Protein kinases are enzymes that add phosphate groups to proteins, changing the protein’s activity, area of localization, and overall function. These kinases tightly regulate aspects of cellular processes such as cell cycle progression and cell metabolism. Therefore, the impairment, or dysregulation, of kinases is closely related to many diseases such as diabetes and cancer. In this respect, understanding the regulatory mechanisms of kinases is of great physiological and clinical importance. Here, we describe our investigation into an understudied aspect of regulation of one important kinase, S6 kinase 1 (S6K1). We found, unexpectedly, that a protein called glycogen synthase kinase-3 (GSK-3) plays a role in S6K1 regulation. This study contradicts concerns that GSK-3 inhibition, a promising drug target for diabetes and other major illnesses, would promote tumor growth.

S6K1 regulates cell growth, proliferation, and differentiation by regulating protein synthesis, cell cycle progression, insulin sensitivity, and metabolism (1). Recent studies suggest that deletion of S6K1 increases lifespan and reduces the incidence of age-related pathologic processes, including insulin resistance and bone, immune, and motor dysfunction (2). Because of its important role in cell growth and insulin sensitivity, aberrant activation of S6K1 plays a major role in the progression of tumors, diabetes, obesity, and aging (1, 2). Therefore, understanding the mechanism of S6K1 regulation will contribute to the ongoing efforts to develop novel drugs for effective treatments to combat diseases that are characterized by deregulation of the S6K signaling pathway. Here, we investigated a poorly understood regulation site on S6K1, a part of the protein known as a turn motif, which regulates the conformation of S6K1. A mutation in this part significantly reduces kinase activity and phosphorylation of another motif (a specific structure), called the hydrophobic motif. However, the mechanism of regulation of the turn motif in S6K1 has not been previously explored.

Here, we provide evidence for two mechanisms of modulating S6K1 turn motif phosphorylation and activity (Fig. P1). First, a protein called mammalian target of rapamycin (mTOR) regulates S6K1 turn motif phosphorylation by inhibiting its dephosphorylation (i.e., removal of a phosphate group). Second, we unexpectedly found that a protein called GSK-3 promotes turn motif phosphorylation. Our studies show that GSK-3 cooperates with the mTOR protein to control the activity of S6K1 (Fig. P1).

This finding sheds light on debates over the potential role of GSK-3 as a drug target. GSK-3 has emerged as a potential target for treating type 2 diabetes mellitus, Alzheimer’s disease, mood disorders, and atherosclerosis. However, the use of GSK-3 inhibitors in clinical trials has been questioned based on concerns that GSK-3 inhibition may promote tumor development and progression by activating pathways that stimulate cell survival and proliferation (3). If GSK-3 inhibits cancer progression, GSK-3 inhibitors should not be used to treat diseases such as type 2 diabetes despite findings that these inhibitors clearly show that GSK-3 can be a good therapeutic target for the treatment of insulin resistance and type 2 diabetes without any significant side effects in mice. Furthermore, type 2 diabetes is associated with elevated risk and increased mortality in several cancers, underscoring the concerns about the use of GSK-3 inhibitors if these inhibitors are indeed promoters of tumor development. However, despite these concerns, no direct in vivo evidence has actually indicated that GSK-3 inhibition promotes tumor development (3). Our findings add credence to a growing body of evidence that GSK-3 can positively regulate cell survival and proliferation, thereby promoting tumor formation and tumor progression (4).

This suggests that GSK-3 inhibitors may actually inhibit cancer as well as these other diseases.

In conclusion, we provide evidence supporting the unexpected finding that GSK-3 positively regulates S6K1 activity and cell proliferation. Considering its roles in many important cellular processes, it will be of great interest to explore the novel downstream targets and functions of GSK-3 in these processes, which...
will provide the rationale for the development of drugs targeting GSK-3 to treat diseases such as diabetes and age-related diseases.


