LXVIII JCET LECTURE, 14.09.2015, 9.00

Platelet Extracellular Vesicles (PL-EVs) are carriers of proteins involved in vascular- and neurodegenerative diseases

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Introduction: During activation and senescence, platelets release increased amounts of platelet extracellular vesicles (PL-EVs). We established an *in vitro* model for size, proteomic, lipidomic and transcriptomic characterization of PL-EVs over 5 days in platelet concentrates to better understand the platelet storage lesion.

Methods: After 5 days standard blood banking, PL-EVs were isolated by filtration and differential gradient ultracentrifugation into 5 platelet microvesicle subfractions (PL-MV F1-F5) and platelet exosomes (PL-EXs) and subjected to Nanoparticle Tracking Analysis, Flow Cytometry, proteomic/lipidomic mass spectrometry, miRNA-microarray profiling and deep sequencing.

Results: PL-EVs showed overlapping particle mean sizes of 180-260 nm, but differed significantly in composition. Less dense, intermediate and dense PL-EVs respectively are enriched in lipidomic and proteomic markers for plasma membrane, intracellular membranes/platelet granules and mitochondria. Alpha-synuclein (81% of total expression) accumulated in F1-F2, amyloid beta precursor protein in F3-F4 (84%) and ApoE (88%) and ApoJ (92%) in F3-5. PL-EXs are enriched in lipid-raft and adhesion markers. During platelet senescence, HDL_3/apoA-I significantly reduce PL-EVs by 62%, and the decrease correlates with the concentration of added apoA-I. Compared to platelets, PL-EVs enriched neurological disease-relevant miRNAs.

Conclusions: Different lipid and protein compositions of PL-EVs suggest their unique cellular origins, partly overlapping with platelet granule secretion. Dense PL-EVs might represent autophagic vesicles released during platelet activation/apoptosis and PL-EXs resemble lipid rafts, with a possible role in platelet coagulation and immunology. Segregation of alpha-synuclein and amyloid beta precursor protein, ApoE/J into less dense and dense PL-MVs, respectively, show their differential carrier role of neurological disease-related cargo. HDL_3/apoA-I influences membrane homeostasis of platelets by reduction of PL-EV release during platelet senescence, improving intracellular lipid processing/vesicle transport and increasing cholesterol CE-efflux.

Publikacje

1. **Mass spectrometric analysis of lipid species of human circulating blood cells.**

Biochim Biophys Acta. 2008 Oct;1781(10): 655-64. doi: 10.1016/j.bbalip.2008.07.008. Epub 2008 Aug 6. (Katharina Leidl, Gerhard Liebisch, Dorothea Richter, Gerd Schmitz)

2. **High-density lipoprotein 3 and apolipoprotein A-I alleviate platelet storage lesion and release of platelet extracellular vesicles.**

Transfusion. 2014 Sep;54(9):2301-14. doi: 10.1111/trf.12640. Epub 2014 Jun 10. (Annika Pienimaeki-Roemer, Astrid Fischer,Maria Tafelmeier, Evelyn Orsó, Tatiana Konovalova, Alfred Böttcher, Gerhard Liebisch, Armin Reidel, Gerd Schmitz)

3. **Stored platelets alter glycerophospholipid and sphingolipid species, which are differentially transferred to newly released extracellular vesicles.**

Transfusion. 2013 Mar;53(3):612-26. doi: 10.1111/j.1537-2995.2012.03775.x. Epub 2012 Jul 15. (Annika Pienimaeki-Roemer, Katharina Ruebsaamen, Alfred Boettcher, Evelyn Orsó, Max Scherer,Gerhard Liebisch, Dzenan Kilalic, Norbert Ahrens, and Gerd Schmitz)

4. **Plateletderived extracellular vesicles in plateletpheresis concentrates as a quality control approach.**

Transfusion. 2015 Jun 1. doi: 10.1111/trf.13128. [Epub ahead of print] (Black A , Pienimaeki Roemer A , Kenyon O , Orsó E , Schmitz G)

Nota biograficzna

- Medical studies and graduation from the University of Cologne
- 1975 he joined the research group of Prof. Dr. med. Gerd Assmann at the University in Cologne and followed him 1978 to the University of Muenster where he worked at the Institute of Atherosclerosis Research and the Institute of Clinical Chemistry and Laboratory Medicine as a postdoc
- He received his Ph.D. degree in clinical pathology in April 1979 (“Disturbances of Lipolysis in Tangier disease”).
- He has become a certified clinical chemist, and specialist in laboratory and transfusion medicine.
- December 1984 he earned the qualification as an independent university teacher (habilitation “Diagnosis and Pathology of Apolipoproteinopathies”)
- From September 1990 till June 1991 he worked as an associate professor at the University of Muenster
- 1991-2004 member of the International Scientific Advisory Board of Bayer Diagnostic Corporation (Terrytown,NY, USA)
- Cofounder of the Regensburg Biopark and the Competence Center for Fluorescent Bioanalysis.
- Initiator of the Institute of Functional Genomics at the University of Regensburg, headed by Prof. P. Oefner
- Coordinator for the DFG-Transregional Collaborative Research Center (SFB-TR13) Membrane Microdomains and their role in Human Diseases
- In 2000 cofounder of the MULTIMETRIX GmbH, the first company in Germany developing multiplex testing for various infections and autoimmune diseases on the LUMINEX platform

- From June 1991 till October 2014 he held the chair of Laboratory Medicine and Transfusion Medicine at the University of Regensburg
- Together with his wife, Dr. rer. nat. Anna Schmitz-Madry, he founded 2014 the LipoConsult GmbH in Havixbeck, near Muenster.
- He is still a member of the Medical Faculty of the University of Regensburg
- The major research interest of Prof. Gerd Schmitz has been the pathogenesis of vascular and metabolic diseases and other chronic degenerative diseases of the elderly with a major focus on the role of the innate immune system (monocytes/macrophages; neutrophils) and particularly in cytomics of blood cells and their microparticles
- His research group was the first who published the genetic defects of the rare diseases Acid Lipase Deficiency (Wolman's Disease/Cholesteryl Ester Storage disease), Apo AI Deficiency with Plane Xantomas and ABCA1 Deficiency (Tangier disease). The group continued identifying new mutations in ABCA3 deficiency, ceroid lipofuscinosis, Hermansky-Pudlack Syndrome and sphingolipidoses, eg. Niemann-Pick disease
- The most frequently cited result is the cloning of ABCA1 (ATP-binding cassette transporter A-1) as the major regulator of plasma high density lipoproteins (HDL) and identification of its loss-of-function mutations leading to the familial HDL-deficiency syndrome in Tangier disease
- In the field of Laboratory Medicine and Transfusion Medicine his major interest is development and implementation of new technologies for liquid,cellular and molecular analyses
- In 1991 he founded the European Working Group on Clinical Cell Analysis (EWGCCA) funded by the EU-BIOMED program(add Website) establishing numerous consensus protocols for clinical cell analysis in hematology, hemostaseology and cellular immunology
- Together with other leading European scientists he organized 2005 the Danubian Biobank Consortium funded by the FP6-EU project SSA 018822(http://www.danubianbiobank.de) to promote health care integrated biobanking (HIB)
- From 2007 till 2012 he was the coordinator of the European FP-7-IP-Project LipidomicNet (here LipidomicNet Website)
- He participates in numerous systems-health projects within national BMBF-SysMBIO (add Website), BMBF-DEEP (add Website) and EU-funded MyNewGut (add Website) Consortia
- Prof. Schmitz is a member of the editorial boards of several scientific journals

Professor Schmitz has published more than 350 scientific papers and over 30 book chapters, receiving more than 15.000 citations.