autophagy in yeast, human cancer cells, and even in mice.[84–86] Furthermore, resveratrol prolonged the lifespan of autophagy-proficient nematodes, whereas this longevity benefit was abolished by the knockdown of essential autophagy modulator beclin-1.[25] The autophagy induced by resveratrol seems to be mediated by sirtuin. The knockdown, knockout, or pharmacological inhibition of SIRT1 prevented the induction of autophagy by resveratrol.[25,77] In addition, the lifespan-extension effect by *sir2.1* overexpression in nematodes was diminished when the beclin-1 was depleted by RNAi, indicating that the longevity benefits by resveratrol is dependent on autophagy.[25,87]

13.2.4.4 Other Molecular Targets

Several evidences indicate that AMPK is a key mediator of metabolic effect by resveratrol. AMPK is an enzyme involved in cellular energy homeostasis, which can be activated by physical exercise, ischemia, glucose deprivation, and caloric restriction.[88–90] Resveratrol 10–50 μM is reported to increase AMPK phosphorylation in HepG2 cells,[91] and 100–300 μM resveratrol is known to decrease the intracellular ATP levels through the activation of AMPK.[92] Although SIRT1 can activate AMPK through deacetylation of upstream kinase LKB1,[65] resveratrol is known to activate AMPK independent of SIRT1.[93] In addition, AMPK is known to increase the NAD^+ level, which promotes the deacetylation of SIRT1 substrates.[94–97] These results—together with the conflicting results regarding resveratrol binding with SIRT1—suggest that AMPK is proposed to be an alternative target of resveratrol. However, to date, there is a lack of experimental evidence about the requirement for AMPK in the longevity effect by resveratrol.

Similar to caloric restriction, resveratrol increased the mitochondrial content in several tissues, including the liver and skeletal muscle, and increased PGC-1α expression, which is a transcriptional cofactor in the regulation of mitochondrial biogenesis, respiration, and glucose homeostasis.[98–100] Furthermore, SIRT1 has been recently shown to function together with PGC-1α in glucose hormeostasis.[101] Moreover, an induction of PGC-1α in the intestine was reported to increase the lifespan of *Drosophila*.[102] Given the above mentioned results, PGC-1α may be the target of lifespan-extending effect of resveratrol, but direct evidence is currently lacking.

13.2.5 Uncertainty of Resveratrol as a Clinical Drug

Despite the obvious benefits of resveratrol on health and lack of apparent toxicity at high doses, use of resveratrol as a clinical drug remains questioned. The concentration of resveratrol is around 50–100 $\mu g\ g^{-1}$ in fresh grapes, and 1.5–3 $mg\ l^{-1}$ in red wine.[61] However, the bioavailability of resveratrol is too low since resveratrol in plasma is quickly taken up by enterocytes of the intestine, and metabolized into glucuronide/sulfate conjugates or dihydroresveratrol. This rapid clearance from plasma leads to poor bioavailability of resveratrol.[103–106] Several *in vitro* studies showed that 10–200 μM