in vivo disrupts mTORC2 in the majority of mouse tissues.[69,82,83] Using genetic mouse models, important metabolic roles for mTORC2 in many tissues have been identified (reviewed in ref. 19). mTORC2 promotes insulin sensitivity in the liver,[35,84,85] white and brown adipose tissue,[86–89] and skeletal muscle.[90,91] mTORC2 plays a critical role in the regulation of lipid homeostasis, regulating lipolysis, lipogenesis and adipogenesis (reviewed in ref. 92). A growing body of work suggests that disruption of mTORC2 by rapamycin is responsible for some of the immunosuppressive effects of prolonged rapamycin treatment.[93–98] Finally, although the mechanism for this effect remains unknown, depletion of *Rictor*, a key subunit of mTORC2, significantly decreases the lifespan of male but not female mice.[81]

Both mice and humans show significant metabolic and immunological side effects when exposed to high doses of rapamycin or its analogs,[99] but these effects appear to be largely dose-dependent. A recent human study of rapamycin, which demonstrated positive effects on rejuvenation of the immune response to vaccination, used very low doses for a short period of time with few serious side effects.[65] Notably, marmosets treated with rapamycin did not experience significant negative side effects, although the low number of animals used in this initial study precludes making definitive conclusions.[100,101] New larger-scale studies now underway in companion animals, including dogs,[102] should answer many questions about both the efficacy and safety of rapamycin in healthy mammals outside the laboratory environment.

The overwhelming negative consequences of mTORC2 inhibition on metabolism and immunity suggest that specifically inhibiting mTORC1 will promote health and longevity with fewer negative side effects.[103] We recently hypothesized that the differential kinetics of mTORC1 and mTORC2 inhibition by rapamycin might create a therapeutic window through which acute, intermittent dosage of rapamycin could specifically inhibit mTORC1, and we demonstrated that not only did this regimen have reduced effects on glucose homeostasis and the immune system, it remained able to extend the lifespan of mice.[104,105] Weekly treatment with rapamycin has similarly promoted survival of mice fed a high-fat diet,[106] and intermittent administration of rapamycin has also been shown to promote weight loss with reduced side effects on glucose metabolism in rats.[107] While intermittent administration of rapamycin may be a clinically useful technique to reduce rapamycin-associated side effects for the treatment of severe age-related diseases, in the long term a true mTORC1-specific inhibitor has the potential to be used much more widely.

14.6 mTORC1 Is a Key Integrator of Nutrient and Hormonal Signaling

In order to discuss potential mechanisms by which mTORC1 can be specifically inhibited, it is necessary for us to discuss how mTORC1 signaling is regulated. Initial studies of mTORC1 determined that the phosphorylation