B Cell Mass & Function & the Development of Type 2 DM

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Diabetes mellitus is a cluster of chronic metabolic disorders triggered by relative or absolute insulin deficiency. The incidence and prevalence of DM are high and are steadily increasing worldwide. In T1D, there is a complete failure of the pancreas to produce insulin.

In contrast, inT2D, there is a fundamental change in insulin secretion and in insulin receptor dynamics. (1)

Insulin is a potent anabolic hormone that mediates glucose uptake in insulin-responsive tissues such as muscle, fat, and liver while inhibiting hepatic glucose production to maintain euglycemia. Type 2 diabetes mellitus occurs when insulin producing B cells are unable to produce &/or release sufficient insulin to overcome peripheral insulin resistance resulting in hyperglycemia. Multiple metabolic & inflammatory cellular stresses ultimately lead to impaired insulin biosynthesis & secretion from B cells in response to glucose culminating in B cell failure. (2) These include oxidative and endoplasmic reticulum (ER) stress, proinflammatory responses, and islet amyloid deposition, which can lead to β cell apoptosis or necrosis. Deteriorating β cell function also leads to impaired insulin gene expression by down-regulating insulin gene promoter activity, resulting in the eventual net decrease in insulin secretion in response to glucose stimulation. (1) Autopsy studies in various populations have reported significant reductions in the amount of pancreatic β-cells in patients with type 2 diabetes compared with non-diabetic individuals. They suggest that the decline in B cell mass precedes the onset of diabetes by almost a decade. Furthermore, those studies show that at the time of diagnosis, diabetic patients seem to have already lost about 50% of their pancreatic B cells. The range can be from 20% to 65%. There is also evidence for a β-cell deficit in prediabetic individuals with impaired fasting glucose. (1) Normally islet β cells respond to insulin resistance by increased insulin secretion & expansion of β cell mass. Increased insulin secretion is caused by expansion of β cell mass, increased insulin biosynthesis, and enhanced nutrient secretion coupling processes with increased sensitivity to glucose, FFAs, and GLP-1 stimuli resulting in increased production of coupling signals necessary for insulin exocytosis. Expansion of B cell mass is caused by increased activity of growth factor signaling pathways, postprandial glucose, and GLP-1 signaling that promote β cell proliferation and neogenesis and prevent apoptosis. Signaling for growth may occur in response to FFAs.(3) Insulin resistance→ compensatory increase in insulin secretion. Compensation involves a heightened response to the normal physiological processes affecting B cell function & mass. It is the progressive exposure to the extra fuel surfeit (both the level & duration of exposure) &/or genetic predisposition with the increased glucotoxicity & lipotoxicity that causes mitochondrial dysfunction & B cell failure. This is well illustrated in fig (1 & 2)

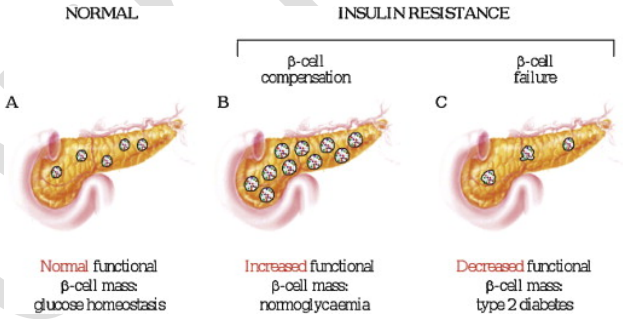

Fig1: Functional pancreatic beta cell mass in diabetes. Diabetes & Metabolism, Volume 35, Issue 2, 2009

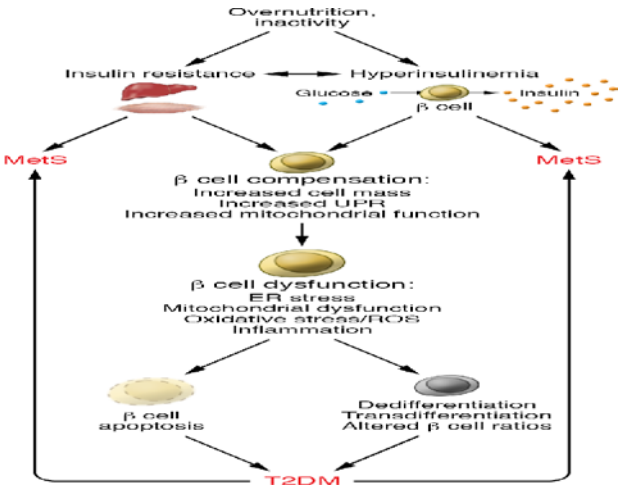

Fig 2:Beta cell dysfunction and insulin resistance. Front Endocrinol ,2013 Mechanism of B cell dysfunction

In T2D, increased metabolic stress due to hyperglycemia and peripheral insulin resistance can induce mitochondrial dysfunction, leading to production of

reactive oxygen species (ROS). It is believed that at a basic level, ROS can serve as physiological signals.(2)
Increased ROS down-regulates respiratory chain proteins and reduces mitochondrial ATP production, which can also impair insulin secretion. These reactive species can substantially damage cell components, including the mitochondria, via lipid peroxidation, protein oxidation, and DNA mutation (1)
Autophagy is the basic catabolic mechanism to degrade dysfunctional proteins as well as defective cellular components. However, persistent metabolic stress on β cells under hyperglycemic conditions leads to dysregulation of autophagy, which can ultimately aggravate β cell function or result in β cell demise (2)
The ER is the site of insulin biosynthesis. In the pre-diabetic stage, two processes occur: insulin resistance and an overexpression of proinsulin and unfolded protein species in the ER lumen.
The accumulation of mis-folded proteins is believed to lead to the estrogen receptors (ERs)of b cells and is associated with an inability to clear mis-folded proteins or dysfunctional autophagy.
This process is associated with a substantial generation of ROS, apoptosis and b cell death (1)
The overload of defective proteins can trigger the unfolded protein response (UPR) through activation of PKR–like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6) pathways, resulting in attenuation of global protein synthesis to promote proper protein folding and degradation of misfolded proteins. However, when UPR can no longer attenuate the increasing protein load on the ER, ER stress–mediated β cell dysfunction and death can occur (2) Islet amyloid polypeptide (IAPP) is a normal product of beta cells co-secreted and stored with insulin in secretory granules. Its functions are not fully understood, but it seems that it limits the glucose-stimulated insulin secretion (although a stimulatory effect on basal insulin secretion has also been described). It has an inhibitory effect on gastric emptying and appetite. (6) Islet amyloid is a pathological lesion found in the pancreas of more than 90% of individuals with T2D. Islet amyloid is formed mainly by abnormal aggregation of the β cell hormone islet amyloid polypeptide. Increased islet amyloid deposition correlates with decreased β cell mass and insulin production via multiple mechanisms including promotion of islet inflammation and activation of apoptotic pathways (2) Increased proinsulin/insulin ratio seen in diabetes might affect fibril formation as insulin seems to form complexes that stabilize IAPP and inhibit fibril formation. The small oligomers and larger fibrils of amyloid are more cytotoxic. These fibrils may insert into the lipid layer of cell membrane and form pores (ion channel-like structures) that change the ion flux or cause a non-specific membrane disruption. B cell apoptosis & death is induced by aggregated IAPP that activate IL 1B through induction of ER stress & UPR. (4-8)

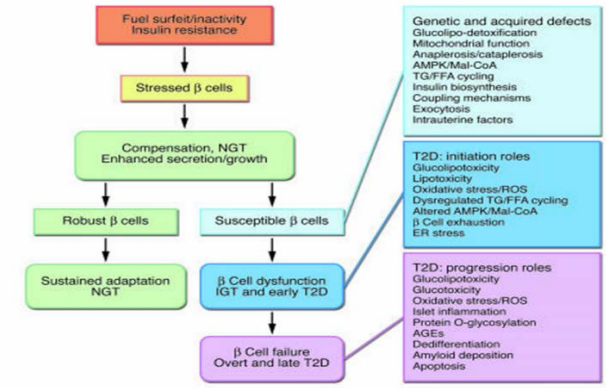

Fig 3:Islet beta cell failure in type 2 diabetes. J Clin Invest. 2006

Inhibition of β-cell dysfunction and death by approved T2D therapeutics The rapid rise in rates of T2DM echoes a similar rise in rates of obesity, which causes insulin resistance and may have additional effects on β-cell health. Interventions that reduce body fat (such as diet and exercise, GLP-1 receptor agonists, or bariatric surgery) or that change fat biology (TZDs) provide the best evidence for slowing or arresting the deterioration of β-cell function that causes T2DM. These interventions should form the basis of interventions to prevent and treat T2DM, particularly early in its course.(9) Intensive Lifestyle Modification: Obesity and lack of physical activity cause insulin resistance and increase the workload on β cells. Weight loss and exercise interventions increase insulin sensitivity and unload the secretory demand on β-cells. (9)
Bariatric surgery has effective and durable effects on the prevention of T2DM in obese adults, particularly among those with IFG. Metformin: Metformin is effective at reducing hyperglycemia primarily by inhibiting hepatic glucose production and by increasing insulin sensitivity. (9) Metformin has been shown to protect rat and human islets from oxidative and ER stress, metabolic dysfunction, apoptosis induced by glucotoxicity and lipotoxicity by activating AMPK/SIRT1/PGC-1α signalling pathway and inducing autophagy in high-glucose

environment (10) Thiazolidinediones: Thiazolidinedione treatment may be a promising approach to preserve β-cell mass and function by inhibiting islet amyloid formation and decreasing ER stress induced by hIAPP.(10) Glucagon-like peptide-1 receptor agonists:
GLP-1 has been reported to alleviate glucotoxicity, lipotoxicity, excess nitric oxide (NO), Ca2+ depletion, oxidative stress, and cytokine-induced ER stress in both primary β-cells and cell lines through several downstream signaling mechanisms. Most recently, GLP-1 has also been implicated in the regulation of autophagy in β-cells. (11) ERS can be reversed using liraglutide which prevents ERS induced apoptosis in B cells. (2) Dipeptidyl peptidase-4 inhibitors: The administration of DPP-4 inhibitors leads to a 2-3-fold elevation of endogenous GLP-1 concentration. (12)
DPP-4 inhibitors improve glucose homeostasis synergistically with metformin even in mild hyperglycaemia, without the adverse effects of weight gain and hypoglycaemia (13) Sodium-glucose co-transporter type 2 inhibitors: Sodium–glucose cotransporter-2 (SGLT2) inhibitors were introduced as a workaround for peripheral insulin resistance. These agents induce glycosuria, thereby reducing the need for insulin to dispose of glucose. Studies in animals and humans suggest that this approach, by reducing chronic hyperglycaemia, may improve insulin sensitivity and beta cell function (14)

Conclusion

Almost half a billion people are living with diabetes worldwide, resulting in decreased quality of life and decreased life expectancy. Thus, diabetes has become one of the most challenging health problems in the 21st century. Although diabetes begins with insulin resistance, β-cell dysfunction (decline of β-cell function and β-cell mass and consequent deficiency in insulin secretion) is the major contributor to the development of diabetes. Glucotoxicity, glucolipotoxicity, lipotoxicity, inflammatory cytokines. and islet amyloids are known to be major risk factors for β-cell dysfunction. These factors contribute to β-cell dedifferentiation, β-cell dysfunction, and β-cell death through diverse mechanisms, such as mitochondrial dysfunction and oxidative stress, impaired autophagy, and ER stress.
These molecular pathways likely play complementary roles; therefore, their crosstalk needs to be studied further at different levels to elucidate β-cell dysfunction, including the mechanism of insulin secretion and the processes responsible for the death of β-cells, such as apoptosis and necrosis. Understanding the molecular mechanisms underlying pancreatic β-cell failure may pave the way for developing T2DM prevention and treatment strategies.

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