

Aging is accompanied with increased prevalence of age-related cognitive disorders like Alzheimer's and Parkinson's diseases. Among different theories of aging, the free radical theory of aging is one of the common theories. Advances in the aging research have established mitochondria as key organelles responsible for the source of free radicals. Dysfunction of ubiquitin proteasome system (UPS), the major proteolysis system responsible for protein homeostasis, has been reported to associate with aging and neurodegenerative disorders. Furthermore, UPS activity declines and mitochondrial functions are impaired over the course of aging. Therefore, UPS, mitochondria and generation of reactive oxygen species (ROS) have been related in vicious cycle of aging and its implicated disorders.

In my thesis, first, the hierarchy of these events under proteasome inhibition was revealed; proteasome inhibition caused mitochondria-mediated oxidation in the cytosol and eventual cell death. Furthermore, mitochondrial antioxidation was found to prevent cytosolic oxidation and cell death caused by proteasome inhibition. Second, screening of dietary antioxidants to mitigate mitochondria-mediated oxidative stress under proteasome inhibition was carried out by visualization of intracellular redox state using a fluorescence redox probe, Redoxfluor. Antioxidants with capability of direct alleviation of ROS, but not induction of cytosolic antioxidant enzymes, prevented mitochondria-mediated oxidative stress in the cytosol. The alleviation of mitochondrial ROS by the effective dietary antioxidants is via scavenging of produced mitochondrial ROS but not by inhibiting its production in mitochondria. In addition, redox visualization using Redoxfluor under mitochondria-mediated oxidative stress was found to be useful for screening potential antioxidants to counteract mitochondrial dysfunction. Finally, the mechanism underlying mitochondrial impairment was elucidated. Inhibition of mitochondrial protein transport concomitant with accumulation of polyubiquitinated proteins is responsible for oxidation of mitochondria by excessive ROS production and mitochondrial dysfunction, which has been implicated with the pathogenesis of various diseases such as neurodegenerative disorders.