
1.10 Aims of current work

It is widely known that mTOR functions as a central regulator of cell growth. However, the molecular mechanisms of how mTOR specifically regulates its downstream targets S6K1/2 and 4E-BP1/2/3, is only poorly understood.

One aim of the present work was to elucidate the mechanism by which mTOR regulates phosphorylation of S6K1 and 4E-BP1. Previous studies had implicated the N-terminus of S6K1 in mTOR signaling as a binding site of a mTOR-regulated phosphatase (Pullen and Thomas 1997). Therefore, it was of interest to identify the region within the S6K1 N-terminus that is required for mTOR-dependent S6K1 regulation, and to characterize the mechanism by which this region mediates mTOR-dependent S6K1 activation. To further examine mTOR signaling to its downstream targets, the mechanism by which 4E-BP1 is regulated through mTOR-dependent inputs was investigated.

Another goal of this study was to gain insights into the regulation of S6K2. The activity of S6K2 is stimulated by a variety of stimuli that activate S6K1, but to a lesser extent than S6K1 (Martin, Schalm et al. 2001). Deletion of the C-terminus of S6K2 increases the specific activity of S6K2, suggesting that the S6K2 C-terminus mediates an additional inhibitory effect, e.g., by binding to an inhibitor of S6K2 (Martin, Schalm et al. 2001). To better understand S6K2 regulation, the region within the C-terminus of S6K2 that is responsible for the inhibitory effect was examined. Furthermore, analysis of this inhibitory region may identify a potential S6K2-binding protein.