

immunity (e.g., surveillance of cancer⁴) be safe and effective as an anti-cancer drug? The rapamycin mystery deepens but first it will be useful for the reader to have a basic understanding of its mode of action in cells.

15.2 The Target of Rapamycin

Since this drug was first identified as a fungicide, yeast was the first organism that investigators used to uncover its mechanism of action. Heitman *et al.*⁵ showed that rapamycin, when bound to the product of the *FPR1* gene (encoding an FK506-binding protein [FKBP], a proline rotamase), inhibited cell cycle progression. These authors also showed that rapamycin sensitivity depended on two other genes (aptly named the target of rapamycin (*TOR*) 1 and *TOR2*) both of which encoded phosphatidylinositol kinase homologues.⁶ Subsequent years of fruitful research by many labs studying budding⁷ and fission⁸ yeast revealed many of the fundamentals of its biological function and significance. Of significance for this chapter, inhibition of TOR in budding yeast increased chronological life span.⁹

Subsequent to the identification of TOR in budding yeast, multiple labs reported identification of one gene encoding the mammalian target of rapamycin.¹⁰⁻¹³ Each dubbed with different names, these coalesced first into mammalian TOR (mTOR), then mechanistic TOR, with some reservation.¹⁴ mTOR is conserved in structure and function in eukaryotes, including plants.¹⁵ It belongs to a family of complexes that Smerdon¹⁶ referred to as “giant’ phosphatidylinositol 3-kinase (PI3K)-like protein kinases (PIKKs).” The conserved structure function domains of this family and the one specific for mTOR are shown linearly in Figure 15.1. Aylett *et al.*¹⁷ identified the horn

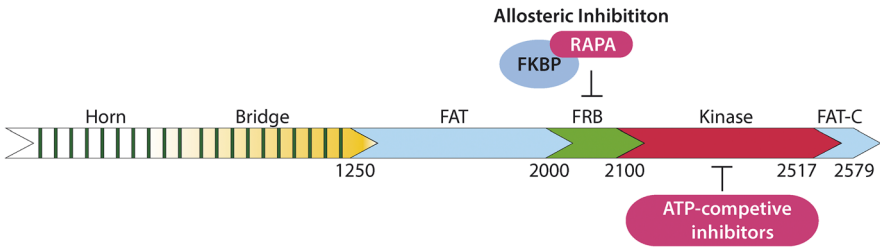


Figure 15.1 Schematic of mTOR structure. Indicated are identified domains. The kinase domain is located near the C-terminus following an N-terminal expanse of helical repeat motifs (HEAT repeats), which are structurally subdivided into a curved solenoid (called the horn) and a straight solenoid (referred to as the bridge).¹⁷ Another tetratricopeptide (TPR)¹⁹ repeat-containing domain named FAT (Frap, ATM and TRRAP). A C-terminal FAT domain (FAT-C) is structurally different from the FAT domain, but was also named after Frap, ATM, TRRAP. The N-terminus of the kinase domain forms the FK506 binding protein (FKBP)–rapamycin binding (FRB) domain, which is necessary for rapamycin allosteric inhibition of mTOR. ATP-competitive inhibitors have been developed that act independently of FRB.