10.4.2 Metabolism of Reactive Oxygen Species

Oxidation of cell components by reactive oxygen species (ROS) is one of the factors that hasten cell deterioration. Now, it has become clear that endogenous production of ROS is well regulated by several signaling pathways. This fine control of the ROS level may even represent a certain kind of biological clock. The control of ROS production is mediated by transcription factor Nrf2 (***N***uclear factor erythroid 2-***r***elated ***f***actor ***2***) and partially by FOXO (***f***orkhead bo***x*** ***O***), which induce expression of antioxidant enzymes.[156] Indeed, increased ROS production is observed in aged animals.[157,158] This increase is caused by mitochondrial dysfunction, leading to ROS-induced damage. CR was shown to decrease production of ROS by mitochondria in various tissues. Also, decreased amounts of damaged macromolecules represent the benefits of CR. However, organism still has to generate energy even if energetic substrates are limited. This problem could be resolved by increase of respiration under CR conditions. However, this logic is rather ambiguous. For instance, it is accepted that mitochondria are ones of the main ROS sources. So, an increase in mitochondrial biogenesis attributable to CR may potentially lead to an increase in ROS production. The steady state level of oxidative damage (including oxidized proteins, lipid peroxides, and modified nitrogen bases) is indeed higher in long-lived naked mole rats compared with mice that have a shorter life span.[159–161]

Oxidative stress is developed when the balance of free radical production and detoxification is changed. ROS, such as superoxide anion, hydrogen peroxide and hydroxyl radical, are produced as side products of energy production by the electron transport chain within mitochondria. In addition, some amount of them can be produced by catalytic action of specific enzymes (*e.g.*, xanthine oxidase). ROS are active molecules that can damage cellular macromolecules if not detoxified by antioxidant enzymes or exogenous antioxidants. Accumulation of oxidized lipids, proteins or nucleic acids during aging has been suggested to affect the life span and supports the free radical theory of aging (FRTA). However, many recent pieces of evidence suggest that FRTA is not correct. Naked mole rats are probably the most exciting evidence against FRTA. Short-, middle- and long-time CR decreases ROS production by mitochondria in many species. The longer life span of CR animals can support FRTA to some extent. However, even if FRTA cannot fully explain aging, ROS definitely play an important role in the regulation of longevity.

It was shown that chemical or environmental stresses of moderate intensity might extend the life span by activation of pro-survival pathways. This phenomenon is called 'hormesis'. It was shown that CR increases organism mobility and exercise to increase ROS production and mitochondrial metabolism.[162–164] This observation may suggest hormesis as a mechanism of CR action. Here we have a contradiction between two processes—decreased ROS production under CR and increased ROS production due to more exercise. Partial explanation of this contradiction came recently. New data reveal more complex links between aging, anabolism, catabolism, autophagy, and