transcription factors results in deep changes to cell metabolism at the level of gene expression. Indeed, this way of nutrient and energy signaling may take place in some cases we describe below. However, more evidence has been obtained, supporting the idea that post-translational modifications can be induced directly by acetyl-CoA and $NAD^+$.[235,262] Particularly, both acetyl-CoA and $NAD^+$ are involved in post-translational modifications of proteins, such as acetylation and deacetylation, respectively. Moreover, $NAD^+$ is a source of ADP-ribose, a modifying molecule for ADP-ribosylation and poly-ADP-ribosylation. The latter two processes were found to be closely connected with stress resistance and extension of life span.[235,262] The levels of $NAD^+$ and acetyl-CoA grow during a lack of nutrients.[230,260] This likely happens because the organism restricted in nutrients tries to use all possible sources of energy for ATP production. They include fatty acids from fat stores and amino acids provided by autophagy, and particularly *via* hydrolysis of proteins. We can see that some of above-mentioned mimetics of CR may mimic the effects of $NAD^+$ and acetyl-CoA. For instance, resveratrol is supposed to activate sirtuins for which $NAD^+$ is a natural co-substrate and activator. Activators of AMP-activated protein kinase promote mitochondrial biogenesis and, as a consequence, utilization of acetyl-CoA by citrate synthase, a tricarboxylic cycle enzyme. Thus, agents decreasing the NADH/$NAD^+$ ratio and those depleting acetyl-CoA are considered to be potent CR mimetics.[230,260] A decrease in the NADH/$NAD^+$ ratio was found to prolong life span.[263,264] Yet, ectopic expression of rotenone-insensitive non-proton-pumping NADH dehydrogenase, which converts NADH to $NAD^+$, extended life span in model organisms in virtually all cases.[263,265–267]

It seems that metformin and other biguanides drop from this logic since they were shown to inhibit NADH:ubiquinone oxidoreductase (also known as complex I), thus they may increase the NADH/$NAD^+$ ratio.[215] However, it was recently found that metformin may indeed decrease the NADH/$NAD^+$ ratio as an inhibitor of mitochondrial sn-glycerol-3-phosphate dehydrogenase[217] or affects neither NADH/$NAD^+$ ratio[213] nor ATP levels.[268]

### 10.6.2 Signaling Pathways

Aging is proven to be closely connected with an organism's growth and reproduction.[136,251] Relatively long-lived organisms have either a high regenerative capacity, are able to re-program their cells, or slow down their metabolism.[129–132] There are a few examples of life span extension due to metabolic slowdown: (1) nematode, *Caenorhabditis elegans*, is able to live longer in the dormancy dauer stage;[269] (2) fruit flies live longer at temperatures moderately lower than the standard cultivation temperature;[270,271] and (3) naked mole rats (*Heterocephalus glaber*), long-lived rodents, have a relatively low metabolic rate.[272] CR was shown to specifically down-regulate cell signaling pathways responsible for regulation of anabolic processes: protein, glycogen, and lipid synthesis, and accumulation. Conversely, CR itself and