ANNALS OF ANATOMY

Polycystic kidney disease
A tale of calcium channels and the actin cytoskeleton

Ralph Witzgall*

Institute of Anatomy and Cell Biology, University of Heidelberg,
Im Neuenheimer Feld 307, D-69120 Heidelberg, Germany

Polycystic kidney disease, which can be inherited in an autosomal-dominant and an autosomal-recessive fashion, is the most common hereditary renal disease, its estimated prevalence is ~1 in 1,000. Despite a lot of effort, the pathogenesis of cyst formation has remained a matter of speculation. An increased mitotic rate of cyst-lining epithelial cells, alterations of the extracellular matrix and a change in cell polarity have all been made responsible for the cystic phenotype, but their direct involvement has not been demonstrated yet (Calvet 1993; Carone et al. 1994; Wilson 1997). The cloning of two genes, which are mutated in the vast majority of patients, has generated hopes for a better understanding of this so far enigmatic disease (Wu and Somlo 2000). One of them, *PKD1*, codes for a large, 4,302-amino acid protein which may be involved in cell-cell and/or cell-matrix contacts. The second gene, *PKD2*, codes for a 968-amino acid protein, which is the focus of our investigations and will be described in more detail below.

Using a polyclonal antibody against the COOH-terminus of polycystin-2, the protein product of the *PKD2* gene, we were able to demonstrate a strong expression of polycystin-2 in the distal portion of the nephron. On a subcellular level, polycystin-2 immunoreactivity was located in the basal compartment of tubular epithelial cells (Obermüller et al. 1999). In order to understand the function of polycystin-2, we conducted a two-hybrid screen in yeast to identify proteins interacting with polycystin-2. We were able to isolate several clones encoding Hax-1, a widely distributed protein with a predicted molecular weight of 35 kDa (Gallagher et al. 2000). Mutagenesis experiments suggest, that a domain in the middle of Hax-1 mediates interaction with polycystin-2. It is noteworthy, that Hax-1 does not interact with polycystin-2L, a protein closely related to polycystin-2. Furthermore we could demonstrate a link between Hax-1 and cortactin, an F-actin-binding protein. In stably transfected cell lines, both polycystin-2 and Hax-1 are located in the endoplasmic reticulum, which has important implications considering the recent finding that polycystin-2 can conduct Ca^{2+} (González-Perrett et al. 2001; Hanaoka et al. 2000). We propose a model, in which a polycystin-2/Hax-1 complex is linked to the actin cytoskeleton through cortactin. In the resting state, the Ca^{2+}-conducting pore of polycystin-2 is closed by Hax-1. Mechanical stimuli, however, are passed on *via* the actin cytoskeleton and cortactin to Hax-1, which is released from polycystin-2 and therefore no longer blocks its Ca^{2+}-conducting pore. As a result, the cell can react to such a mechanical stimulus by local Ca^{2+} currents. In patients with mutations in polycystin-2, this signaling cascade would no longer be functional, thus ultimately leading to the formation of cysts.

*Winner of the Wolfgang-Bargmann-Prize 2001

References

Calvet JP (1993) Polycystic kidney disease: Primary extracellular matrix abnormality or defective cellular differentiation. Kidney Int 43: 101–108

Carone FA, Bacallao R, Kanwar YS (1994) Biology of polycystic kidney disease. Lab Invest 70: 437–448

Gallagher AR, Cedzich A, Gretz N, Somlo S, Witzgall R (2000) The polycystic kidney disease protein PKD2 interacts with Hax-1, a protein associated with the actin cytoskeleton. Proc Natl Acad Sci USA 97: 4017–4022

González-Perrett S, Kim K, Ibarra C, Damiano AE, Zotta E, Batelli M, Harris PC, Reisin IL, Arnaout MA, Cantiello HF (2001) Polycystin-2, the protein mutated in autosomal dominant polycystic kidney disease (ADPKD), is a Ca^{2+}-permeable nonselective cation channel. Proc Natl Acad Sci USA 98: 1182–1187

Hanaoka K, Qian F, Boletta A, Bhunia AK, Piontek K, Tsio-

http://www.urbanfischer.de/journals/annanat

0940-9602/01/183/4–391 $15.00/0

kas L, Sukhatme VF, Guggino WB, Germino GG (2000) Co-assembly of polycystin-1 and -2 produces unique cation-permeable currents. Nature 408: 990–994

Obermüller N, Gallagher AR, Cai Y, Gassler N, Gretz N, Somlo S, Witzgall R (1999) The rat Pkd2 protein assumes distinct subcellular distributions in different organs. Am J Physiol 277: F 914–F 925

Wilson PD (1997) Epithelial cell polarity and disease. Am J Physiol 272: F 434–F 442

Wu G, Somlo S (2000) Molecular genetics and mechanism of autosomal dominant polycystic kidney disease. Mol Genet Metab 69: 1–15

IMPRESSUM

Publisher: Urban & Fischer Verlag GmbH & Co. KG, Branch Office Jena, P. O. Box No. 10 05 37, D-07705 Jena, Germany. Phone ++49(0)36 41/6 26-3; Fax ++49(0)36 41/62 65 00; e-mail: journals@urbanfischer.de

Advertisement bookings: Enquiries should be directed to Urban & Fischer Verlag, Advertising Manager: Sabine Schröter, P. O. Box 10 05 37, D-07705 Jena, Germany. Phone ++49(0)36 41/ 62 64 45, Fax ++49(0)36 41/62 64 21.

Advertising rates: The price list from January 1, 1999 is effective at present.

Distribution and subscription agency:

For customers **in the German speaking countries:** Please turn to your bookshop or to Urban & Fischer Verlag, Abo-Service und Vertrieb: Barbara Dressler, Löbdergraben 14 a, D-07743 Jena, Germany. Phone ++49(0) 36 41/62 64 44, Fax ++49(0)36 41/62 64 43.

For customers **in all other countries:** Please contact your bookshop or The Nature Publishing Group, Linda Still, Brunel Road, Basingstoke, RG21 6XS, UK; Phone ++44(0)12 56/30 26 29, Fax ++44(0)/12 56/46 35 70, E-mail: l.still@nature.com

Subscribers in the **USA** can call toll free on ++1/800/747 3187.

Terms of delivery (2001): 1 volume consisting of 6 issues.

Subscription rate (2001): Volume price: DM 945.00*/GBP 348.00.

Single issue price DM 189.00*/GBP 75.00.

* Suggested list prices. Prices are subject to change without notice.

Discounted price for personal subscribers: DM 424.00/GBP 168.00. Personal subscription orders must be addressed directly to the publisher Urban & Fischer in Jena resp. to The Nature Publ. Group. Subscriptions at a personal rate must include the recipient's name and mailing address. An institutional or business address is only accepted, if the institute or firm has a subscription as well. Personal subscribers can pay by personal cheque or credit card mentioned below.

Prices quoted do not include postage. USdollar prices are converted at the current exchange rate. **We accept the following credit cards:** VISA/Eurocard/Mastercard/American Express. (Please note card-No. and expiry date.)

Banking connections: For customers in the **German speaking countries:** Deutsche Bank Jena, Konto-Nr. 390 76 56, BLZ 820 700 00; Postbank Leipzig, Konto-No. 149 249 903, BLZ 860 100 90.

For customers **in the other countries:** UK Post Office Giro Account No. 5 192 455. Full details must accompany the payment.

Subscription information: Subscription in effect until cancelled by subscriber by October, 31st, otherwise delivery will continue.

Type setting, printing, binding: druckhaus köthen GmbH, D-06366 Köthen.

♾ As of vol. 178, number 1 (1996) the paper used in this publication meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper).

Printed in Germany

New: For detailed journal information see our home page: http://www.urbanfischer.de/journals

Front cover: Scanning electronmicrographs of an absorbable alloplastic implant designed for the surgical reconstruction of abdominal wall defects. The upper micrograph shows bundles of PDS-filaments surrounded by connective tissue matrix three weeks after implantation. The lower micrograph is taken from the same specimen after treatment with 2N NaOH. The alkalinic maceration dissolves the PDS-filaments (black holes) and reveals the architecture of fibrous elements which ensheath the alloplastic material. Magnification 95×. From: A. Entenmann et al. (1999) Ann Anat 181: 237–245.