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TARGETING INCEPTOR: A NOVEL APPROACH FOR ENHANCING INSULIN SIGNALING AND PREVENTING B-CELL FAILURE IN DIABETES MANAGEMENT

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ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic condition characterized by persistent hyperglycemia, affecting millions worldwide and presenting significant public health challenges. Its historical recognition dates back to ancient Egypt, with modern classifications including Type 1, Type 2, and other subtypes such as gestational and hybrid forms. Type 2 diabetes mellitus (T2DM) has exhibited a concerning global rise, driven by obesity, sedentary lifestyles, and genetic predispositions, increasingly affecting younger populations. Advances in treatment since the discovery of insulin in 1921 have significantly improved outcomes, yet the disease remains a leading cause of morbidity and mortality. Current research highlights β-cell dysfunction and insulin resistance as central to T2DM pathophysiology, with novel insights into insulin signaling mechanisms offering therapeutic promise. The discovery of the insulin-inhibitory receptor (inceptor) has opened avenues for enhancing β-cell proliferation and sensitivity to insulin, demonstrating potential in combating insulin resistance. Additionally, targeting inceptor activity has shown promise in improving glucose metabolism without affecting body composition, positioning it as a viable therapeutic target. Continued exploration into the molecular and genetic underpinnings of DM is essential for developing innovative strategies to mitigate its impact. This review encapsulates historical, clinical, and emerging aspects of diabetes management, emphasizing the evolving landscape of therapeutic interventions.

KEYWORDS: Insulin receptor (INSR), insulin-like growth factor 1 receptor (IGF1R), diabetes mellitus (DM), type 2 diabetes mellitus (T2DM), phosphatidylinositol 3-kinase (PI3K), insulin receptor (IR), insulin receptor substrate (IRS), Diet induced obese (DIO).

INTRODUCTION

One of the earliest illnesses to affect human civilization is diabetes mellitus.[1] The Egyptians were the foremost to register hyperglycaemia, that is identified by loss of weight with overactive bladder. However, the Greek physician Aertaeus was the primary to establish the word diabetic mellitus (DM). Despite the Latin word "mellitus" meaning "honey" (Sweetness), the Greek term for diabetes means "to pass through". With almost one fatality every ten seconds, diabetes is a major cause of protracted illness and early mortality, accounting for a greater number of deaths annually than HIV/AIDS.[2] One of the diseases with the fastest rate of growth is diabetes, which is predicted to affect 693 million individuals globally by 2045.[3]

The chronic metabolic condition known as diabetes mellitus is typified by hyperglycemia, or abnormally high blood glucose levels.[4] The Greek term diabetes means to pass across, whereas the Latin term mellitus, which describes high blood sugar levels in diabetic patients' urine, suggests sweetness. Diabetes, one of the earliest illnesses well-known to man, was primary written about in 1552 BC on an Egyptian papyrus. Herbal extracts and dietary changes were the mainstays of the early diabetic treatment initiatives. Herbal extracts and dietary changes were the mainstays of the early diabetic treatment initiatives. Diabetes used to be a death sentence for patients, especially for younger ones, and had a very bad prognosis and terrible quality of life. Life-saving measures were rarely used before the Toronto Institute's Frederik G. Banting and Charles Best discovered insulin in 1921. For their discoveries of insulin, Banting and John Macleod were granted the Nobel Prize in Physiology or Medicine later in 1923. While Macleod divided his gains with James Collip, who helped effectively purify insulin, Banting shared his winnings with his helper Best.[5]

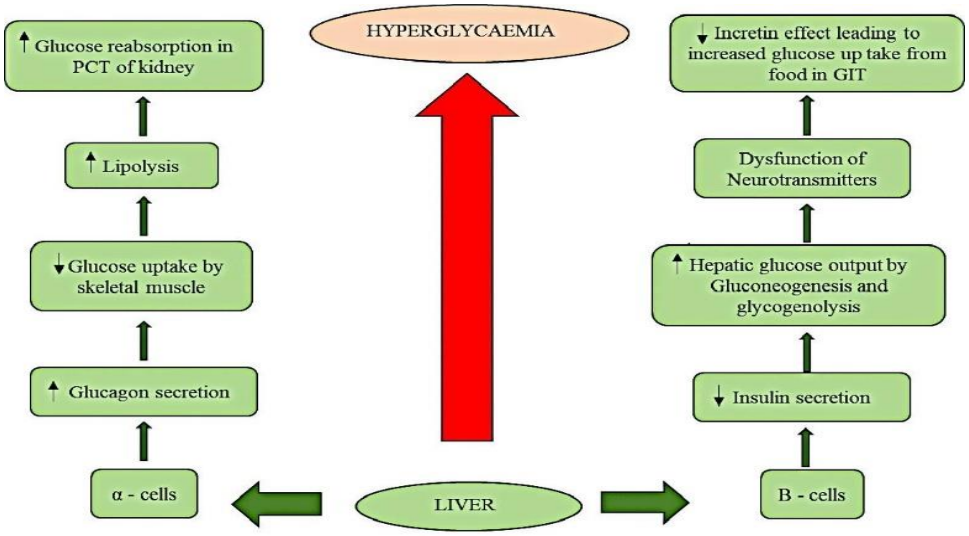

Fig. 1: Pathophysiology of T2DM.[6]

Type I and Type II Diabetes Mellitus: There are two types of diabetes that affect people: Type I and Type II. These are indicated as insulin-dependent and non-insulin-dependent diabetes, or diabetes with juvenile and adult onsets. To put it briefly, type 1 diabetes is caused by the body not producing enough insulin,[7] and type 2 diabetes is caused by the pancreas producing some insulin but not enough.[8]

Expansion in type 2 diabetes mellitus events

The number of senior individuals and the incidence of type 2 diabetes mellitus (T2DM) have raised within the past 50 years. Currently, older adults (those over 65) account for over half of all cases of diabetes mellitus.[9] β-cell dysfunction and insulin resistance are two characteristics of type 2 diabetes mellitus.[10] When type 2 diabetes occurs, a metabolic abnormality generated by a progressive reduction in β cell insulin production, insulin resistance frequently coexists with persistent hyperglycaemia. Type 2 diabetes becoming an increasingly common in young people globally, and it has been associated with emerging speed of obesity, sedentary life along with bad eating habits. It has been suggested that a complicated combination between hereditary and environmental variables accounts for the increased incidence of type 2 diabetes among Inherent Americans, Pacific Islanders, Hispanics, African Americans also South East Asians. Type 2 diabetes affects about 3700 young people in the US each year, and between 2010 and 2050, that number is predicted to treble. Over the past ten years, type 2 diabetes turned out to be more usual among children and adolescents throughout Europe. This age group's type 2 diabetes is turning into a global public health concern.[11]

Classification of DM[5]

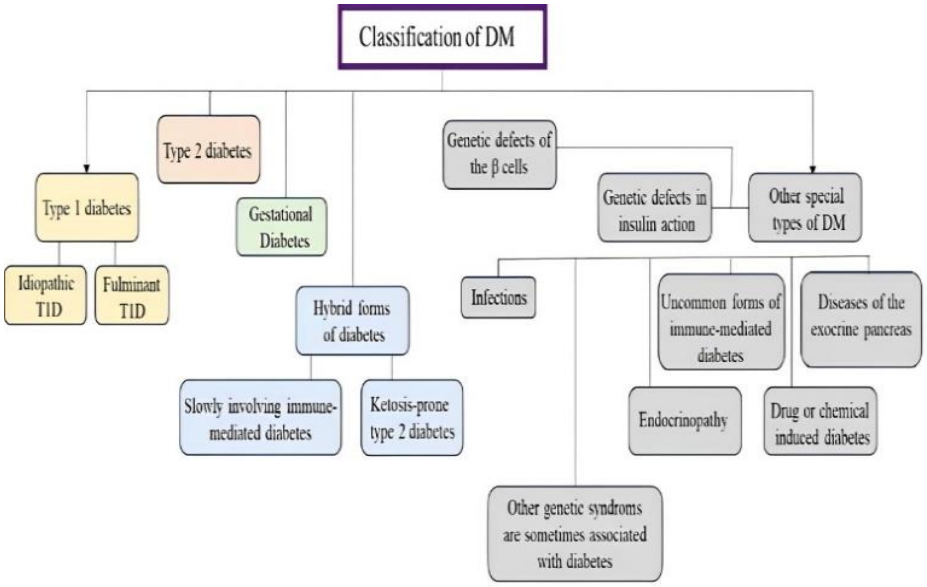

Fig. 2: Type 1 Diabetes, Type 2 Diabetes, Gestational Diabetes, Hybrid Forms of Diabetes (LADA and Ketosis-prone Type 2 Diabetes) and Other Special Types of Diabetes are the various types and subtypes of diabetes that are represented in the most recent classification of DM.

Significant traditional Complexities and Emerging difficulties of diabetes mellitus

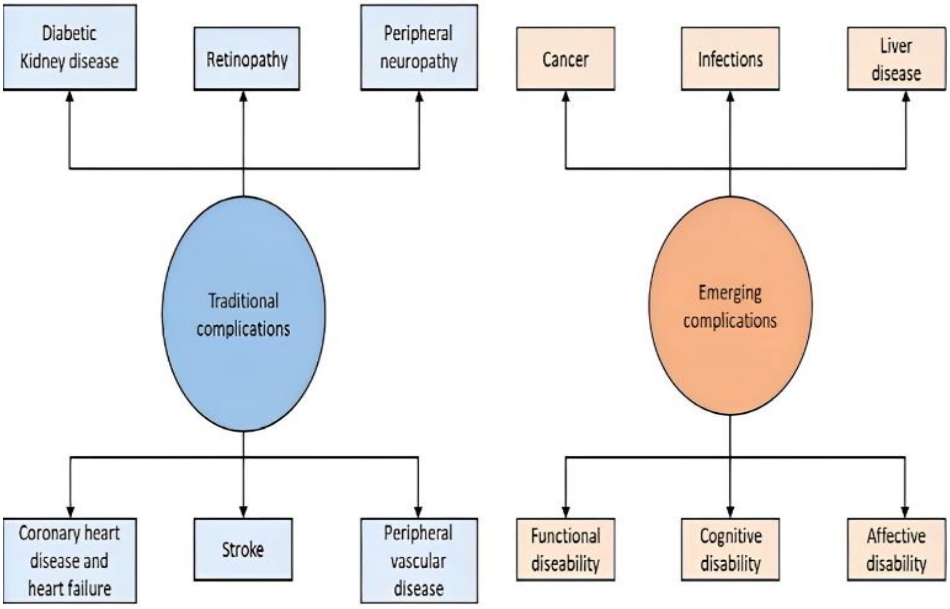

Fig. 3: Shows the main Established and Recent outcomes of diabetes mellitus.

Peripheral nerve dysfunction, diabetic eye disease, diabetic nephropathy, heart failure, coronary heart disease, and peripheral arterial disease are the typical outcomes of diabetes mellitus, as depicted on the diagram's left side. Rather, as the diagram's right-hand side shows, as a result of advancements in diabetes treatment, connections between the condition and infections, cancer, hepatic illness, operational and cognitive impairment, and emotional disorders are starting to surface. The problems linked to diabetes mellitus are not all included here.[12]

Risk Factors and Pathophysiology

The complex interplay of metabolic, hereditary, and natural conditions that influence the occurrence of type 2 diabetes is one of its contraindications. Improved obesity, low physical activity, and an unhealthy diet are the main modifiable risk factors that can prevent many cases of type 2 diabetes, even though individual predisposition to There is a substantial genetic basis for the disease caused by non-modifiable risk variables (race and family history/genetic predisposition).[13,14] The risk of type 2 diabetes and IGT is increased by low weight gain during infancy.[15]

Treatment for diabetes mellitus

Type 1 and 2 diabetes mellitus are the two most prevalent kinds, and each is treated according to its etiopathology. People from simultaneous hereditary predispositions or simultaneous medication treatment, for example corticosteroids, are more possibly to suffer diabetes. The American Diabetes Association (ADA) possesses newly endorsed HbA1c testing as a means of screening for diabetes mellitus, in addition to a 2-hour oral glucose tolerance test. powerful connections among acute care in crucial care settings and persistent diabetes was shown in research, suggesting worse than ideal therapeutic outcomes. Since there is a greater chance of low blood sugar and a possible rise in illness and death, strong diabetes control in this situation is concerning. A continuous intravenous insulin infusion should be used to maintain a glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) in a critically unwell patient.[16]

Usually, medications are consumed to cure indication and protect lives. The subsidiary aim is to extend endurance by eliminating many dangers and help inhibit long-lasting complications from diabetes. For patients with type 1 diabetes, insulin replacement therapy is the cornerstone of care, but for type 2 diabetes, food and lifestyle changes are the cornerstones of management and treatment.[17]

Insulin

The most effective anabolic hormone currently discovered, insulin remains necessary in order to healthy tissue growth with development as well as the upkeep of the body's glucose balance. The pancreatic islets of Langerhans release this hormone after a meal when blood glucose and amino acid levels are raised.[18] Insulin's direct actions on skeletal muscle, liver, and white adipocytes typify its involvement in glucose homeostasis, despite the fact that numerous somatic cell types express insulin receptors.[19]

A metabolic condition known as chronic hyperglycemia is brought on by either insufficient insulin secretion, ineffective insulin, or both.[20] Insulin perform a crucial function as an anabolic hormone and specifically influences how proteins and lipids are metabolized with carbohydrates. By virtue of insulin impedance, the metabolic difficulties connected to diabetes mainly affects tissues like the liver, skeletal muscles with adipose tissue. The nature and period of diabetes can

influence how serious the signs are. Weight loss, polydipsia, dysuria, increased hunger, and vision problems are all signs of elevated blood glucose. Kids and other people with complete insulin deficiency should pay particular attention to this.

Specifically while type 2 diabetes is still in its early stages, some diabetics may not exhibit any symptoms. Uncontrolled diabetes can cause a number of consequences if it is not treated, including coma, disorientation, and in rare instances, death from ketoacidosis or untreated nonketotic hyperosmolar syndrome.[21]

Pancreatic β-cells contain the key elements of the insulin signaling system, such as phosphatidylinositol 3-kinase (PI3K), AKT, insulin receptor (IR), insulin receptor substrate (IRS), and mammalian goal of rapamycin (mTORC1) as a consequence, insulin may control β-cell production and secretion directly. The microhabitat surrounding β-cells, including insulin or sugar concentrations and exposure duration, influence the autocrine impact of insulin on its own release. Low amounts (nanomolar) of insulin increases insulin production in mouse islets, whereas high quantities (micromolar) of insulin decrease it. Insulin production is potentiated by acute treatment, but it is reduced in rat islets following a sustained (30 min) exposure to exogenous insulin. Four hours later, endogenous glucose-stimulated insulin release in humans increases by 40%. Mechanistically, under normal conditions, insulin stimulates the IR/IRS/PI3K signaling pathway to release Ca^{2+} from ER storage, raising the cytosolic Ca^{2+} concentration and inducing granule exocytosis.[22] Furthermore, it is feasible that the PI3KAKT-mTORC1 pathway mediates the insulin autocrine regulatory route. Insulin may activate PI3K-dependent KATP channels at high concentrations in insulin resistance or hyperinsulinemia conditions. This causes the cell membrane to become hyperpolarized and inhibits glucose-induced Ca^{2+} oscillations, which in turn prevents granule exocytosis.[23] Insulin demand is matched in a coordinated manner by this positive and negative autocrine control of insulin. In response to glucose stimulation, insulin first increases secretion; however, secretion is blocked when local insulin concentrations rise.[24]

Insulin for a century

2022, we commemorate the discovery of insulin, which significantly expanded the treatment options available to people with diabetes. Understanding the biology of insulin resistance has advanced significantly since the first time insulin was used to treat diabetes in 1922.[25] In addition to its direct medical applications, insulin has been the focus of four Nobel Prizes and made substantial contributions to the fields of genetics, physiology, autoimmunity, prohormone processing, molecular biology, crystallography, and precision medicine. We will commemorate this centennial by reliving the subsequent molecular characterization of the insulin molecule, which led to the development of new insulin-based treatments, reliving the concurrent clinical discoveries that shaped our current understanding of the etiology and classification of diabetes, and reflecting on the improbable scientific journey that led to the discovery of insulin.[26]

Numerous facets of animal physiology are regulated by insulin signaling. Insulin combines to and stimulates the insulin receptor (IR), a receptor tyrosine kinase at the cell surface. A substantial conformational shift in IR is promoted by insulin, which also settles the active conformation. Insulin-stimulated IR starts indicating cataracts that controls progress, proliferation, and digestion. The internalization of the activated IR occurs by endocytosis mediated by either caveolae or clathrin. The distribution and termination of insulin signaling, as well as the elimination of insulin from the bloodstream, are all notably influenced by IR endocytosis.

Despite decades of rigorous investigation, nothing is known about the process, control, and pathophysiological relevance of IR endocytosis. Here, we go over recent discoveries that provide light on the regulatory networks and molecular mechanisms underlying IR endocytosis.[27]

Insulin resistance (IR) is a serious health care concern of the modern day. Acute insulin resistance (IR) is characterized by beta-cell hypertrophy, progressive hyperinsulinemia, and hyperglycemia, which can lead to the development of type 2 diabetes (T2D) in the end.[28] Long-term abdominal obesity is frequently related to insulin resistance, which is believed to be directly caused by ingesting too much of the high-fat, high-carb western diet. Since the progression of IR to overt T2D might result in gradual β-cell failure and the progression of insulin-dependent diabetes, it is imperative to comprehend the complex etiology of IR. Although its main job is to reduce blood sugar, insulin also drives biological activity through the insulin receptor (INSR) and the insulin-like growth factor 1 receptor (IGF1R), which together control T-cell endurance, proliferation, and work. However, INSR knock-out (KO) only causes gentle diabetic signs, such as damaged insulin secretory role and complete insulin resistance in β-cells, whereas INSR/IGF1R double knock-out causes overt diabetes related with decreased β-cell mass, enhanced programmed cell death, and significantly impaired β-cell function. In order to guarantee sufficient islet INSR/IGF1R signaling, insulin-influenced receptor stimulation must eventually be stopped, and INSR and IGF1R sensitivity to activation by their corresponding ligands must be restored. The gene Iir encodes the insulin inhibitory receptor (inceptor), which we just named, is the primary mediator behind this mechanism in the pancreas. Increased β-cell mass and enhanced glucose tolerance are the outcomes of inductive β-cell specific removal of the inceptor, which advances

signaling through both INSR and IGF1R in thin, chow-fed mice. This behavior is consistent with insulin's capacity to signal via both INSR and IGF1R. The brain and pituitary, aside from the pancreas, are where inceptor expression is highest. However, it is unclear where inceptor is localized specifically in the brain and whether it plays a function in controlling glucose and energy metabolism through central pathways. Changing the activity of inceptors may be a part of pharmacological treatment for insulin resistance (IR) and type 2 diabetes (T2D). This is due to inceptors have the ability to enhance ligand-influenced INSR and IGF1R clathrin-mediated desensitization and endocytosis, both of which can raise islet glucose metabolism. It is unclear, though, if modulating inceptor action also improves glucose metabolism in cases of common, dietinduced obesity and glucose intolerance, as improvement of glucose metabolism by targeted inceptor deletion has only been shown in normoglycemic lean mice.[29]

Novel systems that regulate insulin secretion

Inceptor

No treatment has been able to completely reverse or cure type 2 diabetes, despite the fact that various therapeutic techniques have proven useful in treating the condition. However, recent studies have shown encouraging outcomes since the identification of an insulin-inhibitory receptor (inceptor). By increasing the amount of β-cells, insulator type 2 diabetes stimulates the sensitization of insulin pathways. This lowers hyperglycaemia and increases β-cell activity in insulin secretion. An AP2 adaptor complex found in the cytoplasmic domain of agonists promotes clathrin-mediated endocytosis and eases transport. It would seem logical that research focused at reversing the process would be acceptable and beneficial, since insulin resistance is typified by the desensitization of insulin-responsive tissues and cells to insulin. It has been demonstrated that an inhibitor can cause pancreatic beta cells to regenerate, increasing the cells' sensitivity to insulin as a result.[30]

ELAPOR1 (the inceptor) inhibits insulin signaling in pancreatic β-cells, specifically limiting β-cell proliferation+, by clathrin-mediated IR degradation. While preserving β-cell growth through targeting these intracellular signaling pathways may be a viable approach, it is necessary to determine their relevance to human cells as many of them have been identified in rodents.[22] Because ELAPOR1 blunts the insulin response and reduces the amount of cellsurface receptors, it lowers insulin and IGF1 signaling in beta cells.[31]

Discovery of inceptor

Therapy that stimulates β-cells to insulin might protect diabetic subjects from β-cell failure because insulin resistance to pancreatic β-cells causes overt diabetes in rats. It is commonly known that insulin and IGFs share structural similarities. Both IGF-I and insulin function via specific receptors. Despite the differences in their physiological roles, it has been demonstrated that IGFs and insulin share comparable signaling pathways.[32] Scientists found that in rat βcells, the insulin inhibitory receptor (inceptor; encoded by the Iir gene) suppresses the signaling of the IGF1 receptor (IGF1R) and the insulin receptor (INSR). Similar to INSR and IGF1R, the receptor contains a cysteine-rich region and a mannose 6-phosphate receptor domain, which are both established in the IGF2 receptor-IGF2R. It has traits in common with INSR and IGF1R, such as a cysteine-rich region and a mannose 6-phosphate receptor domain, as does the IGF2 receptor-IGF2R. Rats with no receptor inceptor show signs of hypoglycemia and hyperinsulinemia and only live a short time after birth. Thus, we can deduce that Inceptor regulates glycemic levels by lessening the action of insulin and working against its signaling (Countereffect) in beta-cells.[33]

Diet-induced obese (DIO) mice are frequently employed to study adaptive β-cell proliferation in response to chronic insulin resistance.[34] The therapeutic capacity of the inceptor INSR/IGF1R axis was confirmed by determining the inceptor's dimensional and cellular positioning in the brain and examining its possible effects on energy and/or glucose breakdown in whole-body of diet-induced obese (DIO) mice, beta-cell-specific adult-onset loss of inceptor, or its targeted Cre-mediated removal in the central nervous system. We show that universal adult-onset loss of inceptor decreases the sensitivity of DIO animals to diet-induced glucose intolerance because inceptors are crucial for regulating islet insulin action in lean mice. We also demonstrated that inceptor immune reactivity is elevated in hypothalamic regions that control glucose and energy breakdown, and that inceptor colocalizes with a neuron-specific marker but not with markers indicating microglia, astrocytes, or neuroglia. Reductions in body weight or body composition do not correlate with enhanced glucose metabolism in adult-onset inceptor defective mice, highlighting the therapeutic significance of the inceptor INSR/IGF1R relationship for glucose homeostasis.

This is further supported by the improvement in glucose metabolism in DIO mice, independent of body weight, when inceptors in either CNS neurons or β-cells are targeted for ablation. In conclusion, our research shows that inceptor regulates whole-body glucose metabolism in dietinduced obesity by acting on pancreatic β-cells as well as the central nervous system, all without changing body weight or composition. In addition, we find that CNS neurons are the main brain cells that express inceptors, and that there is a significant amount of co-localization between inceptors and the hypothalamic neurons that control glucose metabolism. Our results support the notion that, in the setting of diet-induced glucose homeostasis deficiencies, blocking the inceptor to sensitize INSR/IGF1R activity may be a promising therapeutic target, potentially preventing N-cell failure and postponing the onset of diabetes.[29]

We carried out additional bioinformatic analysis to obtain a better understanding of the expression of Iir mRNA and the inceptor protein. Iir mRNA was primarily found in the hypothalamic-pituitary-gonadal axis and secretory cells of endocrine glands, according to the EMBL-EBI expression atlas.[35]

We used a peptide with a conserved C-terminal sequence to generate several specific mono- and polyclonal antibodies that detect the extracellular and cytoplasmic domains of mouse and human inceptor.[35]

Because of this, we were able to investigate the inceptor's expression and function in detail. The position of the inceptor in respect to endocrine and exocrine cells in the mature and embryonic pancreas and islets was determined by immunohistochemistry. The high expression of inceptor in the embryonic pancreas, during the peak production of insulin-producing β-cells, and its structural similarities to INSR, IGF1R, and IGF2R in the secondary domain imply that inceptor functions as a regulator of insulin and IGF signaling in the pancreas.[35]

CONCLUSION

Diabetes mellitus (DM) is one of the oldest known diseases, characterized by chronic hyperglycemia due to insulin deficiency or resistance. The discovery of insulin in 1921 revolutionized its treatment, particularly for type 1 diabetes. While insulin therapy remains the cornerstone of management, advancements in understanding type 2 diabetes mellitus (T2DM) have revealed the significant roles of β-cell dysfunction, insulin resistance, and environmental factors such as obesity and sedentary lifestyles in its pathophysiology.

T2DM is increasingly prevalent worldwide, including among younger populations, posing a major public health challenge. The complexities of diabetes extend beyond traditional complications (e.g., cardiovascular and renal issues) to emerging challenges such as cancer and cognitive impairment.

Insulin resistance (IR), a hallmark of T2DM, involves intricate mechanisms including β-cell hypertrophy and impaired insulin signaling pathways. Recent discoveries, such as the insulin-inhibitory receptor (inceptor), have unveiled novel regulatory systems for insulin secretion and β-cell proliferation. Targeting inceptor and related pathways shows promise in enhancing insulin sensitivity and β-cell function, providing potential therapeutic avenues for preventing β-cell failure and delaying the onset of diabetes.

In conclusion, while significant progress has been made in understanding and treating diabetes over the past century, continued research into molecular pathways, genetic influences, and innovative therapies is essential to address the escalating global burden of diabetes and its complications.

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Conflict of interest

No conflict of interest associated with this work.

Contribution of authors

Trupti P. Dongare carried out the writing of manuscript along with referencing and formatting. Swati D. Raysing done the supervision of the work and approved the manuscript for the publication.

Ethical approval

None provided.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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