As H2O2 can act as endothelium-mediated vasodilator we reduces predominately H2O2 and as it has constitutive activity. Nox4 is different to those Nox enzymes at it pro-duce NO-scavenging superoxide, promote athero-sclerosis. It was previously reported that the Nox1 and Nox2, NADPH oxidases of the Nox family are important sources thought to contribute to arteriosclerosis development. Increased formation of reactive oxygen species (ROS) is Main, Germany

Goethe-Universität, Institut für Kardiovaskuläre Physiologie, Frankfurt am Main, Germany

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NADPH Oxidase 4 attenuates the development of atheroscle-rosis in Apoe knockout mice

*C. Schürmann, Y. Yasar, K. Schröder, R. Brandes
Goethe-Universität, Institut für Kardiovaskuläre Physiologie, Frankfurt am Main, Germany

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 H2O2 and as it has constitutive activity. As H2O2 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 molecule expression as observed in lung endothelial cells from Nox4-/- mice. According, monocyte adhesion to endothelial cells of Nox4-/- mice was increased as compared to wild type controls. Thus, the H2O2 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 re-sponses and adaptation to cadmium-induced oxidative stress and toxicity of the kidney proximal tubule in vitro and in vivo

*F. Thévenod1, A. R. Nair2, W.- K. Lee1, A. Cuypers2
1Witten/Herdecke University, Physiology, Pathophysiology & Toxicology, Witten, Germany
2Hasselt University, Center for Environmental Sciences, Hasselt, Belgium

Cadmium (Cd2+) 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 Cd2+ toxicity, the roles of the oxidative signature and mitochondrial function and biogenesis in Cd2+-related stress outcomes were investigated in vitro in cultured rat kidney proximal tubule cells (PTCs) (WKPT-0293 Cl.2) for acute Cd2+ toxicity (1-30µM, 24h) and in vivo in Fischer 344 rats for sub-chronic Cd2+ toxicity (1 mg/kg CdCl2 subcutaneously, 13 days). Whereas 30 µM Cd2+ caused ~50% decrease in cell viability, apoptosis peaked at 10 µM Cd2+ 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 mito-chondrial biogenesis Pparg and mitochondrial DNA were increased and cellular ATP remained unaffected with Cd2+ (1-10 µM). In vivo, active caspase-3, and hence apoptosis, was detected in the kidney cortex of Cd2+-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 Cd2+ exposure with no change in GSSG/GSH ratio and augmented expression of antioxidative enzymes (Gpx4, Prdx2). Mitochondrial DNA, mitofusin 2 and Ppara were aug-mented 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 Cd2+ in renal PTCs as well as in adaptive processes associated with chronic renal Cd2+ toxicity.