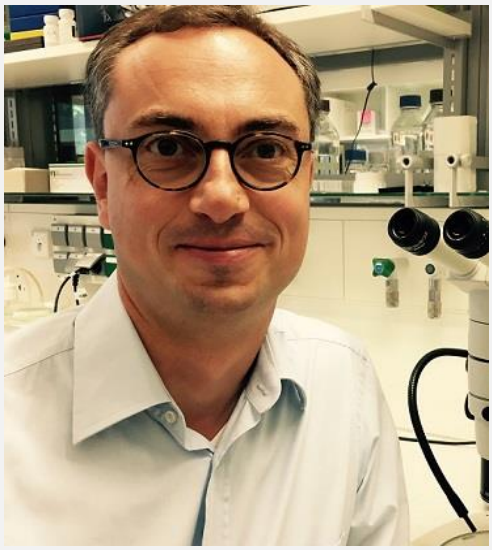
Wykład CX JCET, 17.01.2019 r.

Endothelial control of metabolism



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Vascular Signaling and Cancer (A270)

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It is assumed that many nutrients are transported through the endothelial cell barrier before being metabolized in muscle cells. There is solid evidence that CD36 expression in endothelial cells is needed to allow proper transport of long-chain fatty acids to heart, skeletal muscle, and brown adipose tissue. However, little is known about the regulation of such endothelial transport processes.

Our data indicate that the activity of endothelial Notch signaling in established blood vessels is modulated not only by tumor cells but also by certain fatty acids and glucose. Endothelial specific Notch inhibition by conditional genetic inactivation of Rbp-jκ in adult mice impaired lipase activity and transendothelial transport of long-chain fatty acids to myocytes. In turn, lipids accumulated in the plasma and liver. Mechanistically, Notch controls a number of genes (e.g. CD36) needed for fatty acid transport through the endothelium. In addition, endothelial Notch signaling also controls the flux of insulin to myocytes. This has profound consequences on heart function and insulin sensitivity. As such, the endothelium appears to be critically involved in the control of systemic metabolism.

Curriculum Vitae

Prof. Andreas Fischer

Dr Andreas Fischer is head of the Division Vascular Signaling and Cancer at the German Cancer Research Center (DKFZ) in Heidelberg and adjunct professor at the Medical Faculty Mannheim of Heidelberg University. He is a trained physiologist and specialist in clinical chemistry, who combines basic vascular research and clinical practice at Heidelberg University Hospital. He graduated as Doctor in Medicine in 2003. During his postdoctoral work on angiogenesis at the Biocenter Wurzburg and the Center for Biomedicine and Medical Technology in Mannheim he became interested in mechanisms how endothelial cells instruct the behavior of adjacent cells. In 2012, Dr. Fischer started his own independent group at the German Cancer Research Center in Heidelberg where he was promoted to a Division head in 2017. He received several awards for his scientific work including the Chica and Heinz Schaller research prize and the Hella Buhler award for cancer research. The Fischer lab is currently studying how endothelial cells respond to physiological and pathological changes in blood plasma and their microenvironment and how this subsequently changes the transport of cells, hormones and nutrients across the blood vessel wall.

Selected publications:

Jabs M et al., (2018) Inhibition of endothelial Notch signaling impairs fatty acid transport and leads to metabolic and vascular remodeling of the adult heart. Circulation. 137(24):2592-2608.

Tetzlaff F et al.. (2018) MPDZ promotes DLL4-induced Notch signaling during angiogenesis. eLife. Apr 5;7. pii: e32860.

Klose R, et al., (2018) Inactivation of the serine protease HTRA1 inhibits tumor growth by deregulating angiogenesis. Oncogene. 37(31):4260-4272.

Wieland E et al., (2017) Endothelial Notch1 Activity Facilitates Metastasis. Cancer Cell. 31(3):355-367.

Feldner A, et al., (2017) Loss of Mpdz impairs ependymal cell integrity leading to perinatalonset hydrocephalus in mice. EMBO Mol Med. 9(7):890-905.

Yang W-J et al., (2015) Semaphorin-3C signals through Neuropilin-1 and PlexinD1 receptors to inhibit pathological angiogenesis. EMBO Mol Med. 7 (10):1267-1284.

Adam MG, et al., (2013) Synaptojanin-2 binding protein stabilizes the Notch ligands DLL1 and DLL4 and inhibits sprouting angiogenesis. Circ Res. 113:1206-1218.