant cells (5.08 ± 0.33), which exceed the control values. The developed set of registration – statistical data to a great extent of probability is the quality performance of health of the children's population and the integrated characteristic of quality of environment. Using these data, one can assume that the Mogilev children have the high ecologically dependent risk of atherosclerosis as far as genomic instability and endogenic intoxication in combination with the dysfunction of lipide interchange have been revealed.

Disclosure of interest: none declared.

PP-WE-821

Association study between variants in GAS6-TAM genes and atheroma carotid plaque

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Background: Previous studies of our group indicated an association between a single nucleotide polymorphism (SNP) and a haplotype of *GAS6* and stroke [1]. Carotid atherosclerosis (CA) is the most common cause of stroke and recent studies suggest that pathways initiated by the interaction of the plasma vitamin K-dependent protein *GAS6* with the tyrosine kinase receptors *TYRO3*, *AXL* and *MERTK* (TAM) may have a relevant role in atherogenesis.

Goal: The aim of this study was to analyze the genetic association between SNPs and haplotypes in *GAS6-TAM* genes and CA.

Material and Methods: We selected 19 SNPs from both public databases and our previous studies. We performed a case-control study with DNA samples from 145 patients who had CA confirmed by nuclear magnetic resonance (NMR) and 162 patients who suffered from cardioembolic (non-atherogenic) stroke. For all patient and control samples there was information on traditional risk factors. Genotyping was performed by real-time PCR, using both FRET (Roche) or TaqMan (Applied Biosystems) probes.

Results: Minor allele frequencies (MAF) were different between atherogenic and non-atherogenic populations for the rs2277537 and rs16971872 SNPs in *TYRO3*. Adjusted logistic regression (LR) analyses indicated that one SNP in *TYRO3* (rs2277537) and one in *MERTK* (rs869016) associated with CA, respectively increasing (OR: 2.72 95%CI: [0.95–7.78]) and decreasing (OR = 0.39 [0.10–0.79]) the risk of CA. Linkage disequilibrium results were in concordance with the haplotype blocks described in HapMap and adjusted LR analyses revealed that the haplotypes GCTCA in *TYRO3* and the ACAA in *MERTK*, both containing the minor allele of the associated SNPs, were also associated with CA.

Conclusion: The association between SNPs and haplotypes in *TYRO3* and *MERTK* and carotid atherosclerosis suggests a physiological role of these genes and the *GAS6-TAM* pathway in atherogenesis.

Reference: I. Muñoz X, Obach V, et al. Association of specific haplotypes of *GAS6* gene with stroke. *Thromb Haemost*; (2007) 98:406–412.

Disclosure of interest: none declared.

PP-WE-822

Protein S and tyrosine kinase receptors TYRO3, AXL and MERTK are differentially expressed in carotid atherosclerotic plaques

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Background: Interaction of the plasma vitamin K-dependent proteins *GAS6* and protein S (PS) with the tyrosine kinase receptors *TYRO3*, *AXL* and *MERTK* (TAM) initiates different signalling pathways which may have a relevant role in atherogenesis. Furthermore, association between polymorphisms in *GAS6*, *TYRO3* and *MERTK* and both, carotid atherosclerosis and stroke, indicates a possible implication of this system in carotid atherogenesis.

Goal: To analyze mRNA and protein expression of PS, *GAS6* and their TAM receptors in carotid atherosclerotic plaques.

Material and Methods: mRNA and protein samples isolated from 20 carotid plaques of endarterectomized (CEA) patients were analyzed by real-time quantitative RT-PCR using TaqMan Low Density Arrays and by western blot assays. We knew plaque morphology, intra-plaque angiogenesis and type of stroke suffered. As controls, we included 6 normal carotid arteries obtained from organ donors or post-mortem autopsies.

Results: There was no difference in *GAS6* expression. *PROS1*, *AXL* and *TYRO3* mRNA was less expressed in carotid plaques than in normal arteries, independently of the plaque characteristics. Subexpression was greater in samples from patients who suffered from stroke than in asymptomatic ones. mRNA expression of *MERTK* was higher in plaques than in normal carotid arteries but this was not statistically significant. Western blot results of *GAS6* (no change), *AXL* (decreased) and *MERTK* (increased) were in concordance with the mRNA results. By contrast, PS expression was higher in the carotid plaques than in normal arteries, thereby suggesting infiltration of this protein from plasma.

Conclusion: Increased abundance of PS and the *MERTK* receptor in carotid atheroma plaques reinforces a role of the PS-*MERTK* interaction in carotid atherogenesis and it also confirms a role for PS independent of its traditional anticoagulant role.

Disclosure of interest: none declared.

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Human atherosclerotic plaques potentiate platelet aggregation: role of MMP-2

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Matrix metalloproteinases (MMPs), a family of enzymes able to degrade and to remodel extracellular matrix in several physiologic and pathologic conditions, play a crucial role in atherosclerotic plaques formation and rupture. In atherosclerotic plaques the degree of

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