

its mimetics up-regulate pro-longevity catabolic processes like autophagy, oxidation of monosaccharides and organic acids, including amino and fatty acids, by means of mitochondria.

### 10.6.2.1 Insulin Signaling Pathway

Numerous studies on centenarians show that long-lived humans bear single nucleotide polymorphisms that lead to downregulation of the insulin signaling pathway.<sup>273–275</sup> This pathway regulates processes of tissue growth and, in case of insulin as a first messenger, results in accumulation of glycogen and lipid stores in cells.<sup>276</sup> It starts from receptor tyrosine kinase and through a series of downstream kinases leads to phosphorylation of effectors: transcription factor FOXO (*Forkhead box O*) and glycogen synthase kinase 3 $\beta$ , which become inactivated, and proteins involved in glycogen and lipid synthesis, which become activated.<sup>276,277</sup> Many components of this pathway, namely phosphatidylinositol-3 kinase (PI3K) and protein kinase B (PKB; also called Akt), are pro-carcinogenic proteins.<sup>278</sup> Protein kinase B is at the crossroads of several signaling pathways regulating the mTOR pathway.<sup>20,249,279,280</sup> The insulin signaling pathway is switched on in animals when the blood glucose level is increased. Conversely, food restriction may turn off this pathway by multiple mechanisms: a decrease in insulin release, activation of AMPK (*via* an increase in the AMP level), which in turn phosphorylates and inactivates Akt, and activation of sirtuins, which in turn activate FOXO.

There are several compounds that prolong life span by affecting the insulin signaling pathway. Wortmannin and LY-294002, well-known inhibitors of PI3K, were found to extend median and maximum life span in *Drosophila* and mice.<sup>281–283</sup> The effect of these drugs was, however, not so pronounced as that of rapamycin.<sup>153,252,283,284</sup> A greater effect, though denied by some studies,<sup>285–287</sup> was found regarding life span extension by resveratrol, which is believed to activate sirtuins.<sup>10–12,288–290</sup> A few types of sirtuins deacetylate FOXO, thus enabling its re-localization from the cytoplasm to the cell nucleus.<sup>277,291</sup> In turn, FOXO controls expression of pro-longevity genes coding for antioxidant enzymes (catalase and mitochondrial superoxide dismutase), DNA repair proteins (Gadd45 and DDB1), inhibitors of cell cycle (p27<sup>Kip1</sup>),<sup>277</sup> heat shock proteins,<sup>292</sup> and so forth. Life extending properties of the medicinal herb *Rhodiola rosea* may also be accounted for by its action on the insulin signaling pathway. Particularly, it was shown that Daf-16, a FOXO homolog in nematode *Caenorhabditis elegans*, re-localizes from the cytoplasm to the nucleus after the consumption of *R. rosea* extract by worms.<sup>223</sup> In addition, the *R. rosea* extract induced expression of heat shock proteins.<sup>223,293</sup> Interestingly, genes that code for both orexigenic (promoting food consumption) and anorexigenic proteins are among FOXO targets.<sup>277,294,295</sup> In humans, these are Agouti-related protein and neuropeptide Y, which foster appetite, and proopiomelanocortin, which suppresses food consumption. Similar