

The Diabetic Platelet

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Platelets from patients with diabetes are hyper-reactive and demonstrate increased adhesiveness, aggregation, degranulation and thrombus formation; processes that contribute to the accelerated development of vascular disease. Finding a potential therapy to normalize platelet function in diabetes is hampered by the fact that numerous signaling pathways are defective. This seminar outlines the link between elevated platelet Ca^{2+} levels with post-translational changes in the platelet proteome.

Looking at the myriad of platelet pathways altered in the diabetic platelets one of the earliest described is an increase in basal Ca^{2+} levels as well as an exaggerated response to agonist stimulation. It has been possible to link this with the oxidative stress associated with diabetes as the peroxynitrite generated results in the tyrosine nitration and inhibition of the Ca^{2+} ATPase SERCA2, and thus increases cytosolic Ca^{2+} levels.¹ The dysregulated platelet Ca^{2+} signaling stimulates the activation of calpains; Ca^{2+} -activated proteases which results in the limited proteolysis of substrate proteins and subsequent alterations in signaling. We found that the activation of μ - and m-calpain in patients with type 2 diabetes has profound effects on the platelet proteome and identified septin-5 and the integrin-linked kinase (ILK) as novel calpain substrates. The calpain-dependent cleavage of septin-5 disturbed its association with syntaxin-4 and promoted the secretion of α -granule contents; including TGF- β and CCL5. Calpain was also released by platelets and cleaved CCL5 to generate a variant with enhanced activity. Calpain activation also disrupted the ILK-PINCH-parvin complex and altered platelet adhesion and spreading. In diabetic mice, calpain inhibition reversed the effects of diabetes on platelet protein cleavage, decreased circulating CCL5 levels, reduced platelet-leukocyte aggregate formation and improved platelet function.² These findings indicate that diabetes-induced platelet dysfunction is mediated largely by calpain activation, and suggest that calpain inhibition may be an effective way of preserving platelet function and eventually decelerating atherothrombosis development.

References

- (1) Randriamboavonjy V, Pistrosch F, Bolck B, Schwinger RHG, Dixit M, Badenhoop K, Cohen RA, Busse R, Fleming I. Platelet sarcoplasmic endoplasmic reticulum Ca^{2+} -ATPase and μ -calpain activity are altered in type 2 diabetes mellitus and restored by rosiglitazone. *Circulation* 2008 January 1;117(1):52-60.
- (2) Randriamboavonjy V, Isaak J, Elgheznawy A, Pistrosch F, Frömel T, Yin X, Badenhoop K, Heide H, Mayr M, Fleming I. Calpain inhibition stabilizes the platelet proteome and reactivity in diabetes. *Blood* 2012;120(2):415-23.

Curriculum Vitae

NAME:

Fleming, Ingrid

POSITION TITLE:

Director, Institute for Vascular Signalling, and Chairperson of the Center for Molecular Medicine, Goethe University, Frankfurt, Germany

INSTITUTION AND LOCATION:

Aston University, Birmingham, England: BSc in 1989 of Biochemistry/Pharmacology

Pasteur University, Strasbourg, France: PhD in 1991 of Pharmacology

Goethe University Frankfurt, Germany: Habilitation in 1999 of Physiology

POSITIONS AND HONORS (CHRONOLOGICAL ORDER):

1991 - 1993 Postdoctoral Research Fellow, Institute for Applied Physiology, University of Freiburg, Germany

1993 - 1999 Senior Research Fellow, Institute for Cardiovascular Physiology, Goethe University, Frankfurt, Germany

1999 - 2004 Associate Professor, Institute for Cardiovascular Physiology, Goethe University, Frankfurt, Germany

2004 Full Professor of Physiology (Vascular Signalling), Goethe University, Frankfurt, Germany

2007 - 2008 Chairperson Center of Physiology, Goethe University, Frankfurt, Germany

Since 2008 - Director of the Institute for Vascular Signalling, Goethe University, Frankfurt, Germany

Since 2012 - Chairperson Center for Molecular Medicine, Goethe University, Frankfurt, Germany

ADDITIONAL POSITIONS:

Since 2006: Member board of directors, German Research foundation (DFG) Excellence Cluster "Cardio-Pulmonary System (ECCPS)". Since 2010: Speaker of the DFG funded Collaborative Research Center (SFB 834) "Endothelial Signalling and Vascular Repair"; Since 2013: Steering committee member, DFG research program on "Disease-Relevant Signal Transduction by Fatty Acid Derivates and Sphingolipids" (SFB 1039).

AWARDS AND HONORS:

1988: Greenshield award for Biochemistry, Aston University, Birmingham
1999: Heinz Meise-Preis of the German Heart Foundation
2000: Nitric Oxide Society Young Investigator Award
2002: Arthur-Weber-Prize from the German Cardiac Society
2003: Schunk-Preis für Medicine, University of Giessen, Germany

EDITORIAL BOARD MEMBERSHIPS:

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PUBLICATIONS:

>180 Peer Reviewed Publications, >13,000 Citations, *h*-Index 62

CURRENT AND ANTICIPATED GRANT SUPPORT:

DFG Excellence Cluster 147 "ECCPS Excellence Cluster Cardio-Pulmonary System"; German Center for Cardiovascular Research (DZHK), Vascular Research Area "Metabolism"; DFG Collaborative Research Center SFB/TR23 "Vascular Differentiation", Project A6: The cytochrome P450/ soluble epoxide hydrolase axis in angiogenic endothelial cell signalling and vascular differentiation; DFG Collaborative Research Center 815 "Redox Signalling", Project A16: Redox-regulation and functional consequences of calpain activation in platelets; DFG Collaborative Research Center 834 "Endothelial Signalling and Vascular Repair, Project A4: A kinase anchoring proteins in endothelial cells, and Project A5: The AMP-activated protein kinase (AMPK) in endothelial cell signalling and in cellular crosstalk in diabetes; DFG Collaborative Research Center 1039 "Disease relevant signal transduction by fatty acids and Sphingolipids", Project A6: Role of fatty acid epoxides and diols in the development of the metabolic syndrome.

PREVIOUS EXPERIENCE IN COLLABORATIVE RESEARCH:

European Vascular Genomic Network (EVGN) an EU Network of Excellence; Eicosanoids and Nitric Oxide (Eicosanox) an EU FP6 integrated project; ENOG, COST Network funded by the EU, Area leader Excellence Cluster ECCPS between the Universities Frankfurt and Giessen, German Center for Cardiovascular Research (DZHK) member between 7 German leading Universities in Cardiovascular Research.