Type 2 diabetes:

Pathogenesis and Treatment

HDRC Essay

Introduction

Type 2 diabetes (T2D) is a clinical syndrome characterized by relative insulin deficiency due to pancreatic β-cell dysfunction and insulin resistance (Robertson *et al.*, 2004; Chatterjee *et al.*, 2017). Its epidemic has developed into a global pandemic (Unnikrishnan *et al.*, 2017). The global prevalence of diabetes In 2017 reached 8.4% (Ogurtsova *et al.*, 2017), and could still be underestimated (Ogurtsova *et al.*, 2017; Zheng *et al.*, 2018). Over 90% of diabetes cases are T2D (Zhang *et al.*, 2009; Zheng *et al.*, 2018). To solve this crisis, we need to make the best of our pathophysiological knowledge to find the best treatments for T2D.

Modern biomedical research, which comprises of the integration of basic research (*from bench*) and translational studies (*to bedside*), bridge the gap between the treatment and pathophysiology of T2D. (Beigh, 2016; Flier & Loscalzo, 2017; Rivas Rios *et al.*, 2018) Since there is no “one size fit all” solutions for T2D, better understandings of treatment and pathophysiology in the context of biomedical research will be essential for us to optimize the treatment (Garfield *et al.*, 2003; Pozzilli *et al.*, 2014; Narayan, 2016).

In this article, we will first review T2D pathogenesis, especially the pathogenesis related to insulin, including the pathogenesis of insulin resistance and impaired insulin secretion, in the context of biomedical research, and then explain how biomedical research improves the treatment for T2D. Lastly, we will summarize and conclude the article by the thoughts underlying different parts.

From insulin deficiency to insulin resistance

Discovery of insulin and glucagon

Biomedical research contributes to what and how we understand type 2 diabetes today. (see Table 1) (Zaccardi *et al.*, 2016) The discovery of insulin could be the most important one among all research related to T2D, as the related biomedical research provided the first scientific insight into both pathogenesis and treatment.

The post-pancreatectomy canine model of diabetes stressed the importance of the pancreas in glucose control. The sequent studies on pancreatic extracts enabled the discovery of insulin and glucagon. (Karamitsos, 2011; Valverde, 2016) The two hormones form the basis

of blood glucose control (see Figure 1). Insulin induces a glucose-lowering mechanism when the glycemic level is high, while glucagon induces a glucose-elevating mechanism when the glycemic level is low. Thus, insulin deficiency was considered to be the cause of diabetes. (Röder *et al.*, 2016; Czech, 2017)

Awareness of insulin resistance

Radioimmunoassay enabled precise measurement of blood insulin level, and discover hyperglycemia in diabetic patients, which challenged the hypothesis that insulin deficiency causes diabetes (Röder *et al.*, 2016). Reduced response to insulin, termed insulin resistance, rather than insulin deficiency seemed to cause the disease (Yalow & Berson, 1960; Taylor, 2004). Independent measurements of blood insulin, using standardized methods like glycemic clamps (Defronzo *et al.*, 1979; Reaven, 1983), confirming insulin resistance in patients. Insulin resistance became well-recognized in T2D pathogenesis. (Zaccardi *et al.*, 2016) Meanwhile, the medical community has classified diabetes into type 1 (insulin-dependent) diabetes and type 2 diabetes (non-insulin-dependent). (Hedgecoe, 2002)

Immunology/radiology and glycemic clamps also deepen our understandings of T2D pathogenesis beyond hyperinsulinemia. For example, these tools and related biomedical research enabled the discovery of insulin receptors and insulin signalling. (De Meyts, 2016) Even so, insulin resistance is still too complex to understand, which we will expand on in the next section.(Eroschenko & Fiore, 2008)

Pathogenesis of insulin resistance

Glucose homeostasis and insulin action

Glucose homeostasis is sustained by insulin and glucagon that are both produced by the pancreas. During the fed state, the pancreas can sense the high glycemic level and respond to it by secreting insulin to promotes the uptake of glucose in the liver and muscle and other insulin-sensitive tissues. During the fasting state, the pancreas release glucagon to promote glucose production via gluconeogenesis. It also promotes glycogenesis to increase the glycemic level. (see Figure 1) (Röder *et al.*, 2016; Czech, 2017) Thus, in theory, insulin

resistance can be resulted from reduced glucose uptakes in any of the insulin-sensitive tissues due to either wrong response or reduced sensitivity to insulin.

To understand the pathogenesis of insulin resistance, we need to conceptualize the normal insulin action, which has been mapped in a series of biochemical works. The binding of insulin to insulin receptor will phosphorylate IRS protein on the tyrosine residue and then initiate a PI3K/Akt signalling pathway, where Akt is required. (see Figure 2) (Czech, 2017) As the mutation in any of genes encoding for insulin receptor, PI3K, and Akt are sufficient to cause severe insulin resistance (Parker *et al.*, 2011). The activation of the pathway can promote the activity of GLUT4, an insulin-sensitive glucose transport, in adipose and muscular glucose uptake and can reduce gluconeogenesis in the liver. (Czech, 2017)

The Akt-dependent pathway is highly conserved across species (Hemmings & Restuccia, 2012), adding to the credibility of animal experiments. Pathogenic change to this pathway, especially when it is related to Akt, may cause insulin resistance. (Czech, 2017) For example, the Baf60c/Deptor signalling pathway is essential in avoiding diet-induced insulin resistance in the muscle, while transgenic rescue of Baf60c in diabetic mice can restore Akt phosphorylation and reduce insulin resistance. (Meng *et al.*, 2014)

Hyperinsulinemia and insulin resistance

Based on our understanding of glucose homeostasis, it is easy to assume such a hypothesis of T2D pathogenesis as below (see Figure 3), which is often described (Stumvoll *et al.*, 2005; Shanik *et al.*, 2008; Taylor, 2008).

1. Chronic energy excess induces insulin resistance.
2. β-cells overproduce insulin to compensate for insulin resistance in order to keep the glycemic level in the normal range.
3. Long-term exposure to energy excess damages β-cell function.
4. When impaired β-cells fail to compensate for insulin resistance, insulin resistance develops into T2D with hyperglycemia as a major symptom.

The question here is whether insulin resistance causes hyperinsulinemia. In high-fat diet (HFD)-fed mice and human subjects, hyperinsulinemia often happen before other metabolic symptoms, as summarize and analyzed by Czech (2017) according to data from more than 10 studies. Also, in obese people, hyperinsulinemia happens even when the glycemic level

is low (Beck-Nielsen, 2012). Hyperinsulinemia is sufficient to cause insulin resistance, as mice with extra copies of the insulin gene, which can cause hyperinsulinemia without obesity, also insulin resistance, glycemia, hypertriglyceridemia.(Marbán & Roth, 1996) Shanik et al (2008) suggest that hyperglycemia could be both a cause and result of insulin resistance.

Limitation of insulin resistance

Genetics provides extra insights into the role of insulin resistance. In tissue-specific knockout mice, severe insulin resistance in muscles and the brain fails to induce T2D (see Figure 4) (Stumvoll *et al.*, 2016). Double knockout mouse models with one gene required by insulin secretion and the other required by insulin sensitivity develop diabetes, whereas those with only one knockout do not develop diabetes. (Brüning *et al.*, 1997; Terauchi *et al.*, 1997) We can suggest from these studies that insulin alone is not the cause of T2D, which means other causes of T2D should be studied. These biomedical studies have added much complexity to T2D pathogenesis, which could imply that a new angle should be introduced.

Obesity and T2D: a non-glucocentric perspective

Linking T2D to obesity: the Randle cycle

Insulin resistance is closely related to glucose intolerance, abdominal obesity, dyslipidemia, hypertension and other metabolic disorders. (Reaven, 1988; Cornier *et al.*, 2008) Reaven (1988) termed this clustering of metabolic disorders as the metabolic syndrome, which suggests links between insulin resistance and other metabolic processes.

Randle et al (1963) described how energy is distributed to different mammalian organs in a glucose-fatty acid cycle, which is now known as the Randle cycle. This cycle suggests chronic hyperlipidemia can suppress glucose oxidation (Shuldiner & McLenithan, 2004), which brings new angles to understand glucose metabolism, that is, the lipid metabolism.

Reduce glucose transport in T2D

Normally, the secretion and production of insulin in β-cells is dependent on glucose transport into the cell, which is mediated by the glucose transporter 2 (GLUT2). High-fat diet (HFD)-fed mice have a reduced GLUT2 function and reduced GnT-4a glycosyltransferase

encoded by Mgat4a gene. Pancreas-specific knockout of Mgat4a in mice reduces GLUT-2 function, which impairs glucose-stimulated insulin secretion (see Figure 2 and 5) (Ohtsubo *et al.*, 2005; Thorens, 2006). Further research shows that the increased free fatty acid reduces transcription factor FOXA2 and HNF1A's expression, leading to pathogenic Mgat4a expression (Ohtsubo *et al.*, 2011).

Insulin secretory defects

T2D is related to both hyperlipidemia and hyperglycemia, both of which could lead to toxicity for the cells. Markers for oxidative stress, including 8-hydroxy-deoxyguanine and etc., are upregulated in T2D patients or animal models for T2D. Low antioxidant capacity of islets has been indicated by the small activity of antioxidants, such as Mn superoxide dismutase, whereas antioxidant drugs can protect the cells from glucotoxicity. On the other hand, long-time exposure to high lipid level can induce lipotoxicity that can impair insulin secretion, insulin gene expression and promote cell death. (Robertson *et al.*, 2004) The cellular stress is likely to induce inflammation, promoting cell death the fibrosis that can damage β-cells. (Donath & Shoelson, 2011)

Optimization of the treatments

Insulin discovery

Insulin discovery by Banting and Best in the 1920s exemplifies how increments of the knowledge of diabetes can cause a breakthrough in treatment. Previously described pancreatic duct occlusion, diabetic dog models and hypothesis of a substance in the pancreas extracts to avoid glycosuria were essential to the study. (see Table 1)(Rosenfeld, 2002; Zaccardi *et al.*, 2016; Vecchio *et al.*, 2018) Every step before the discovery is notable to the final breakthrough.

Regulating the regulators

As the role of homeostasis extends beyond glucose, new treatment and considerations can be introduced. For example, as more and more evidence suggests that hyperinsulinemia is also a cause of insulin resistance (as described previously), use of high-dose insulin, like U-

500, in already insulin-resistant patients may not produce an outcome as expected, except “specific types of diabetes”, as described by the researchers (Cochran *et al.*, 2005).

The missing part of homeostasis could be the new targets for treatment, as indicated by the incretin-based drugs. Animal models and reliable measurement of glycemic levels enabled earlier studies on incretins, which showed contradicting results. Improved biochemical techniques allowed the description of incretin effects, i.e. stimulating insulin and inhibiting glucagon release. This triggered the clinical trials and use of GLP-1, one of the incretins. Further research showed DPP-4 degrades incretins, which inspires the hypothesis of DPP4 inhibition as a therapeutic option. (Creutzfeldt, 2005; Mudaliar & Henry, 2012)

More than glucose control

It has become increasingly crucial to acknowledge that glucose homeostasis is not the only impaired function. For example, as growing research indicates inflammation’s role in T2D, many anti-inflammatory drugs are used in clinical trials (Pollack *et al.*, 2016). Besides, metformin, a commonly used drug for T2D, is found to have a direct anti-inflammatory effect (Cameron *et al.*, 2016). The clinical use of thiazolidinedione is supported by research detailing PPAR’s roles in the Randle cycle. (Spiegelman, 1998; Hue & Taegtmeyer, 2009) All in all, there could be numerous examples of how new pathophysiological understandings inspire new treatment where biomedical research plays an essential role.

Conclusions

In this article, we unfold the evolving understandings of T2D pathogenesis and treatment, with extra attention to how research methods uncover the underlying mechanisms. First, we have described how technological advances and biomedical research have contributed to our understandings of T2D pathogenesis and treatment, such as the discovery of insulin and insulin resistance. With the development of omics and other technologies (Kahn *et al.*, 2014), they will undoubtedly provide significant insights into the future. Second, we have also noticed the new thoughts in this field, including the role of hyperinsulinemia and lipid metabolism, which has already brought new pathophysiological understandings and new treatment. Perhaps, to make the best of these known drugs, more stratified, personalized medicine might be helpful and beneficial (Fitipaldi *et al.*, 2018).

Figures & Tables

Table 1. Chronicle of the major research discoveries in T2D pathophysiology

Discovery 1: Insulin discovery	
1889	Post-pancreatectomy dogs proved to develop diabetes.
1910	It was first hypothesized that insulin a substance produced by pancreatic islets should be present in non-diabetic people but deficient in diabetic patients.
1921-1923	Insulin extracted and purified from canine pancreas showed glucose-lowering ability in post-pancreatectomy dogs. (Karamitsos, 2011)
Discovery 2: Insulin resistance	
1936	"Insulin-sensitive" and "insulin-insensitive" diabetes was described. (Rodger, 1991; Zaccardi *et al.*, 2016)
1951	Bornstein and Lawrence (1951) reported hyperinsulinemia was first found in plasma from non-insulin-dependent patients.
1959	Yalow and Berson (1960) confirmed hyperinsulinemia in diabetic patients using the latest radioimmunoassay.
1970	A standardized method to measure insulin resistance.
Discovery 3: Non-glucocentric insights into pathogenesis	
1967	Based on a twin study, Cerasi and Luft (1967) proposed that impaired β-cell function related to genetics should be a cause of T2D in addition to insulin resistance.
1960s- today	Inflammation in β-cells: paving roads for β-cell regeneration? Possible anti-inflammatory drugs in T2D treatment? (Donath *et al.*, 2009)
1990s- today	The role of ectopic lipid accumulation and the mechanism of lipotoxicity: explaining the association between obesity and T2D? (Goodpaster *et al.*, 1997; Hocking *et al.*, 2013; Loher *et al.*, 2016)
	(still in progress)

Table 1. Chronicle of the major research discoveries in T2D pathophysiology, adapted from Zaccardi et al (2016). As Taylor (2004) described, insulin discovery, insulin resistance and non-glucocentric insights into pathogenesis is three major key advances in understanding T2D. These discoveries are based on a series of biomedical research.

(Figure removed)

Figure 1. Pancreatic regulation of blood glucose. Glucagon acts on the liver to promote glycogenolysis and gluconeogenesis, which increases the glycemic level, while insulin acts on adipose tissues and muscles to promote glucose uptake, on the liver to promote glycogenesis and to reduce gluconeogenesis. (Röder *et al.*, 2016)

(Figure removed)

Figure 2. Insulin signaling transduction after insulin-insulin receptor interaction. (Czech, 2017) Insulin is a kind of tyrosine kinase that can bind to insulin receptor, which is tyrosine kinase receptor. The interaction activates an Akt-dependent signaling pathways to inhibit gluconeogenesis and promote muscular and adipose uptake of glucose via GLUT, a glucose transporter protein. The mechanism noted in red only happens in obesity.

(Figure removed)

Figure 3. The metabolic staging of T2D, during which insulin resistance develops into diabetes. (Saltiel, 2001) Chronic energy excess could be caused by multiple reasons including genes, obesity, and ageing and leads to insulin resistance in the muscle and other target cells of insulin action.

(Figure removed)

Figure 4. The effects of tissue-specific knockout of insulin receptor expression in animal models and the function of insulin. (Stumvoll *et al.*, 2016) As is shown, tissue-specific knockout of insulin receptors in brain, muscle, adipose tissues do not cause frank diabetes in mice. Knockout of insulin receptors in pancreas and liver can induce diabetes. Severe insulin resistance in the brain and in muscles do not induce diabetes, proving that insulin resistance alone is unable to induced T2D.

(Figure removed)

Figure 5. The role of glucose transport.

Normal control of glucose transport in (Panel A), compared to the defected control due to lack of cell-surface retention by galectin-9 (Panel B). (Thorens, 2006) In the defected control,

lack of cell-surface retention induces abnormal endocytosis of GLUT-2. The rise in ATP/ADP ratio, which is an indicator of the energy supply, is less, leading to a smaller depolarization of ATP-dependent K^+ channel, and the sequent reduced Ca2+ influx and reduced insulin secretion. (Ohtsubo *et al.*, 2005; Thorens, 2006)

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