

## OVEREXPRESSION OF GLUTATHIONE PEROXIDASE 4 PROTECTS MICE FROM OXIDATIVE STRESS INDUCED APOPTOSIS

H Liang<sup>2</sup>, M Gu<sup>1</sup>, W Qi<sup>1</sup>, H Van Remmen<sup>1,3,4</sup>, A Richardson<sup>1,3,4</sup>, Q Ran(P)<sup>1,3,4</sup>

<sup>1</sup>Department of Cellular and Structural Biology, <sup>2</sup>Department of Physiology and <sup>3</sup>the Sam and Ann Barshop Institute for Longevity and Aging Studies at the University of Texas Health Science Center at San Antonio, San Antonio Texas 78229, and <sup>4</sup>the Geriatric Research, Education and Clinical Center, South Texas Veterans Health Care System, San Antonio, Texas 78284

Glutathione peroxidase 4 (Gpx4) is a unique enzyme that detoxifies oxidative damage of biomembranes. To study the effect of overexpressing Gpx4 *in vivo*, we generated two lines of transgenic (Tg) mice overexpressing Gpx4. Gpx4 mRNA and protein levels were elevated in all the tissues tested. We observed that cells from Tg(Gpx4) were resistant to oxidative stress, e.g., cell death induced by oxidative stressors such as *t*-butyl hydroperoxide (*t*-BuOOH) and diquat was significantly less in murine embryonic fibroblasts (MEFs) from Tg(Gpx4) mice compared to wildtype (Wt) mice. The decreased cell death in MEFs from Tg(Gpx4) mice was associated with a reduction in caspase-3 activity. We also used a diquat model to study the response to oxidative stress *in vivo*. In Wt mice, diquat treatment resulted in an increase in serum levels of alanine aminotransferase (ALT), an indicator of liver damage, and plasma levels of F2-isoprostanes, a biomarker of lipid peroxidation. However, the levels of ALT activity and F2-isoprostanes were greatly attenuated in Tg(Gpx4) mice. In addition, diquat induced apoptosis was significantly decreased in Tg(Gpx4) mice, as evidenced by the inhibition of caspase-3 activation and cytochrome c release from the mitochondria. Together, our data demonstrated that the overexpression of Gpx4 can protect mice against oxidative stress and prevent oxidative stress induced apoptosis by inhibiting the release of cytochrome c. Gpx4 Tg mice could be a potential animal model to study the role of oxidative stress in aging process.