ribosomal 60S subunits promotes longevity while deletions of 40S ribosomal subunits that have similar effects on translation do not,[42] suggesting that the specific composition of the ribosome may impact which mRNAs are translated. This idea of a ribosome code is supported by yeast studies, which identify distinct roles for ribosomal paralogs in the translation of localized mRNAs.[72] While it is not yet clear if mammals have a similar ribosome code, it is now clear that mTOR specifically promotes the translation of mRNAs with 5' terminal oligopyrimidine (TOP) motifs,[73] and thus mTOR inhibition shifts the set of mRNAs being translated.

A different theory is that mTOR inhibition may promote longevity by decreasing insulin/IGF-1/PI3K signaling.[74,75] This is supported by correlative evidence from numerous other mouse models with both decreased insulin/IGF-1/PI3K/mTOR signaling and extended lifespan, including mice heterozygous for either *Igf1r* or *Akt1* and mice lacking *IRS1*.[76–78] Deletion of the insulin receptor specifically in adipose tissue or deletion of *IRS2* specifically in the brain also promotes longevity.[79,80] Notably, just as with rapamycin treated animals, many of these mutants display either systemic or tissue-specific insulin resistance, leading to the suggestion that insulin resistance that decreases insulin/IGF-1/PI3K/mTOR signaling is beneficial.[74] In contrast to this view, depletion of *Rictor*, an essential component of mTORC2 signaling, either specifically in the liver or in the whole body of mice, greatly impairs male longevity.[81] This divergent phenotype suggests the possibility that male survival may require signaling downstream of mTORC2 that is mediated by other substrates, such as SGK1.

14.5 Side Effects of Rapamycin Treatment—The Role of mTORC2

While rapamycin and its analogs (rapalogs) are FDA approved for specific indications, they are far from ideal drugs when considered from the perspective of using rapalogs as anti-aging compounds. The side effects of rapamycin are as diverse as they are numerous, and include: metabolic disturbances (*e.g.* hyperglycemia, hyperlipidemia, insulin resistance); dermatological events, including painful ulcers; in males, testicular dysfunction; and most acutely serious, an increase in infections, stemming from the potent immunosuppressive effects of rapalogs (reviewed in ref. 49). These side effects do not outweigh the potential benefits of rapalogs during cancer treatment or in the context of organ transplantation, but must be weighed heavily in the context of an anti-aging medication that may need to be taken prophylactically for a long period of time by otherwise healthy individuals.

Over the last several years, our laboratory and others have demonstrated that many of these side effects result not from inhibition of mTORC1, the canonical target of rapamycin, but from inhibition of the 'rapamycin-resistant' mTORC2.[69] In brief, mTORC2 is resistant to acute treatment with rapamycin in *vitro* and i*n vivo*, yet chronic, prolonged treatment with rapamycin