range calibrations confirm the functionality of the expressed redox sensors in neonatal, juvenile and adult stages of these mouse lines. Accordingly, availability of these redox-indicator mice now allows subcellular analyzes of ROS/redox signaling at all postnatal stages. This will reveal for example compartment- and organelle-specific alterations of cellular redox balance in brain tissue during development, maturation and aging. Furthermore, cross breeding of redox-indicator mice with various disease mouse models will unveil the detailed contribution of ROS formation and redox imbalance in the onset and progression of various neuronal disorders and/or degenerative conditions.

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NADPH Oxidase 4 attenuates the development of atherosclerosis in ApoE knockout mice

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Increased formation of reactive oxygen species (ROS) is thought to contribute to arteriosclerosis development. NADPH oxidases of the Nox family are important sources of ROS. It was previously reported that the Nox1 and Nox2, by producing NO-scavenging superoxide, promote atherosclerosis. Nox4 is different to those Nox enzymes at it produces predominately H_2O_2 and as it has constitutive activity. As H_2O_2 can act as endothelium-mediated vasodilator we hypothesized that Nox4 may delay arteriosclerosis development.

Spontaneous atherosclerosis-development was determined in tamoxifen-inducible Nox4 conditional knockout mice crossed into ApoE-/- mice under normal chow. Accelerated atherosclerosis was determined in the same line in the partial carotid artery ligation model during high fat Western diet treatment. In the partial ligated carotid artery model, micro-CT revealed a more prominent lumen loss in Nox4 KO mice as compared to Cre negative control animals ($p<0.05$). By histology, an increased plaque burden was observed in Nox4 KO animals. Similarly, in the long term study of spontaneous atherosclerosis-development, planimetry revealed a significant higher aortic plaque burden. Moreover, plaque collagen content was increased after Nox4 knockout. Mechanistically, deletion of Nox4 induced endothelial cell activation. This resulted in an increase in adhesion molecule expression as observed in lung endothelial cells from Nox4-/- mice. Accordingly, monocyte adhesion to endothelial cells of Nox4-/- mice was increased as compared to wild type controls.

Thus, the H_2O_2 producing NADPH oxidase Nox4 is an endogenous anti-atherosclerotic enzyme. Inhibition of Nox4 in humans may accelerate atherosclerosis development.

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Glutathione and mitochondria determine acute defense responses and adaptation to cadmium-induced oxidative stress and toxicity of the kidney proximal tubule *in vitro* and *in vivo*

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Cadmium (Cd^{2+}) induces oxidative stress that ultimately defines cell fate and pathology. Mitochondria are the main energy-producing organelles in mammalian cells, but they also have a central role in formation of reactive oxygen species, cell injury and death signaling. As the kidney proximal tubule (PT) is the major target in Cd^{2+} toxicity, the roles of the oxidative signature and mitochondrial function and biogenesis in Cd^{2+}-related stress outcomes were investigated *in vitro* in cultured rat kidney proximal tubule cells (PTCs) (WKPT-0293 Cl.2) for acute Cd^{2+} toxicity (1-30μM, 24h) and *in vivo* in Fischer 344 rats for sub-chronic Cd^{2+} toxicity (1 mg/kg $CdCl_2$ subcutaneously, 13 days). Whereas 30 μM Cd^{2+} caused ~50% decrease in cell viability, apoptosis peaked at 10 μM Cd^{2+} in PTCs. A steep dose-dependent decline in reduced glutathione (GSH) content and an increase of the oxidized glutathione (GSSG)/GSH ratio occurred after acute exposure. Quantitative PCR analyses evidenced increased antioxidative enzymes (Sod1, Gclc, Gclm), proapoptotic Bax, metallothioneins 1A/2A, and decreased antiapoptotic proteins (Bcl-xL, Bcl-w). The positive regulator of mitochondrial biogenesis Pparg and mitochondrial DNA were increased and cellular ATP remained unaffected with Cd^{2+} (1-10 μM). *In vivo*, active caspase-3, and hence apoptosis, was detected in the kidney cortex of Cd^{2+}-treated rats after FLIVO injection together with an increase in Bax mRNA. However, antiapoptotic genes (Bcl-2, Bcl-xL, Bcl-w) were also upregulated. Both GSSG and GSH increased with sub-chronic Cd^{2+} exposure with no change in GSSG/GSH ratio and augmented expression of antioxidative enzymes (Gpx4, Prdx2). Mitochondrial DNA, mitofusin 2 and Ppara were augmented indicating enhanced mitochondrial biogenesis and fusion. Hence these results demonstrate a clear involvement of mitochondrial biogenesis and function in acute defense against oxidative stress induced by Cd^{2+} in renal PTCs as well as in adaptive processes associated with chronic renal Cd^{2+} toxicity.