N2 - Progress Report

01.11.2009 - 31.10.2015

Immune system as regulator of volume and blood pressure

Prof. Dr. Jens Titze, IZKF - Junior Research Group 2

We have found that the immune system regulates salt and water balance, and that tissue Na^+ storage significantly boosts innate and adaptive immune responses. The finding has opened an entirely new perspective on immune function that extends ancient protection from invaders to physiological adaptation to environmental conditions and blood pressure control. We have developed ^{23}Na magnetic resonance imaging methods for rapid transfer of our basic research findings into the clinical arena.

Understanding Na^+ storage in humans

We have implemented ^{23}Na-MRI technology to non-invasively visualize Na^+ reservoirs in humans. Now skin tissue can be imaged up to a resolution of 0.9 mm. The improved images directly show that human skin sodium is predominantly found in the upper layers of the skin (dermis + epidermis) but only little in the subcutaneous fat layer. Nephrological, metabolical and dermatological questions can be studied with this technique. In 2014, we have published a clinical study on tissue Na^+ removal in dialysis patients. Age and inflammation augmented Na^+ storage in the patients, and prevented Na^+ mobilisation with therapy.

Immune cells are physiologic regulators of salt water balance and blood pressure control

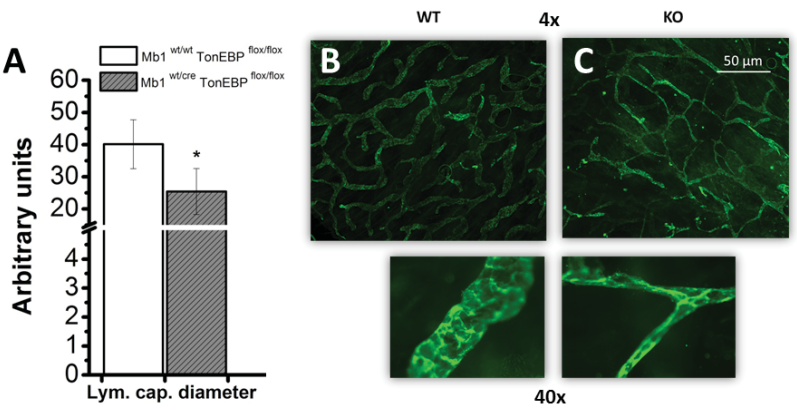
We showed that Na+ storage in the skin and the resulting disequilibrium in interstitial Na^+ concentration attracts macrophages, which then exert a homeostatic-regulatory or autoimmune phenotype.

We could show that a hypertonic microenvironment increases the ability of macrophages to eliminate microbes and serves as barrier against infections. We have extended this work to the role of B-cells (collaboration: Prof. Jäck) and the finding that B cells are critical homeostatic regulators of tissue Na^+ and systemic blood pressure.

Mars500 salt balance studies reveal that high-salt intake induces catabolism in humans

We have performed the first ultra-long term Na+ balance study in humans where we identified weekly (circaseptan) rhythms in human Na^+ balance, and showed that dietary salt intake activates the immune system in humans. We recently study the effect of salt intake on protein catabolism in the Mars500 series.

Contact:
Prof. Dr. Titze
phone: +49 9131 85 39300
e-mail: jens.titze@uk-erlangen.de



Left to right: Panel A-C. Lymph capillaries in control (mb1wtTonEBPflox/flox) and TonEBP-deficient mice (mb1creTonEBPflox/flox). TonEBP-deficiency in B cells reduces the size of the lymph capillary network. Clearance, and leads to a 15-20 mmHg increase in mean arterial blood pressure (not shown). The findings identify B cells as regulators of blood pressure homeostasis.

Prof. Dr. Titze

Invited lectures

06/01/2014 “The interstitium as a sodium sensor and the immune system as a regulator of volume and BP homeostasis” 51st ERA-EDTA Congress, Amsterdam, The Netherlands

05/29/2014 “Skin and Sodium Rhythms in Human Body” Salt in Human Health and Sickness: Building on the Current Scientific Evidence Working Groups” National Heart, Lung, and Blood Institute of the National Institute of Health, Bethesda, USA

04/28/2014 “Hypertension is only skin deep”, Renal Grand Rounds, Division of Nephrology/Hypertension, Feinberg School of Medicine, Northwestern University

10/03/2014 „Lymph vessels and immune cells control skin electrolyte composition and blood pressure“ Gordon Research Conference on Molecular Mechanisms in Lymphatic Function & Disease, Il Giocco Resort Lucca (Barga), Italy

07/03/2014 “Sodium, blood pressure, and homeostatic immune function” Cardiovascular Science Institute Seminars, University of Edinburgh, Edinburgh, USA

06/02/2014 “Sodium balance is not just a renal affair” Center for Cardiovascular Research Seminars, Washington University, St. Louis, USA

01/26/14 Keynote Address “Non-osmotic sodium storage as a pathogenetic factor in hypertension in CDK & ESRD” 16th International Conference on Dialysis, Las Vegas, Nevada, USA

Awards

2014 Election to the American Society of Clinical Investigation, Jens Titze, April 25th, Chicago, USA

2014-2018: AHA 14SFRN20770008 “Lowering tissue Na^+ stores to reduce blood pressure in aging humans”. Role: Principal Investigator

2014-2018: NIDDK 2R01DK062794-11A1 (PI: Harris, R) “The role of cyclooxygenase-2 in salt-sensitive hypertension”. Role: Co-Investigator

Patents/ Licenses during funding period

US Patent Application 20130096415 Method to determine sodium values describing the content of $23Na^+$, and local coil for use in such a method

Selected publications during funding period

Dahlmann A, Dörfelt K, Eicher F, Linz P, Kopp C, Mössinger I, Horn S, Büschges-Seraphin B, Wabel P, Hammon M, Cavallaro A, Eckardt KU, Kotanko P, Levin N, Johannes B, Uder M, Luft FC, Müller DN, and Titze J (2014) Magnetic resonance-determined sodium removal from tissue stores in hemodialysis patients. Kidney International: Aug 6. doi: 10.1038/ki.2014.269. [Epub ahead of print]

Wiig H, Schröder A, Neuhofer W, Jantsch J, Kopp C, Karlsen TV, Boschmann M, Goss J, Bry M, Rakova N, Dahlmann A, Brenner S, Tenstad O, Nurmi H, Mervaala E, Wagner H, Beck FX, Müller DN, Kerjaschki D, Luft FC, Harrison DG, Alitalo K, Titze J (2013) Immune cells control skin lymphatic electrolyte homeostasis and blood pressure. J Clin Invest 123: 2803-2815

Kleinewietfeld M, Manzel A, Titze J, Kvakan H, Yosef N, Linker RA, Müller DN, Hafler DA (2013). Sodium chloride drives autoimmune disease by the induction of pathogenic Th17 cells. Nature 496: 518-22

Rakova N, Jüttner K, Dahlmann A, Schröder A, Linz P, Kopp C, Rauh M, Goller U, Beck L, Agureev A, Vassilieva G, Lenkova L, Johannes B, Wabel P, Moissl U, Vienken J, Gerzer R, Eckardt KU, Müller DN, Kirsch KA, Morukov B, Luft FC, Titze J (2013) Long-term space flight simulation reveals infradian rhythmicity in human Na^+ balance. Cell Metabolism 17: 125-31

Kopp C, Linz P, Dahlmann A, Hammon M, Jantsch J, Müller DN, Schmieder RE, Cavallaro A, Eckardt KU, Uder M, Luft FC, Titze J (2013) 23Na magnetic resonance imaging-determined tissue sodium in healthy subjects and hypertensive patients. Hypertension 61: 635-40

Helle F, Karlsen TV, Tenstad O, Titze J, Wiig H (2013) High-salt diet increases hormonal sensitivity in skin pre-capillary resistance vessels. Acta Physiol (Oxf) 207(3): 577-81

Kopp C, Linz P, Hammon M, Schofl C, Grauer M, Eckardt KU, Cavallaro A, Uder M, Luft FC, Titze J (2012) Seeing the sodium in a patient with hypernatremia. Kidney Int 82: 1343-1344

Kopp C, Linz P, Wachsmuth L, Dahlmann A, Horbach T, Schöfl C, Renz W, Santoro D, Niendorf T, Müller DN, Neininger M, Cavallaro A, Eckardt KU, Schmieder RE, Luft FC, Uder M, Titze J (2012) 23Na magnetic resonance imaging of tissue sodium. Hypertension. 59: 167-172

Machnik A, Dahlmann A, Kopp C, Goss J, Wagner H, van Rooijen N, Eckardt KU, Muller DN, Park JK, Luft FC, Kerjaschki D, Titze J (2010) Mononuclear phagocyte system depletion blocks interstitial tonicity-responsive enhance binding protein/vascular endothelial growth factor C expression and induces salt-sensitive hypertension in rats. Hypertension 55: 755-761

Machnik A, Neuhofer W, Jantsch J, Dahlmann A, Tammela T, Machura K, Park JK, Beck FX, Muller DN, Derer W, Goss J, Ziomber A, Dietsch P, Wagner H, van Rooijen N, Kurtz A, Hilgers KF, Alitalo K, Eckardt KU, Luft FC, Kerjaschki D, Titze J (2009) Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. Nat Med 15: 545-552