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METABOLISM

DNA double-strand breaks and p53 activity in β-cell failure

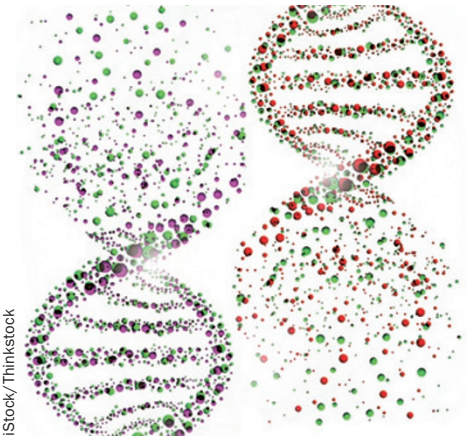
Researchers have identified a new feature of β-cell failure, a key step in the development of type 2 diabetes mellitus (T2DM). The study published in *Cell Metabolism* reveals that hyperglycolysis in β cells, due to genetic activation of glucokinase (as in patients with congenital hyperinsulinism [CHI]) or due to chronic hyperglycaemia (as in patients with T2DM) causes DNA double-strand breaks, followed by activation of p53.

To unravel the dynamics of β cells exposed to chronically high rates of glycolysis, the investigators generated transgenic mice with β cells that express an active mutant of glucokinase that is found in humans with CHI. They also analysed histological specimens from patients with CHI or T2DM and revisited a family with CHI characterized 15 years ago to determine whether these individuals had developed T2DM.

"An important aspect of the work is the realization of a deep similarity between T2DM and CHI," highlights corresponding author Yuval Dor from the Hebrew University–Hadassah Medical School. "These are diseases with an opposite clinical phenotype (hyperglycaemia in T2DM versus hypoglycaemia in CHI), but we show that they are characterized by similar dynamics: in both, β cells initially respond well to hyperglycolysis by increasing insulin secretion, β-cell proliferation and mass. However, in both, eventually β cells fail. And the signalling pathway that is responsible for the two phases of the response is similar in both diseases."

The study led by Dor and Benjamin Glaser (Hadassah Medical Centre) raises another important issue: the dual activity of glucose in β cells. On one hand, glucose exposure leads to increased insulin secretion, β-cell proliferation and mass; on the other hand, it causes DNA breaks, p53 activity and β-cell failure. "We are trying to understand what drives the decision of β cells to respond to increased glucose flux—whether to divide or to die," says Dor.

Increasing β-cell proliferation is one approach that could be exploited as a regenerative therapy in diabetes mellitus,



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and Dor believes that "glucose metabolism may hold the key for boosting β-cell proliferation". However, strategies to avoid the negative effects of hyperglycolysis will be needed. One approach might be the coadministration of glucokinase activators and GLP-1 analogues, which Dor and co-workers show can rescue the toxicity of hyperactive glucokinase.

Linda Koch

Original article Tornovsky-Babeay, S. *et al.* Type 2 diabetes and congenital hyperinsulinism cause DNA double-strand breaks and p53 activity in β cells. *Cell Metab.* doi:10.1016/j.cmet.2013.11.007