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 a rapid transfer of our basic research findings into the clinical arena.

Understanding Na^+ storage in humans

We have implemented ^{23}NaMRI technology to non-invasively visualize Na^+ reservoirs in humans. We are now pursuing clinical studies to better understand Na+ balance in health and disease.

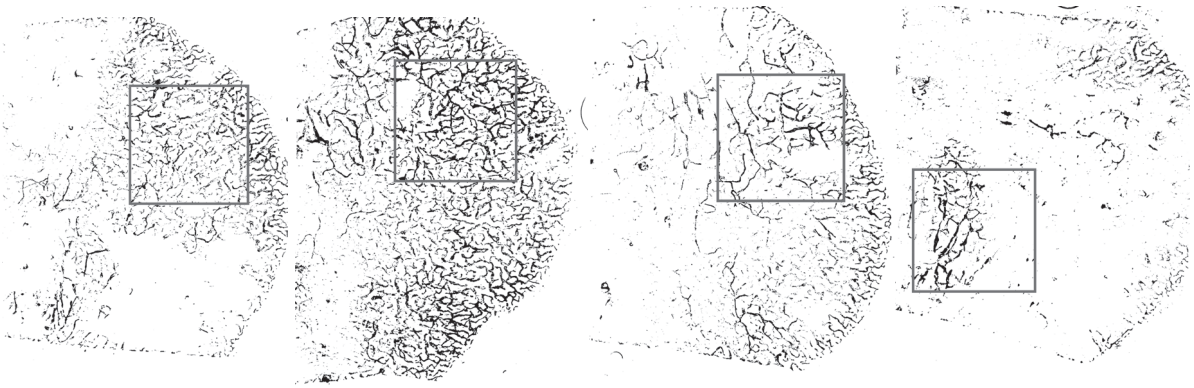
Immune cells are physiologic regulators of salt and water balance and blood pressure control

We showed that Na^+ storage in the skin and the resulting disequilibrium in interstitial Na^+ concentration attracts immune cells which then exert a homeostatic-regulatory or autoimmune phenotype. The cells either regulate interstitial electrolyte homeostasis, or deteriorate auto-immune disease.

Mars500 salt balance studies reveal body's Na^+ rhythms

At constant salt intake, daily Na^+ excretion in humans exhibits aldosterone-dependent, weekly (circaseptan) rhythms. The findings go beyond the currently accepted steady-state concept of Na^+ balance. The paper has been included into the "Best of Volumes 16 and 17" supplement by Cell Press (http://www.cell.com/bestof).

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



Left to right: Lymph capillary density from mice fed a low salt, high salt diet, or mice fed low or high salt diets treated with a drug to disrupt immune-cell driven changes in capillary density. The findings have identified a role of macrophages in blood pressure regulation via modification of the cutaneous lymph capillaries (http://blog.jci.org/2013/1084/june-3rd-titze-60113)

Prof. Dr. Titze

Invited lectures

Workshop on Landmark Discoveries in Hypertension, Kidney, and Cardiovascular Disease, High Blood Pressure Research Scientific Sessions, 2013/09/11, New Orleans, USA, "The skin as the Golden Hinde of sodium homeostasis. Dermal or renal regulation of body salt stores"

3rd Annual Cardiovascular Research Center Symposium on Lymphatics in Health and Disease, Yale School of Medicine & The North American Vascular Biology Organization, 2013/05/04, New Haven, USA, "Lymphatic control of blood pressure"

ISN World Congress of Nephrology 2013, 2013/06/02, Hong-Kong, China, "What's new in salt balance?" (http://www.theisn.org/index.php?option=com_k2&view=item&id=993:what-s-new-in-salt-balance&tmpl=component&print=1)

Kidney Week 2013 of the American Society of Nephrology, 2013/11/08 Atlanta, USA, "Evolving concepts in sodium homeostasis"

5th Annual Meeting of the Germany Society of Nephrology, 2013/10/06, Berlin, Germany, "Non-osmotic sodium reservoirs: insights from a mission to Mars"

Awards

Franz-Volhard-Prize of the German Society of Nephrology to Jens Titze, 2013/10/05, Berlin, Germany.

Mid-Career Award for Research Excellence, Council for High Blood Pressure Research of the American Heart Association to Jens Titze, 2013/09/13, New Orleans, USA.

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. Filed: October 4, 2012; Issued: April 18, 2013. Inventors: Jan Ruff, Jens Titze, Peter Linz, Thoralf Niendorf, Davide Santoro, Wolfgang Renz, Alexander Cavallaro, Michael Uder

Publications during funding period

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

Titze J (2013) Interstitial fluid homeostasis and pressure: News from the black box. Kidney Int 84: 869-71

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

Titze J, Machnik A (2010) Sodium sensing in the interstitium and relationship to hypertension. Curr Opin Nephrol Hypertens 19: 385-392

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