

ORAL PRESENTATION

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cGMP-dependent kinase 2, Na⁺/H⁺ regulatory factor 2, and Na⁺/H⁺ exchanger isoform 3 assemble within lipid rafts in murine small intestinal brush border membrane

Min Luo^{1,2}, Ayesha Sultan¹, Qin Yu^{1,2}, Brigitte Riederer¹, Weiliang Xia^{1,3}, Min Luo^{1,2}, Mingmin Chen¹, Simone Lissner⁴, Engelbert Gessner⁵, Enrico Patrucco⁶, Franz Hofmann⁶, Mark Donowitz⁷, Chris C Yun⁸, Hugo de Jonge⁹, Georg Lamprecht¹⁰, Ursula Seidler^{1*}

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Trafficking, brush border membrane (BBM) retention, and signal-specific regulation of the Na⁺/H⁺ exchanger NHE3 is regulated by Na⁺/H⁺ Exchanger Regulatory Factor (NHERF) family of PDZ-adaptor proteins, which enable the formation of multiprotein complexes. It is unclear, however, what determines signal specificity of the very homologous NHERFs. We studied the association of NHE3, as well as NHERF1 (EBP50), NHERF2 (E3KARP) and NHERF3 (PDZK1) with lipid rafts in murine small intestinal BBM and their possible association with signaling molecules. NHE3 was found to partially associate with glycosphingolipid-enriched microdomains in the native BBM, and NHE3 raft association had an impact on NHE3 transport activity as well as on second-messenger-dependent regulation *in vivo*. NHERF1, 2 and 3 were differentially distributed to rafts and non-rafts, with NHERF2 being most raft-associated and NHERF3 entirely non-raft associated. A search for other signalling molecules that are implicated in regulating NHE3 through a NHERF interaction, cGMP-dependent kinase II, which together with NHERF2 is essential for guanylin/heat stable enterotoxin of *E.coli* (STa)-mediated NHE3 inhibition in the intestine, was found exclusively lipid-raft associated. In conclusion, the differential association of the NHERFs, as well as kinases, with the raft-associated and the non-raft fraction of NHE3 in the brush border membrane is likely one

component of the differential and signal-specific NHE3 regulation by the different NHERFs.

Authors' details

¹Dept. of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Germany. ²Dept. of Gastroenterology, Tongji Hospital, Huazhong University of Science and Technology, China. ³Key Lab of Combined Multiorgan Transplantation, ^{1st} Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China. ⁴1st Medical Department, University of Tübingen, Tübingen, Germany. ⁵Dept. of Immunology and Rheumatology, Hannover Medical School, Germany. ⁶Forscherguppe 923, Institut für Pharmakologie und Toxikologie, TU München, Biedersteiner Str. 29, 80802, München, Germany. ⁷Division of Gastroenterology, Department of Medicine and Physiology, John Hopkins School of Medicine, Baltimore, USA. ⁸Division of Gastroenterology, Dept. of Medicine, Emory University, Atlanta, USA. ⁹Dept. of Gastroenterology, Erasmus MC, Rotterdam, The Netherlands. ¹⁰Dept. of Gastroenterology, University of Rostock, Germany.

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* Correspondence: seidler.ursula@mh-hannover.de

¹Dept. of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Germany

Full list of author information is available at the end of the article