NRF2/KEAP1 axis modulates endothelial cell phenotype and impacts abdominal aortic aneurysm formation

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Abdominal aortic aneurysm (AAA) is an age-related permanent dilatation of the abdominal aorta, which bears a high risk of rupture and sudden death of the patient. The pathogenic mechanisms of AAA remain elusive and the involvement of endothelial cells (ECs) in the formation of aneurysms is still a matter of debate. We have previously shown that NRF2/KEAP1 axis is a crucial regulator of aging and EC biology, and thus may impact AAA formation. Here, we aimed to address the significance of NRF2-related phenotypic, structural and functional features of the ECs in the etiology of AAA.
NRF2 transcriptional deficiency in mice leads to premature aging of the aorta and predisposes to AAA, which may be related to impaired response to oxidative stress. Furthermore, we observed that the structural stiffness depicted by atomic force microscopy could be significant, and we found a potential role of scanning electron microscopy-illustrated intimal aortic structural changes. They strongly correlate with the AAA incidence and may be caused by excessive vascularization of the aorta and surrounding adipose tissue. Peering closer at the detailed mechanisms of NRF2-related aging, we found that it is related to the interplay between KEAP1 and an abnormal innate immune response in ECs.
To sum up, we conclude that EC ability to proliferate and tighten the arterial wall can be the primary determinant of the onset of AAA. Therefore, contrary to current opinions, the age-dependent proneness to AAA does not rely on the functional endothelium features
but could instead stem from the cessation of EC proliferation.

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