Inhibition of Nrf2 transcriptional activity favors abdominal aortic aneurysm formation in mice

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Background: Abdominal aortic aneurysm (AAA) is a significant cause of death in older adults. The pathogenesis of AAA is strongly associated with inflammation and oxidative stress which is regulated by nuclear factor erythroid 2 (NF-E2)-related factor 2 (Nrf2).

Purpose: This study was undertaken to verify the role of Nrf2 transcriptional activity on abdominal aortic aneurysm development in mice.

Methods: We used a model of angiotensin II (Ang II)- induced abdominal aortic aneurysm in old adult mice (6 m.o.) with inhibited transcriptional activity of Nrf2 (Nrf2/-/-) and normal activity of Nrf2 (Nrf2+/+). Mice were administrated with Ang II (1000 ng/kg/min) or saline (sham group) for 28 days via osmotic minipumps placed subcutaneously. Every week systolic and diastolic blood pressure (SBP and DBP) changes (tail-cuff) and aneurysm growth (USG) were analysed. After 28 days blood and plasma samples for morphology and immunoenzymatic assay, as well as tissue specimens for histology, immunofluorescence and analysis of gene expression were obtained.

Results: Ang II-infusion resulted in twice as high AAA appearance in Nrf2/-/- mice (64%; 7/11) compared to the Nrf2+/+(33%; 3/9; p=0.39 exact Fisher’s test) which was associated with a significant increase in aortic diameter (USG) of Nrf2/-/- mice at day 21 and 28 after Ang II (p<0.05 vs. Nrf2 +/+ ; 2-way ANOVA). The increase in aortic diameter in Nrf2/-/- mice was accompanied by a significant elevation of SBP and DBP at day 21 of Ang II infusion (p<0.001 vs. sham; Student t-test). Interestingly, although Nrf2+/+ mice had a rapid and significant increase in SBP (p<0.01 vs. sham; Student t-test) and an elevation of DBP at day 2 of Ang II infusion, they did not developed aneurysm as frequently as Nrf2/-/- mice.

Further biochemical and histological analysis showed that Ang II-treated mice had inhibited infiltration of leucocytes (CD45 cells) and macrophages (F4/80 cells) into the aortic wall and a significant reduction of plasma MCP-1 (p<0.05 Nrf2 -/- mice vs. sham; Student t-test). However, the gene expression of proinflammatory IL-6 and IL-1ß reminded unchanged. Nevertheless, we noticed that lack of Nrf2 transcriptional activity had significantly changed expression of genes involved in glutathione metabolism. There was a reduced expression of GCLC mRNA in the sham group (p<0.01 vs. Nrf2+/+; Student t-test) and a significant reduction of Gsta1 and Gpx1 mRNA expression in the Ang II-treated group (p<0.05 vs. Nrf2/-/- sham; Student t-test). A simultaneous decrease in GPx and Gsta1 in Nrf2/-/- but not Nrf2+/+ mice under Ang II-treatment may be an indicator of oxidative injury within the aorta.

Conclusion(s): Nrf2 may be associated with aortic aneurysm formation in mice. Lack of transcriptional activity of Nrf2 may increase the frequency of abdominal aortic aneurysm formation which might be associated with changes in redox status rather than inflammation.
Abstract: Inhibition of Nrf2 transcriptional activity favors abdominal aortic aneurysm formation in mice.

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