SFB 35 Colloquia in Membrane Transport

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"Mitochondrial K+/H+ exchange in Health and Disease: From Ion and Volume Homeostasis to Seizures in the Wolf Hirschhorn Syndrome"

Mitochondrial K+/H+ exchange in Health and Disease: From Ion and Volume Homeostasis to Seizures in the Wolf Hirschhorn Syndrome The protein family Mdm38/LETM1 is essential for the mitochondrial electro-neutral K+/H+ exchange (KHE), driven by the inside-directed H+ gradient. To qualify the proteins as a component of the mitochondrial KHE and measure the K+ fluxes, we have developed a novel method involving H+ and K+ sensitive fluorescent dyes entrapped in submitochondrial particles (SMPs). Our data showed that the KHE activity was nearly abolished in mutant SMPs. LETM1 is a part of a protein complex whose components are presently under study. In the absence of LETM1, yeast mitochondria swell due to an overload of K+, the most abundant cation in the organelle, and are subjected to autophagic degradation (´mitophagy´). Up- or downregulation of the human LETM1 expression results in early cell death. Importantly, nigericin, an ionophore catalyzing KHE, fully reverted all LETM1 deletion phenotypes. Moreover, transcriptional profiling associated to compromised mitochondrial K+ homeostasis in yeast revealed a significant induction of intracellular Zn2+ transporters and changes in ergosterol biosyn-thetic pathways. Human Wolf-Hirschhorn Syndrome (WHS) is a complex disease resulting from the hemizygous termi-nal deletion on chromosome 4. A critical region as been defined (WHSCR1) which correlates with the hallmark of WHS including growth and mental retardation and facial dysmorphismus. LETM1 is 80 kb distal to this region and is always deleted in WHS patients with seizures while it is preserved in patients without seizures. These findings suggest that LETM1 is the candidate gene for seizures events associated with WHS. Using Drosophila as a model organism for understanding the molecular defects in Wolf-Hirschhorn Syndrome we demonstrated the function of LETM1 as a mitochondrial osmoregulator through its KHE activity. Genetic studies allowing the conditional inactivation of LETM1 function in specific tissues showed that depletion of LETM1 resulted in roughening of the adult eye, mitochondrial swelling and developmental lethality in third-instar larvae, possibly the result of deregulated mitophagy. Neuronal specific down-regulation of LETM1 resulted in impairment of locomotor behavior in the fly and reduced synaptic neurotransmitter release. These results will prompt us to study in more details presynaptic mitochondria in absence of LETM1.