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Role of Signal Dynamics in the Link Between Type 2 Diabetes and Cancer

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Epidemiological studies revealed a connection between several types of cancer and type 2 diabetes (T2D), and suggested that T2D is both a symptom and a risk factor of pancreatic cancer. High level of circulating insulin (hyperinsulinemia) associated with obesity has been implicated in promoting aggressive types of cancers. Peripheral insulin resistance, a symptom/risk factor of T2D, pressures pancreatic β-cells to increase insulin secretion, which results in hyperinsulinemia. This in turn, is believed to lead to a poorly understood gradual loss of functional β-cell mass, thus suggesting the existence of a fine-balance and interplay between β-cell function and mass. While the mechanisms of these connections are unclear, the mammalian target of rapamycin complex 1 (mTORC1) pathway has been implicated in controlling β-cell function and mass, and mediating a link between cancer and T2D. However, the mechanism by which the mTOR pathway does so remains unclear. Moreover, incomplete understating of how the pathway is regulated and how it integrates body metabolism has hindered its efficacy as a clinical target. The IQ motif containing GTPase-activating protein 1 (IQGAP1) is a growth factor- and nutrient-sensor that couples cell growth and division, and regulates glucose-stimulated insulin secretion from β-cells. Dysregulation of IQGAP1 is associated in humans with several carcinomas and with T2D. Here we discuss how IQGAP1, through differential interactions with Rho-type of small guanosine triphosphatases (GTPases), acts as a rheostat that fine-tunes the mTORC1 and the mitogen-activated protein kinase (MAPK) signals, and potentially integrates β-cell function and mass with insulin action. Dysfunction of IQGAP1 provides a plausible molecular mechanism for understanding cancer initiation in diabetes, and a potential clinical target for treating both cancer and diabetes with high selectivity.