mammals.[251,252] It suggests that mTOR signaling is a universal pathway that regulates the impact of nutrients on senescence in eukaryotic organisms. It is proven that the mTOR pathway is activated by nutrients, especially amino acids. The activation of mTOR by amino acids is mediated by small GTPases called Rag, which get the signal by directly binding amino acids like leucine.[253–256] In this case, rapamycin may mimic CR effects by preventing utilization of ingested nutrients for tissue proliferation. However, there is no direct connection of mTOR with cell energy state, *i.e.* ATP level. An indirect connection is possible *via* AMPK. Particularly, AMPK activates adaptor tuberous sclerosis proteins, hamartin (also known as TSC1) and tuberin (TSC2), which, in turn, indirectly inhibit TOR by means of small GTPase Rheb.[247,248,254] Thus, mTOR seems to be a common final target for biguanides and rapamycin.

Despite beneficial effects on longevity, rapamycin also confers negative side effects, including its immunosuppressant action and, as a consequence, an increased probability of infectious diseases.[257,258] Derivatives of rapamycin (rapalogs), temsirolimus, everolimus, zotarolimus, zidaforolimus and a few others were designed in order to treat cancer *via* inhibition of the mTOR pathway. The rapalogs exhibited only moderate anti-cancer properties in clinical trials.[248] Nevertheless, it does not exclude the use of rapalogs as anti-aging drugs. A possible way to decrease the side effects of rapalogs is to elaborate a chemical inhibiting the mTOR pathway by direct binding of mTOR kinase complexes or even their downstream target P70 S6 kinase. The deletion of ribosomal P70 S6 kinase 1 was shown to be sufficient to prolong life span in mice.[155,259]

10.6 Intracellular Targets of CR

10.6.1 Sensors of Nutrient and Energy State

In previous subsections we have shown that a number of compounds that suppress catabolism led eventually to accumulation of certain crucial metabolites, namely NAD^+ and acetyl-coenzyme A (hereinafter, acetyl-CoA). Of note, these two compounds appear to be on the crossroads of metabolic pathways. For example, acetyl-CoA can be formed as a product of fatty acid β-oxidation, while dietary polysaccharides are converted into glucose and then into pyruvate, which, in turn, yields acetyl-CoA, being oxidized by the pyruvate dehydrogenase complex. Proteins are broken into amino acids, some of which are turned into ketoacids by transamination or deamination. Many ketoacids can easily be converted into acetyl-CoA.[138,230,260,261] Thus, we expect that acetyl-CoA is the compound that may signal about a lack of specific nutrients.

True signaling suggests the presence of a specific receptor and a signaling pathway that regulates cell processes mainly by post-translational modification of specific enzymes and transcription factors. The modification of