Cancer cells often reprogram metabolic pathways in favour of glucose metabolism, glycolysis and anapleurotic pathways that promote growth and survival. Interestingly, many genes that are associated with type 2 diabetes — which is a disorder of glucose metabolism — are proto-oncogenes and regulators of proliferation. Making further connections between type 2 diabetes and cancer, George Daley and colleagues identify a role for LIN28 and the let-7 microRNA family in glucose metabolism.

The let-7 microRNAs inhibit the translation of various target genes (including oncogenes and cell cycle regulators), and so they are often suppressed in cancer cells. One way this occurs is through the RNA-binding proteins LIN28A and LIN28B, which bind and suppress the processing of let-7 microRNAs; LIN28A and LIN28B can therefore be upregulated in cancer.

Daley and colleagues showed that transgenic mice overexpressing LIN28A or LIN28B exhibit enhanced glucose metabolism, having a higher glucose tolerance and insulin sensitivity than wild-type mice. The common phenotypes shared by these mice indicate that LIN28A and LIN28B function in the same pathway in order to regulate RNAs that are associated with glucose metabolism. To investigate whether let-7 is a target in this pathway, the authors produced transgenic mice overexpressing a *let-7g* mutant that is resistant to LIN28 regulation. These mice were glucose intolerant but had normal insulin sensitivity, and crossing with mice overexpressing LIN28B prevented the increase in glucose tolerance that is observed in LIN28B-transgenic mice. This indicates that LIN28B-mediated suppression of *let-7g* regulates glucose metabolism *in vivo*, but that LIN28B also targets other RNAs.

To further investigate the mechanism of glucose metabolism regulation by LIN28, the authors overexpressed LIN28A in C2C12 myoblasts that were cultured in the presence of insulin. These cells exhibited suppression of let-7 expression and increased glucose uptake, as well as phosphorylation of AKT, S6 ribosomal protein and 4EBP1, which are members of the PI3K–mTOR pathway. Indeed, treatment with the PI3K–mTOR inhibitor LY294002 or rapamycin (which inhibits mTOR) suppressed glucose uptake. Next, they investigated the role of let-7 in the insulin–PI3K–mTOR pathway. By transfecting a mature *let-7f* duplex (which cannot be suppressed by LIN28A) they found that AKT phosphorylation was partially reduced and that S6 and 4EBP1 phosphorylation was inhibited in insulin-stimulated myoblasts, indicating that *let-7f* suppression at least partially mediates the induction of the PI3K–mTOR pathway following LIN28A overexpression. Analyses of the quadricep muscles of transgenic mice showed that LIN28B and LIN28A induce the upregulation of insulin receptor (INSR) and insulin-like growth factor 1 receptor (IGF1R). Furthermore, using a bioinformatic screen of mRNAs that exhibit increased stability when LIN28A was overexpressed in C2C12 myoblasts, the authors found that 16 genes in the insulin–PI3K–mTOR pathway have *let-7*-binding sites, several of which were confirmed *in vitro* and *in vivo*. Therefore, LIN28A and LIN28B derepress let-7-mediated suppression of the insulin–PI3K–mTOR pathway to increase glucose metabolism but also have let-7-independent targets.

> “LIN28A and LIN28B derepress let-7-mediated suppression of the insulin–PI3K–mTOR pathway to increase glucose metabolism”

The authors found that genes regulated by let-7 and LIN28 are associated with type 2 diabetes; this pathway may also regulate glucose metabolism in cancer cells. Interestingly, LIN28A and LIN28B are expressed in embryogenesis (when energy demands also favour glucose metabolism) and are then re-expressed in cancer, which indicates that the further analysis of embryonic metabolism could teach us more about metabolic reprogramming in cancer cells.

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ORIGINAL RESEARCH PAPER Zhu, H. *et al.* The *Lin28/let-7* axis regulates glucose metbolism. *Cell* **147**, 481–494 (2011)