PLVAP in diabetic retinopathy: A gatekeeper of angiogenesis and vascular permeability

Wiśniewska-Kruk, J.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Nowadays, approximately 4 million people worldwide experience blindness or severe vision loss caused by diabetic retinopathy. Diabetic retinopathy is a multifactorial disease that can progress from minor changes in vascular permeability, into a proliferative retinal disorder. The increasing incidence of diabetes diagnosis and lack of effective treatments make the development of new therapies an urgent issue. Previous studies have reported increased plasmalemma vesicle-associated protein (PLVAP) expression in the retinal vasculature of diabetic retinopathy patients, which co-localized with vascular permeability. In this thesis, the role of PLVAP in development and progression of diabetic retinopathy is explored. The performed in vitro and in vivo research revealed the key role of PLVAP in regulating Vascular Endothelial Growth Factor (VEGF)-induced angiogenesis and increased vascular permeability. This makes PLVAP an interesting, endothelial cell-specific therapeutic target for diabetic retinopathy.
PLVAP IN DIABETIC RETINOPATHY
A GATEKEEPER OF ANGIOGENESIS
AND VASCULAR PERMEABILITY

Joanna Wisniewska-Kruk

Most people say that it is the intellect which makes a great scientist. They are wrong: it is character.
- Albert Einstein (1879-1955)
The studies described in this thesis were performed at the departments of Ophthalmology and Cell Biology and Histology of the Academic Medical Center (AMC), University of Amsterdam, Amsterdam, The Netherlands.

Printing of this thesis was financially supported by the University of Amsterdam and by Landelijke Stichting voor Blinden en Slechtzienden (LSBS).

Cover design: Joanna Wisniewska-Kruk

Retinal vasculature of 5 days old C57BL/6 (wild type) mice.

Blood vessels were visualized by using Isolectin IB4- Alexa Fluor 488 conjugate probe (Life Sciences). Image was recorded using confocal microscopy (Leica, SP8) and processed using graphical software.

Design and lay-out: Arkadiusz Kruk

Printing: Off Page; www.offpage.nl

Copyright ©2014 by J. Wisniewska-Kruk. All rights reserved. No parts of this publication may be reproduced, stored or transmitted in any way without prior permission from the author.
PLVAP IN DIABETIC RETINOPATHY
A GATEKEEPER OF ANGIOGENESIS
AND VASCULAR PERMEABILITY

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. D.C. van den Boom
ten overstaan van een door het college voor promoties
ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op dinsdag 28 oktober 2014, te 10:00 uur

door

Joanna Wiśniewska-Kruk

geboren te Szczecinek, Polen
Promotiecommissie

Promotores: Prof. dr. R.O. Schlingemann
            Prof. dr. C.J.F. van Noorden

Co-promotor: Dr. I. Klaassen

Overige leden: Prof. dr. E.T. van Bavel
               Prof. dr. C.J.M. de Vries
               Prof. dr. V. Everts
               Prof. dr. A.W. Griffioen
               Prof. dr. H.E. de Vries
               Prof. dr. P.E. Rakoczy

Faculteit der Geneeskunde
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>General introduction and scope of the thesis</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>Molecular analysis of blood-retinal barrier loss in the Akimba mouse, a model of advanced diabetic retinopathy</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>A novel co-culture model of the blood-retinal barrier based on primary retinal endothelial cells, pericytes and astrocytes</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>Lipoprotein phospholipase A2, a potential therapeutic target in preventing retinal vascular leak during diabetic retinopathy and diabetic macular edema</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>Plasmalemma vesicle-associated protein (PLVAP) has a key role in VEGF-induced blood-retinal barrier permeability</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>Endothelial cell-specific plasmalemma vesicle-associated protein (PLVAP) regulates angiogenesis through VEGFR2</td>
<td>103</td>
</tr>
<tr>
<td>7</td>
<td>PLVAP, an endothelial-specific gatekeeper of angiogenesis and vascular permeability</td>
<td>131</td>
</tr>
<tr>
<td>8</td>
<td>General discussion and summary</td>
<td>151</td>
</tr>
<tr>
<td>Addendum</td>
<td>Nederlandse samenvatting en conclusie</td>
<td>161</td>
</tr>
<tr>
<td></td>
<td>Curriculum vitae</td>
<td>165</td>
</tr>
<tr>
<td></td>
<td>Portfolio</td>
<td>166</td>
</tr>
<tr>
<td></td>
<td>List of publications</td>
<td>169</td>
</tr>
<tr>
<td></td>
<td>Acknowledgements</td>
<td>171</td>
</tr>
</tbody>
</table>