

Rapamycin (sirolimus), B-cell mass, B-cell function, and insulin action

The mammalian target of rapamycin (mTOR) is an evolutionary conserved Ser/Thr kinase that regulates cell growth and metabolism in response to environmental stimuli.^{1,2} Ribosomal protein S6 kinase 1 (S6K1), an effector of mTOR, is sensitive to both insulin and nutrients.² Activation of S6K1 by insulin and amino acids, through mTOR, stimulates protein and glycogen synthesis in muscle, lipid accumulation in fat, pancreatic β -cell growth, and insulin secretion.² However, there is some evidence that mTOR-S6K1 activation may be implicated in a negative feedback loop resulting in impaired insulin action, as Ser/Thr phosphorylation of insulin receptor substrates 1 and 2 (IRS1 and IRS2) by S6K1 was found to lead to their degradation and subsequent interruption of insulin signaling.^{1,2} These findings suggested that states of nutrient overload (such as obesity) can lead to insulin resistance through overactivation of the mTOR-S6K1 pathway,^{1,2} and prompted the hypothesis that inhibition of mTOR could be a therapeutic goal in insulin resistant states.

A recent article³ revealed that, in fact, mTOR-S6K1 inhibition by rapamycin worsened, rather than improved, hyperglycemia in diabetic *Psammomys obesus*, a rat model of obesity and type 2 diabetes. Treatment of diabetic animals with rapamycin abolished their hyperinsulinemia, and resulted in a loss of body weight and an increase in serum lipids and ketone bodies. Rapamycin treatment also decreased muscle insulin sensitivity. Interestingly, in diabetic animals, rapamycin reduced β -cell mass by 50% through increased apoptosis. Furthermore, glucose-stimulated insulin secretion and proinsulin biosynthesis were impaired in islets treated with rapamycin.³ An earlier study⁴ had shown that S6K1-deficient mice are hypoinsulinemic, glucose intolerant, and have diminished β -cell size. Along the same line, it has been reported that sirolimus (ie, rapamycin) decreases ductal cell number in culture and impairs glucose-stimulated insulin secretion in vivo.⁵ It has also been shown that sirolimus is associated with reduced islet engraftment and impaired β -cell function in vitro,⁶ and with an impaired rate of β -cell proliferation in vivo.⁷ Importantly, a recent study⁸ revealed that, in kidney transplant recipients, sirolimus treatment was independently associated with new-onset diabetes within the first 3 years post-transplantation.

Reduced β -cell mass and function is not the sole consequence of chronic mTOR-S6K1 inhibition. Unexpectedly, such inhibition also caused downregulation of IRS 1 and 2, resulting in PKB-Akt inactivation and insulin resistance.^{3,9} Therefore, whereas in vitro studies had suggested that short-term inhibition of mTOR-S6K1 could improve insulin sensitivity, it is apparent that its chronic inhibition is deleterious for both β -cell mass and function, and for insulin action.

In conclusion, chronic inhibition of mTOR-S6K1 by systemic administration of rapamycin (sirolimus) and rapamycin-like analogues may aggravate metabolic disturbances in patients with diabetes. Also, long-term use of sirolimus and its analogues as immunosuppressive treatment may be diabetogenic in nondiabetic kidney transplant patients, and it may compromise a successful islet graft

transplant in patients with diabetes. Long-term trials are needed to fully appreciate the risk and to take it into account in immunosuppressive regimens.

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