HIGHLIGHT

Beta-cell apoptosis in the pathogenesis of human type 2 diabetes mellitus

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Type 2 diabetes is accompanied by chronic insulin resistance and a progressive decline in β-cell function (1). Obesity is a major risk factor for the development of type 2 diabetes (2, 3) and is thought to confer increased risk for type 2 diabetes through obesity-associated insulin resistance (4). However, most people who are obese do not develop diabetes but compensate their relative insulin resistance by increasing insulin secretion (5). In rodent models of obesity without diabetes there is (as opposed to non-obese littermates) an adaptive increase in β-cell function (6). Although not many data are available, studies suggest that β-cell mass is also adaptively increased in non-diabetic obese humans (7, 8). β-cell mass is regulated by a balance of β-cell replication and apoptosis, as well as development of new islets from exocrine pancreatic ducts (neogenesis) (9, 10). Disruption of any of the pathways of β-cell formation or increased rates of β-cell death would result in decreased β-cell mass and thus reduced capacity to produce insulin. There is controversy whether β-cell mass is decreased in type 2 diabetes mellitus (8, 11–17). These discrepancies are in part due to the paucity of available data in humans. Furthermore, it is controversial whether β-cell apoptosis is truly increased in type 2 diabetes.

A recent (18) very carefully conducted study gives new and convincing data indicating that increased apoptosis rather than decreased neogenesis or replication may be the main mechanism leading to reduced β-cell mass in type 2 diabetes. Autopsy material from obese patients with diabetes or with impaired fasting glucose (IFG) or without diabetes as well as from lean patients was examined. The authors report that obesity in non-diabetic humans is accompanied by a 50% increase in relative β-cell volume as compared with lean non-diabetic humans. However, the non-diabetic obese humans died younger than the non-diabetic lean humans and the difference found on autopsy may be due to difference in age. Obese humans with IFG and type 2 diabetes had a respective 40 and 63% deficit in relative β-cell volume. The decreased β-cell volume in patients with type 2 diabetes was due to a reduced number of β-cells rather than a smaller volume of individual cells and occurred irrespectively of whether they were treated with diet alone or oral medications or insulin. There was no difference in the mean fasting plasma glucose levels among these three treatment groups. Lean subjects with type 2 diabetes had a 41% deficit in relative β-cell volume compared with lean non-diabetic subjects. These findings are consistent with other carefully conducted recent studies in which β-cell mass is decreased in type 2 diabetes (8, 15, 17). Neogenesis, while increased in obesity, was comparable in all groups. Decreased β-cell replication was found with aging (18).

Because new islet formation, the predominant input into the β-cell mass, appears intact in type 2 diabetics (18), the mechanism for the decreased β-cell mass would have to be increased β-cell apoptosis. Indeed, a significantly increased frequency of apoptotic events were detected in lean type 2 diabetic vs non-diabetic cases. When normalized to the β-cell volume, the frequency of apoptosis was 3-fold higher in obese cases of type 2 diabetes and 10-fold higher in lean cases of type 2 diabetics as compared with their controls.

Thus, relative β-cell volume and therefore β-cell mass is decreased in both obese and lean humans with type 2 diabetes compared with non-diabetic age- and weight-matched controls. The fact that patients with IFG, a risk group for developing diabetes, had a 40% deficit in relative β-cell volume indicates that loss of β-cells is an early process in the pathogenesis of diabetes mellitus (18).

Once β-cell mass decreases below a critical level and insulin production no longer meets metabolic demands we have hyperglycemia. Does a 60% decrease in β-cell mass – as found in this study – translate into impaired glucose metabolism? Humans who have undergone 50% pancreatectomy have impaired glucose tolerance and insulin secretion in response to a hyperglycemic clamp (19–23). On this basis we may assume that a 60% reduction in β-cell mass in the face of insulin resistance may be sufficient to result in hyperglycemia.

What are the mechanisms for the increased apoptosis found in the islets of type 2 diabetics? The islet in type 2 diabetes is characterized by deposits of propeptide (IAPP) (15, 24–29). This peptide causes apoptosis of β-cells (30, 31), particularly when it is in...
the form of small IAPP oligomers (32). In addition, both
glucotoxicity and lipotoxicity cause β-cell apoptosis.
The molecular mechanisms behind gluco- and
lipotoxic apoptosis in the human β-cell have recently
been further elucidated.

A series of studies (33–36) report on the roles of
high glucose concentrations and different free fatty
acids (FFAs) on β-cell proliferation, apoptosis and func-
tion in cultured human islets. The results showed that
prolonged exposure of cultured human islets to high
glucose levels increased β-cell apoptosis in a dose-
dependent manner. In addition, chronic exposure of
cultured human islets to the saturated fatty acid palmitic
acid results in increased markers of β-cell apoptosis
and decreased β-cell proliferation. However, the mono-
unsaturated fatty acids palmitoleic acid and oleic acid
did not affect DNA fragmentation and induced β-cell
proliferation. Moreover when co-supplemented, each
of the monounsaturated fatty acids prevented apopto-
sis, prevented impairment of β-cell proliferation and
improved insulin secretion that was caused by palmitic
acid and/or hyperglycemia.

Federici et al. (37) have demonstrated that cultures
of human pancreatic islets exposed to elevated glu-
cose levels showed overexpression of proapoptotic
genes Bax, Bid and Bik, while the expression of
anti-apoptotic gene Bcl-2 was unaffected, suggesting
modulation of the balance towards apoptosis and
β-cell death. β-cells produce and release interleukin
(IL)-1β in response to chronic exposure to hypergly-
cemia (33). This subsequently results in activation
of an apoptotic pathway (NF-κB activation, FAS up-
regulation, DNA fragmentation) which is prevented
by an IL-1 receptor antagonist. Moreover, IL-1β-pro-
ducing β-cells are reported in pancreatic sections of
type 2 diabetic patients but not in normal control
pancreata (33).

Chronic exposure to elevated levels of FFA leads to
lipid overload of pancreatic cells, dysregulated insulin
secretion (38, 39) and apoptotic cell death (36, 40–42).
FFA-induced apoptosis and reduced β-cell proliferation capacity were observed in rodent
(36, 41) and human pancreatic islets (40). Studies
demonstrate that lipotoxicity is attributed to accumu-
lation of saturated fatty acids, and not associated with
exposure to unsaturated fatty acids (36, 43, 44).

Apart from the deleterious effects of saturated fatty
acids on the pancreatic β-cell, elevated serum FFAs
contribute to the pathogenesis of the metabolic syn-
drome and heart disease. While adipocytes store
excess fatty acids in the form of triglyceride in lipid
droplets, non-adipose tissues have a limited capacity
for storage of lipids. In hyperlipidemic states,
accumulation of excess lipid in non-adipose tissues
leads to cell dysfunction and/or cell death. This lipo-
toxicity appears to be specific for saturated fatty acids
in several tissues studied and is ameliorated by
unsaturated fatty acids (36, 43–46).

How should we understand this difference in the
effects of fatty acids? In their recent work
Listenberger et al. (47) provide evidence that exogenous or endogenously generated unsaturated FFAs
induce incorporation of saturated fatty acids into tri-
glycerides, thus diverting saturated fatty acids from
pathways that can lead to β-cell apoptosis. In their
cell culture system (47), oleic acid does not affect
uptake and accumulation of palmitic acid. However,
the intracellular fate of the saturated palmitic acid
is altered with co-supplemented oleic acid. The pre-

sence of oleic acid resulted in incorporation of palmiti-
tate to triglyceride stores, while absence of oleic acid
showed no channeling of palmitate into triglyceride
stores. Appropriate controls ensured that this effect
was not simply due to increased total fatty acids in
the media available to cells. Moreover, cells derived
from mice lacking the enzyme for the final step of tri-
glyceride synthesis (acyl CoA:diacylglycerol transfer-
ase 1 knockout mice (48)), fail to accumulate exogenously applied fatty acid and are more sensitive
to fatty acid (saturated or not)-induced cell death as
compared with controls. Thus it appears that the
ability to synthesize triglyceride plays an important
role in the protection from lipotoxicity. Triglyceride
accumulation in response to increased cellular levels
of unsaturated fatty acids may be a general metabolic
phenomenon. Listenberger et al. (47) hypothesize
that palmitate channeled toward triglyceride storage may
be unavailable for pathways leading to cell death,
such as the generation of reactive intermediates and
ceramide.

While we have possible mechanisms to explain gluco-
and lipotoxicity of β-cell apoptosis, it remains unclear
what underlies the apoptotic loss of β-cells before we
have frank hyperglycemia and/or hyperlipidemia. The
occurrence of apoptosis in patients with IFG suggests
an inherent defect in the β-cells of people who sub-
sequently develop type 2 diabetes mellitus. A possibility
for slowing the progression or even preventing type
2 diabetes may be to develop dietary and pharmaco-
logical strategies aiming at ameliorating increased β-cell
apoptosis in people with a defined high risk for
developing type 2 diabetes.

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References

1 DeFronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 1988
37 667–687.
2 Burke JP, Williams K, Gaskill SP, Hazuda HP, Haffner SM & Stern MP. Rapid rise in the incidence of type 2 diabetes from
1987 to 1996; results from the San Antonio Heart Study. Archives of Internal Medicine 1999 159 1450–1456.
7 Ogilvie BE. The islands of Langerhans in 19 cases of obesity. Journal of Pathology 1933 37 473–481.
20 Robertson RF, Lanz KJ, Sutherland DE & Seagust ER. Relationship between diabetes and obesity 9 to 18 years after hemipancreatectomy and transplantation in donors and recipients. Transplantation 2002 73 736–741.

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45 Hardy S, Langelier Y & Prentki M. Oleate activates phosphatidylinositol 3-kinase and promotes proliferation and reduces apoptosis of MDA-MB-231 breast cancer cells, whereas palmitate has opposite effects. *Cancer Research* 2000 **60** 6353–6358.


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