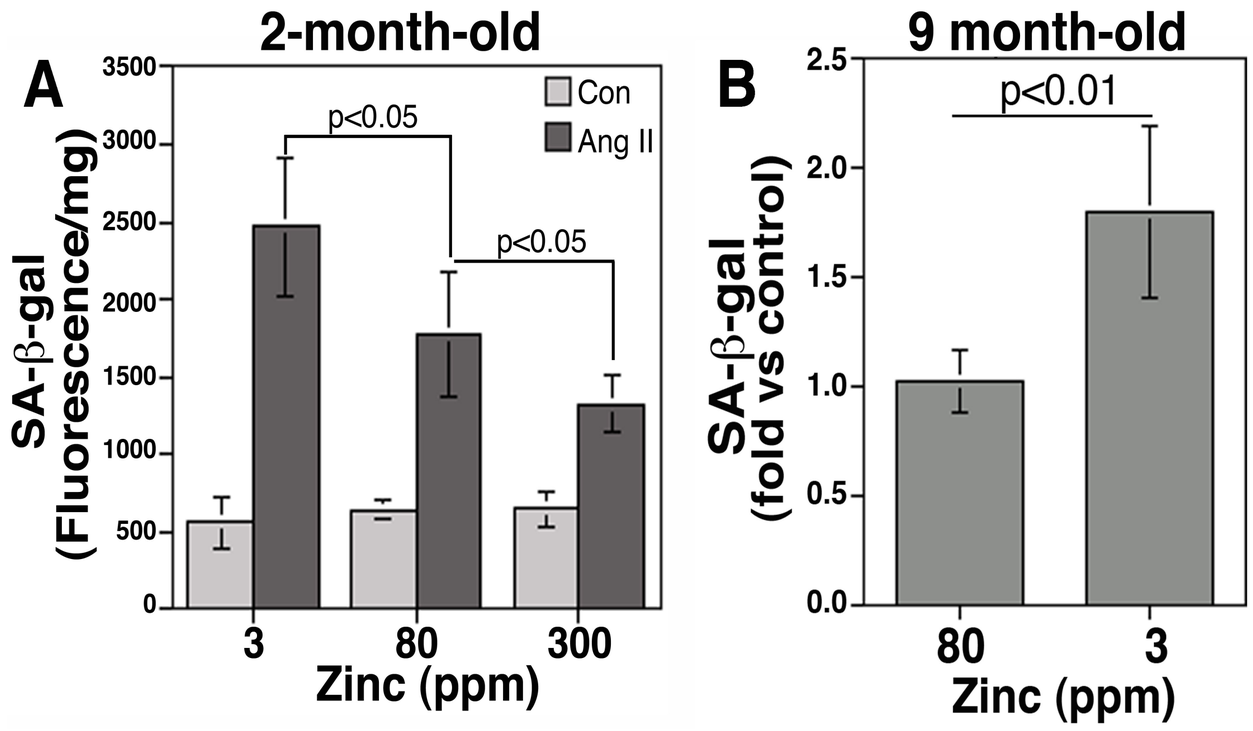
Determining the Role of Zinc Metabolism in Vascular Senescence Using Ex-vivo Animal Models

Zinc is an essential micronutrient that promotes health beneficial effects, however its deficiency is associated with diverse diseases including cardiovascular and neurodegenerative diseases by incompletely understood mechanisms. Using ApoE knockout mice fed zinc deficient (ZD, 3 ppm zinc), zinc adequate (ZA, 80 ppm zinc) and zinc supplemented (ZS, 300 ppm zinc) diets, we found that zinc deficiency accelerates senescence (Fig. 1A), a hallmark of mammalian aging, which is associated with the onset and progression of cardiovascular disease. Senescence was determined by measuring the senescence marker senescence-associated-β-galactosidase (SA-β-gal). In contrast, zinc supplementation decreased senescence induced by Angiotensin II (Ang II) (Fig. 1A), a strong stimulator of vascular aging and disease. Further, zinc deficiency increased senescence in older mice in the absence of Ang II stimulation (Fig. 1B).

Senescence is associated with damage to DNA and cellular components induced by oxidative stress. To test the role of zinc deficiency in oxidative stress, we measured the expression of the NADPH oxidase Nox1, an enzyme that produces superoxide and is associated with cardiovascular disease. Aortas isolated from ApoE KO mice fed ZD diets expressed significantly higher levels of Nox1 compared to mice fed control diet (Fig. 2A and B). To test the role of Nox1 in senescence, we over-expressed Nox1 using adenoviruses, in aortic vascular smooth muscle cells (VSMCs) and found that in fact, Nox1 over-expression increases senescence (Fig. 2C). The novel regulatory role of zinc deficiency in Nox1 function, suggest that dietary zinc interventions may have a broader impact in oxidative stress-mediated diseases, including cardiovascular and neurodegenerative diseases.



Diets (ppm Zn)	Saline	Ang II
ZD (3)	102 ±11, n=5	159 ± 15, n=7
ZA (80)	102± 8, n=5	160 ± 15, n=5
ZS (300)	99 ± 11, n=5	152 ± 16, n=7

Figure 1. Dietary zinc modulates vascular senescence, but not blood pressure in response to Ang II in ApoE$^{-/-}$ mice.

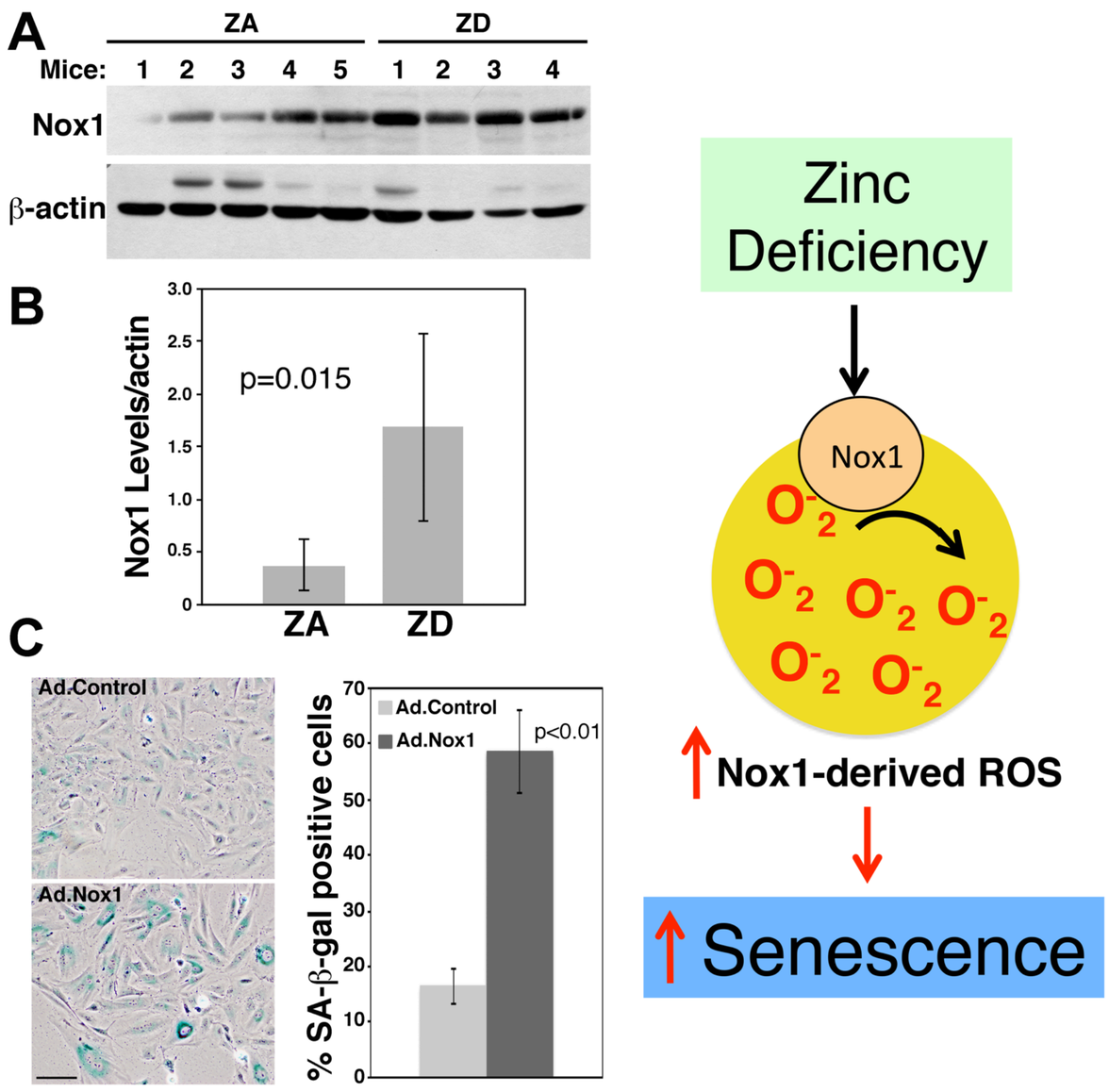


Figure 2. Nox1 is up-regulated by zinc deficiency and causes senescence of VSMCs.

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