Synopsis of Original Research Paper

Elucidation of malfunction of collagen synthesis caused by defected oxidative protein folding in endoplasmic reticulum

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Vitamin C (ascorbic acid; AsA) is an essential nutritional factor and required for collagen production as well as antioxidation in human. We have analyzed genetically modified mice regarding Akr1a, which catalyzes a step in the AsA biosynthesis, and the embryonic fibroblasts derived from the mice (MEFs). The body weight of the knockout (KO) mice was the same as the wild-type (WT) mice up to ~20 weeks. The KO mice started dying around 10 weeks of age and all had died within one year under the AsA-deficient diet. However, supplementation of AsA contributed to maintaining body weight and extended the life-span of the KO mice. We then used MEFs from WT and human Akr1a-transgenic (Tg) mice to investigate the potential roles of Akr1a under culture conditions. Tg MEFs showed higher acrolein-reducing activities than WT MEFs and were more resistant to cytotoxicity. While the administration of ascorbic acid to the cells increased the intracellular levels of ascorbic acid, it had no effect on the resistance to acrolein. Thus, one of the principle roles of Akr1a in primates is the reductive detoxification of aldehydes, notably acrolein, and protection from its detrimental effects. We also examined the impact of a deficiency of Akr1a on fibrotic damage caused by unilateral ureteric obstruction in the mice. Even though Akrla-deficient mice could produce only about 10% of the AsA produced by WT mice, no difference was observed in collagen I synthesis under pathological conditions. The data implied either a low demand for AsA or the presence of another electron donor for collagen I production in the mouse kidney. Application of the genetically modified mice would give us an advantage in elucidation of in vivo-roles of AsA such as collagen synthesis and anti-oxidation.