the cellular energy state, using oxidized nicotinamide adenine dinucleotide (NAD^+) as the substrate and being inhibited by nicotinamide.[235] An increase in NAD^+ occurs during intensive mitochondrial respiration, indirectly indicating about the rate of ATP production by oxidative phosphorylation.[236] Some studies have shown the direct interaction of resveratrol with sirtuins.[134,234] Other studies suggest a more global effect of resveratrol based on its ability to activate mitochondrial complex I.[236] However, this action of resveratrol contradicts the supposed life span-prolonging mode of metformin mentioned above. It can also be possible that cellular longevity can be promoted by either inhibition of complex I or its activation. At the same time, undisturbed operation of complex I may be attributable to a "healthy" cell senescence.

Recently, a few more explanations of life span extension by resveratrol have been proposed. The transcription factor Nrf2 (***N***uclear factor erythroid 2-***r***elated ***f***actor ***2***), which regulates genes of antioxidant response and xenobiotic detoxification, has been found to be crucial for cellular longevity.[237–240] This factor is, in turn, regulated by redox sensing mechanism: thiol-containing adaptor protein Keap1 binds Nrf2 when reduced and targets this transcription factor for ubiquitination and subsequent proteolytic breakdown by proteasome. Under oxidative stress, thiol groups of Keap1 are oxidized and form disulfide bonds, leading to conformational changes and, eventually, the inability to bind Nrf2.[239,241] As a result, Nrf2 is directed to the nucleus, where it activates expression of target genes. Nrf2 target genes are those encoding antioxidant enzymes like superoxide dismutase and catalase,[239,240,242] NADPH-producing enzymes—glucose-6-phosphate dehydrogenase and malic enzyme,[243,244] cytosolic NAD(P)H-quinone dehydrogenase, and thioredoxins.[239,243,245] It was shown that resveratrol and natural plant phenols (*e.g.*, curcumin) are able to bind and inactivate Keap1, inducing Nrf2.[239,240]

10.5.5.3 Rapamycin

Rapamycin (also known as sirolimus) is a macrolide immunosuppressant drug. Its ability to prolong life span in yeast was first observed in 2006.[246] Soon, it was found that the target of rapamycin in animals is peptidylprolyl isomerase FKBP12 (FK-binding protein 12).[247–249] The complex of FKBP12 with rapamycin inhibits downstream kinase, literally called mammalian (or mechanistic) target-of-rapamycin (mTOR) kinase. This kinase was shown to be involved in regulation of protein synthesis and autophagy. Particularly, mTOR kinase phosphorylates downstream P70 S6 kinase, which promotes protein biosynthesis and inhibits autophagy. The final result of this regulation is fostering of cell division and tissue growth, and accumulation of storage metabolites like fat.[136,250] The processes such as tissue growth and accumulation of reserve metabolites rely on calorie and nutrient intake, and are considered to be pro-aging ones.[136,251] The anti-aging properties of rapamycin have been confirmed on many model organisms, including