development of age-related degenerative chronic diseases, or whether these chronic pathologies cause the inflammatory state observed in aging. But regardless of the cause–effect relationship between age-related diseases and inflammation, oxidative stress has been recognized to play a major role in determining and maintaining the low-grade inflammation observed in aging and age-associated diseases,[72] a process called inflamm-aging.[73]

It was also found in several studies (see ref. 74 for a review) that DNA damage by excess ROS may cause telomere erosion. Experiments in mice suggest that an increase in ROS-mediated DNA damage might enhance telomere dysfunction and thus accelerate accumulation of senescent cells. In turn, cell senescence stimulates chronic inflammation, limits tissue regeneration and accelerates ageing.[75]

In invertebrates, mROS also seem to be linked to aging. It was found that mitochondria of the mud clam *Arctica islandica*, one of the longest-living metazoan species (maximum reported longevity = 507 years), produced significantly less H_2O_2 than those of the two short-lived species.[76] The susceptibility of membrane lipids to peroxidation was also lower in *A. islandica* compared to that in short-lived bivalve mollusks.[77] (A similar situation is inherent in the long-living rodent naked mole rat).

Experiments in annelids *Aeolosoma viride* revealed that oxidative stress status in these worms significantly depended on age, following a Gaussian function centered at nearly half-life.[78] These small limnetic freshwater worms age rather quickly (average survival is 69 days) and share many metabolic processes with nematodes and vertebrates, including some related to the aging process. The radical scavenger bis(1-hydroxy-2,2,6,6-tetramethyl-4-piperidinyl)-decandioate (IAC), which effectively quenches ROS (including peroxyl radicals and superoxide radical-anion) and is able to attenuate several pathologies associated with oxidative stress,[79,80] was shown to prolong the mean lifespan of *A. viride*. IAC added to the cultured medium to a final concentration of 1.25 μM increased the resistance of *A. viride* to oxygen-derived damage without affecting mitochondrial respiration or reproductive activity, and extended the mean lifespan by 170%. Another antioxidant, super-oxide dismutase (SOD)-mimetic EUK134, also extended *A. viride*'s lifespan, although by mere 50%,[78] a figure very close to the 44% increase in the mean lifespan observed previously in the EUK134-treated *C. elegans*.[81]

9.4 Mitochondria-Targeted Rechargeable Antioxidants

Small molecules targeted to mitochondria recently became a powerful new tool for drug delivery, as well as for fundamental studies of mitochondrial functions, including the role of mitochondria in aging. Several comprehensive reviews (ref. 44,82–87) published in the last 10 years cover this topic in great detail.