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**ABSTRACT**

Cancer is one of the major causes of death in diabetic patients, moreover the association between antidiabetic drugs and cancer risk has been reported. These evidence implies a strong connection in pathogenesis between diabetes and cancer. Recently, glucagon is recognized as a pivotal factor implicated in the pathophysiology of diabetes. Glucagon acts through binding to its receptor, glucagon receptor (GCGR), and cross-talk between GCGR-mediated signals and signaling pathways that regulate cancer cell fate has been unveiled. In the current study, we demonstrated the expression of GCGR in colon cancer cell lines and colon cancer tissue obtained from patients. Glucagon significantly promoted colon cancer cell growth, and GCGR knockdown with small interfering RNA attenuated the proliferation-promoting effect of glucagon on colon cancer cells. Molecular assays revealed that glucagon acted as an activator of cancer cell growth through deactivation of AMPK and activation of MAPK in a GCGR-dependent manner. Moreover, a stable GCGR knockdown mouse colon cancer cell line, CMT93, significantly grew slower than control in a syngeneic mouse model of type 2 diabetes with glycemia and hyperglucagonemia. The present observations provide experimental evidence that hyperglucagonemia in type 2 diabetes promotes colon cancer progression via GCGR-mediated regulation of AMPK and MAPK pathways.