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The Molecular Basis of Insulin Resistance in Type 2 Diabetes Mellitus: A Chemical and Pathophysiological Perspective

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Abstract

Type 2 Diabetes Mellitus (T2DM) constitutes a global health epidemic, characterized by hyperglycemia caused by peripheral insulin resistance and deteriorating pancreatic β-cell failure. Insulin resistance, the reduced responsiveness of target cells to physiological levels of insulin, is the prevalent defect in the overwhelming majority of T2DM. This review examines the intricate molecular and chemical origin of insulin resistance, from beyond the classic clinical presentation to the subcellular dysregulation that typifies the disease. We first define the elementary chemistry and biology of typical insulin signaling as a point of reference from which pathogenic deviations can be sensed. The review's center methodically dissects the major mechanistic hypotheses of insulin resistance, such as the roles of chronic low-grade inflammation, lipotoxicity, mitochondrial dysfunction, and endoplasmic reticulum stress. Detailed analysis is given on the chemical nature of major inhibitors, such as Ser/Thr phosphorylation of insulin receptor substrates (IRS) by several kinases (JNK, IKK, PKCθ), and bioactive lipid metabolite formation like diacylglycerols (DAG) and ceramides. Furthermore, we explore the action of adipose tissue as an endocrine organ, gut microbiota, and potential genetic/epigenetic mechanisms. The review also discusses the ensuing hyperglycemia-mediated molecular damage by advanced glycation end-products (AGEs) production and oxidative stress that constitute a vicious cycle to perpetuate insulin resistance. By integration of current knowledge, the current review aims to provide a chemically-based paradigm for the explanation of insulin resistance, identifying potential molecular targets for therapeutic intervention and new areas of research, of particular interest given the rising burden of T2DM in North African and Middle Eastern regions.

Keywords: Insulin Signaling, Insulin Receptor Substrate, JNK, Lipotoxicity, Ceramides, Advanced Glycation End-Products, Inflammation, Mitochondrial Dysfunction.

1. Introduction

Type 2 Diabetes Mellitus (T2DM) represents a metabolic disease with epidemic global prevalence and, in Egypt and the Middle East, with high and rising prevalence (Magliano et al., 2021). The pathophysiological feature of T2DM is both insulin resistance and an absolute insulin secretion deficiency. While β-cell dysfunction is eventually the pathogenic cause of the hyperglycemia, insulin resistance often makes up the first and causative defect, developing decades prior to clinical diagnosis (Solis-Herrera et al., 2021). Insulin resistance has been defined as a condition of diminished responsiveness of target tissues—predominantly skeletal muscle, liver, and fat—to the normal action of insulin. This impairment manifests as reduced insulin-stimulated glucose oxidation in fat and muscle, and the inability of insulin to suppress hepatic glucose production (Kahn et al., 2006).

Insulin resistance becomes a clear concept when one changes their perspective from a clinical syndrome to a molecular process. It is, at its core, a dissection of chemical communication; the insulin molecule, a particular peptide hormone, is not able to transfer its message past the plasma membrane and through the intricate intracellular web of proteins and second messengers. This review aims to examine this dissection at the molecular and chemical level. We shall cover the structure of the canonical insulin signaling pathway and then systematically touch on how this pathway is disrupted. The "toxic" effect of excess nutrients, the inflammatory signaling cascades that blunt insulin action, the role of cellular organelle stress, and the pathologic consequences of the resulting hyperglycemia will be covered. Placing insulin resistance on a chemical pathophysiology platform, we are in a position to fully appreciate the potential of targeted therapies intervening at specific molecular nodes, transcending glycemic control to disease root causes. Most pertinent is for the Egyptian Journal of Chemistry readership of researchers, bridging the gap between biochemical principles and clinical medicine.

The Canonical Insulin Signaling Pathway: A Baseline for Understanding Dysregulation

It is necessary to further comprehend the physiology of normal insulin function to grasp the pathology of insulin resistance. The initial chemical event that leads to a complicated intracellular cascade is insulin binding (Figure 1).

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The Insulin Receptor and Its Initial Activation

The insulin receptor (IR) is a transmembrane glycoprotein with a quintessential shape for signal transduction across the lipid bilayer. It exists as a homodimer, in which one subunit is a totally extracellular α-subunit and a transmembrane β-subunit containing intracellular tyrosine kinase activity (Yunn et al., 2023). Chemically speaking, insulin binding to α-subunits induces a far-reaching conformational change to bring the two β-subunits together. This spatial rearrangement enables trans-autophosphorylation on distinct tyrosine residues in the activation loop of the kinase domain (Turvey et al., 2022). This tyrosine autophosphorylation is the critical chemical switch to turn on the catalytic activity of the receptor to allow it to phosphorylate downstream substrates.

The IRS/PI3-Kinase/Akt Pathway: The Metabolic Arm of Signaling

The principal substrates of activated IR are the Insulin Receptor Substrate (IRS) proteins, i.e., IRS-1 and IRS-2. These docking proteins have no inherent enzymatic activity but serve as scaffolds, recruiting a signaling complex. The IR phosphorylates IRS proteins on multiple tyrosine residues in YXXM motifs (DeVito-Moraes et al., 2022). The phosphorylation creates specific binding sites for Src homology 2 (SH2) domains of the effector downstream molecules. Above all, the most important among these is the p85 regulatory subunit of Class IA Phosphoinositide 3-Kinase (PI3K). The activation and recruitment of PI3K are essential steps, as it phosphorylates the plasma membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP2) to form phosphatidylinositol 3,4,5-trisphosphate (PIP3) (Cantley, 2002). PIP3 is a critical second messenger that recruits PH domain-containing proteins to the plasma membrane.

The most significant PIP3-dependent serine/threonine kinase is Akt (also known as Protein Kinase B). Once recruited to the membrane, Akt is activated and phosphorylated by phosphoinositide-dependent kinase-1 (PDK1) and mTORC2 complex (Manning & Toker, 2017). Activated Akt is the central hub for most of insulin's metabolic actions. It promotes glucose uptake in muscle and fat by triggering the translocation of intracellular vesicles of the GLUT4 glucose transporter to the plasma membrane. This is achieved through phosphorylation and inhibition of AS160, which is a Rab-GTPase activating protein that, during normal circumstances, retains GLUT4 vesicles (Sano et al., 2003). In the liver, glycogen synthase kinase-3 (GSK3) is phosphorylated and inhibited by Akt, resulting in the de-inhibition and activation of glycogen synthase, thus glycogen synthesis (Cross et al., 1995). Besides, Akt suppresses gluconeogenesis in the liver by phosphorylating the transcription factor FOXO1, leading to its exclusion from the nucleus and suppression of transcription of genes like phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) (Altomonte et al., 2003).

The MAPK Pathway: The Mitogenic Arm

Another parallel signaling pathway, the Ras-MAPK pathway, is similarly activated by insulin. IRS proteins can recruit the adaptor protein Grb2 via tyrosine phosphorylation, which results in activation of the Son of Sevenless (SOS) protein, initiating a cascade that involves Ras, Raf, MEK, and ultimately ERK1/2 (Boulton et al., 1991). This pathway of insulin signaling is less concerned with short-term metabolic regulation and more concerned with regulating gene expression, cell growth, differentiation, and mitogenesis. This exquisitely choreographed cascade of chemicals is notoriously prone to disturbance. The following descriptions detail the molecular mechanisms by which this system is perturbed during states of insulin resistance.

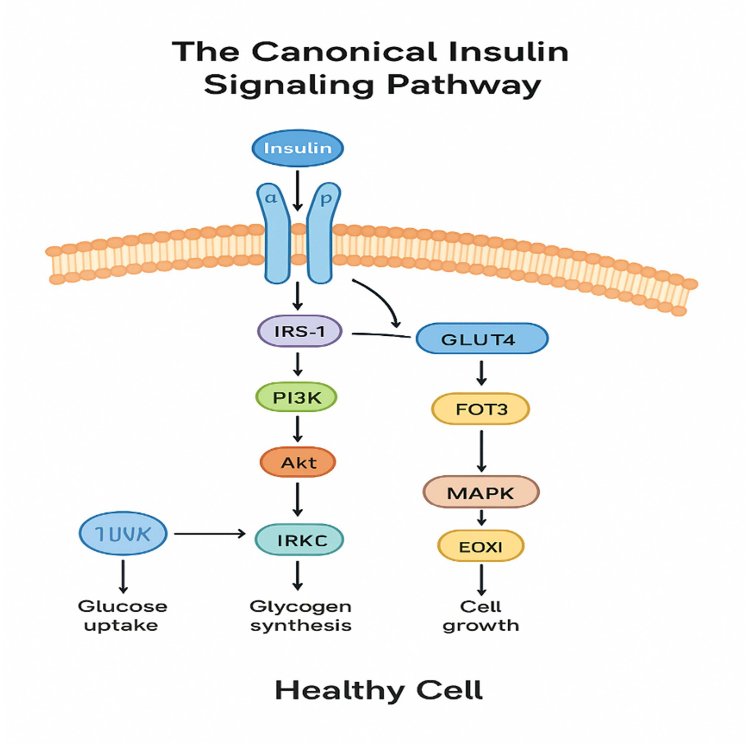

Figure 1: Canonical Insulin Signaling Pathway

Central Mechanisms of Insulin Resistance

The pathogenesis of insulin resistance is multifactorial and involves a complex interaction between the environment and genetics, largely overnutrition, chronic, and physical inactivity. The resulting excess nutrient triggers a sequence of pathogenically related processes, and inflammation and lipotoxicity are among the most basic and well-defined processes.

Chronic Inflammation as a Causal Mechanism

Chronic low-grade inflammation is becoming more and more established as an underpinning of insulin resistance, particularly in obesity. Ectopically grown adipose tissue, especially visceral fat, also undergoes a deep-seated pathological alteration into an inflammatory focus. This abnormal tissue secretes high levels of pro-inflammatory cytokines and chemokines, namely Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6) (Hotamisligil, 2006). The cytokine-stimulated signaling pathways create a direct molecular link between inflammation and insulin dysfunction. For instance, TNF-α activates several serine/threonine kinases, including Inhibitor of Kappa B Kinase beta (IKKβ) and c-Jun N-terminal Kinase (JNK).

These kinases phosphorylate Insulin Receptor Substrate 1 (IRS-1) on some serine residues (e.g., Ser307 in human IRS-1), a molecular "off-switch" process that shuts down insulin signaling (Aguirre et al., 2002). This inhibitory phosphorylation of serine undermines the tyrosine phosphorylation activity of IRS-1 by the Insulin Receptor, promotes its release from the receptor, and subjects it to destruction by the ubiquitin-proteasome system (Yang et al., 2023). The significance of this inflammatory pathway is further highlighted by the report that suppression of IKKβ by high-dose salicylates enhances insulin sensitivity (Yuan et al., 2001). Similarly, JNK is also triggered by inflammatory cytokines, free fatty acids (FFAs), and endoplasmic reticulum (ER) stress. JNK also phosphorylates IRS-1 at inhibitory serine residues, disrupting insulin signal transduction, and genetic deletion of JNK1 was recently shown to protect mice from diet-induced insulin resistance (Hirosumi et al., 2023).

Lipotoxicity and Ectopic Lipid Deposition

The lipotoxicity hypothesis is that overloading and generally deranged adipose tissue storage depot, with overflow of lipids into non-adipose tissues, such as the liver, skeletal muscle, and pancreas, is a major etiology of insulin resistance (Thomas et al., 2023). It is not merely neutral triglyceride storage itself that is fatal, but the presence of specific bioactive lipid intermediates that actively impair insulin signal cascades. One such key mediator is diacylglycerol (DAG), an effective second messenger. Intracellular DAG accumulation leads to activation of novel Protein Kinase C isoforms (nPKCs), such as PKCθ in muscle and PKCε in the liver (Samuel & Shulman, 2012). Activated PKCs phosphorylate the Insulin Receptor and IRS-1 on inhibitory serine residues, bluntly inhibiting the insulin signal directly. This mechanism has good physiological relevance supported by human studies with the application of magnetic resonance spectroscopy, which all demonstrate high correlation between intramyocellular and intrahepatic DAG content and severity of insulin resistance (Petersen & Shulman, 2018).

Ceramides, a group of sphingolipid lipid mediators, are another highly effective group. Elevated concentrations of ceramides inhibit insulin signaling through direct interaction with Akt, a central kinase in the metabolic cascade. Ceramides are active by two principal mechanisms: initially, by the induction of dephosphorylation and inactivation of Akt by protein phosphatase 2A (PP2A), and secondly, by blocking the translocation of Akt to the plasma membrane that is needed for activation (Summers, 2006). Ceramides have also been reported to activate PKCζ and contribute to inflammatory signaling and thus form a pathogenic nexus that closely interconnects lipotoxicity with inflammation (Summers & Goodpaster, 2016).

Mitochondrial Dysfunction

Insulin-resistant and T2DM skeletal muscle has typically impaired oxidative capacity and a susceptibility to preferential carbohydrate over fat oxidation. This has led to the hypothesis that mitochondrial dysfunction, or a relative defect in oxidizing fatty acids, is responsible for the accumulation of the lipid intermediates described above (Petersen et al., 2004). MitoNumber morphologic (e.g., reduced kinetics of fission/fusion) and electron transport chain function defects have been reported, but are a controversial primary or secondary defect (Montgomery & Turner, 2015). This metabolic incompetence in the oxidation of fat primes the system for the production of DAG and ceramides, further enhancing insulin resistance.

Endoplasmic Reticulum Stress

The ER is the site of cellular protein folding and lipid synthesis. Increased nutrients, inflammatory signals, and increased metabolic requirement may disturb ER homeostasis in a manner that causes the accumulation of unfolded proteins—ER stress. The cell responds by activating the Unfolded Protein Response (UPR). One of the arms of the UPR, mediated by kinase IRE1α, activates JNK, thereby linking ER stress with direct serine phosphorylation of IRS-1 and insulin resistance (Ozcan et al., 2004). This creates a feed-forward loop wherein metabolic overload is stressful to the ER, which in turn further debilitates the cell's ability to handle that load. Table 1 and Figure 2 show the principal molecular inhibitors of insulin signaling.

Table 1: Principal Molecular Inhibitors of Insulin Signaling

Inhibitor/Pathway	Mechanism of Action	Consequence for Insulin Signaling
Serine Kinases (JNK, IKK)	Phosphorylate IRS-1/2 on specific serine residues (e.g., Ser307).	Inhibits IR-IRS interaction; promotes IRS-1 degradation.
PKCθ (Muscle)	Activated by DAG; phosphorylates IR/IRS-1 on serine residues.	Blunts insulin receptor tyrosine kinase activity; impairs IRS-1 function.
PKCε (Liver)	Activated by hepatic DAG; phosphorylates the insulin receptor.	Impairs insulin receptor tyrosine kinase activity, contributing to hepatic insulin resistance.
Ceramides	Activate PP2A, leading to Akt dephosphorylation; block Akt membrane translocation.	Directly inhibits the key effector Akt, halting GLUT4 translocation and glycogen synthesis.
SOCS-3	Ubiquitin ligase adapter induced by cytokines; targets IRS-1/2 for proteasomal degradation.	Reduces the cellular pool of IRS proteins available for signaling.
PTP1B	Protein tyrosine phosphatase that dephosphorylates the insulin receptor and IRS proteins.	Terminates the insulin signal prematurely.

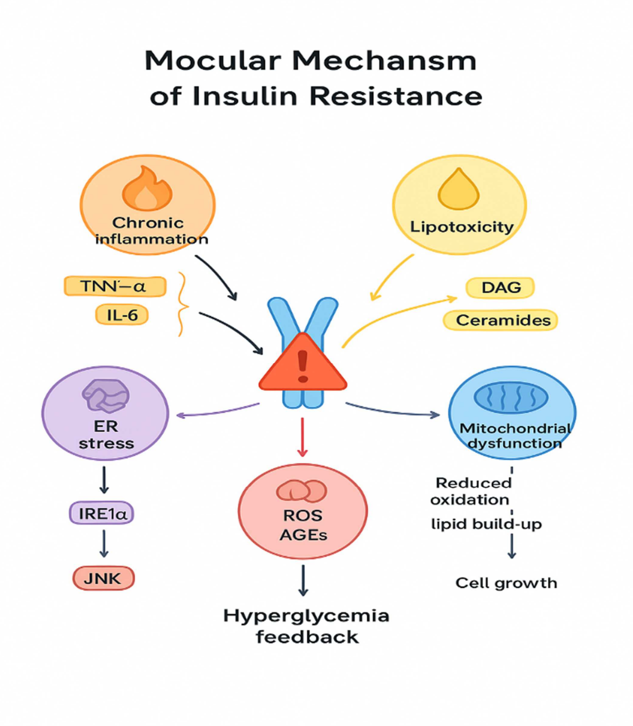

Figure 2: Molecular Mechanisms of Insulin Resistance

Tissue-Specific Expressions of Insulin Resistance

While the molecular mechanisms are usually shared, the phenotypic manifestation of insulin resistance varies enormously between the major insulin-responsive tissues.

Skeletal Muscle

Skeletal muscle is the primary location for postprandial glucose disposal. Insulin resistance within this tissue is characterized by a severe inhibition of insulin-stimulated glucose uptake. The primary molecular lesion is dysfunction of the PI3K-Akt pathway, often accompanied by increased intramyocellular DAG levels and PKCθ activation, and inflammatory signaling from resident macrophages (Schenk et al., 2008).

Liver

Hepatic insulin resistance occurs with a twofold presentation: an insulin failure to suppress gluconeogenesis, but with preservation of the capacity of insulin to stimulate de novo lipogenesis (DNL). This "selective" insulin resistance is paradoxically hyperinsulinemia-driven. The pathway to SREBP-1c, the master lipogenic transcription factor, remains sensitive to insulin, but the Akt-FOXO1 pathway responsible for regulation of gluconeogenesis is dampened (Brown & Goldstein, 2008). This produces simultaneous overproduction of glucose and lipids and results in both hyperglycemia and hypertriglyceridemia.

Adipose Tissue

White adipose tissue insulin resistance not only disrupts glucose uptake but, more importantly, abolishes the anti-lipolytic effect of insulin. This results in increased basal liberation of FFAs into the bloodstream, which further promotes lipotoxicity in muscle and liver (Roden, 2004). Furthermore, hypertrophic, dysfunctional adipocytes release abnormally high amounts of pro-inflammatory cytokines (e.g., TNF-α, IL-6, MCP-1) and suppress production of the insulin-sensitizing adipokine, adiponectin (Ouchi et al., 2011).

The Impact of Hyperglycemia: A Cycle of Molecular Damage

Hyperglycemia caused by insulin resistance is not merely a biomarker but an active causative agent for ongoing molecular damage through two principal chemical mechanisms.

Advanced Glycation End-Products (AGEs)

The chronic hyperglycemia that characterizes T2DM promotes the formation of Advanced Glycation End-products (AGEs), a polyheterogeneous group of products formed by the non-enzymatic reaction between reducing sugars (e.g., glucose) and amino groups of proteins, lipids, and nucleic acids. This is through the initial creation of reversible Schiff bases at a fast rate, followed by an Amadori rearrangement to create stronger, though still reversible, Amadori products. These early products subsequently undergo further complicated chemical reactions—dehydration, condensation, and cross-linking—over weeks and months to create irreversible and stable AGEs (Singh et al., 2014). The speed of this entire process is proportional to the magnitude and duration of hyperglycemia, and hence, AGE accumulation is a direct chemical consequence of inadequate glycemic control.

The pathophysiological action of AGEs is mediated by two primary mechanisms. First, by inducing covalent cross-links on long-lived structural proteins such as collagen and elastin, AGEs radically alter their physical and functional properties, leading to increased vascular stiffness, reduced vascular compliance, and basement membrane thickening, which inhibits nutrient diffusion (Brownlee, 2001). Second, AGEs induce their effects through a specific cell-surface receptor known as the Receptor for AGE (RAGE). The binding of AGEs to RAGE on cells such as endothelial cells and macrophages activates robust pro-inflammatory signaling pathways, with the NF-κB pathway leading most significantly. This leads to an upregulation of cytokines, adhesion molecules, and other inflammatory mediators (Bierhaus et al., 2005). Subsequent RAGE-mediated inflammation also creates a vicious cycle, in that it worsens the original insulin resistance responsible for the hyperglycemia, thus perpetuating and amplifying the metabolic disorder.

Oxidative Stress

Hyperglycemia leads to oxidative stress by several mechanisms, including increased mitochondrial production of superoxide anions, auto-oxidation of glucose, and activation of the polyol pathway (Brownlee, 2001). Reactive oxygen species (ROS) can directly oxidize and damage cellular structures. ROS also activate stress-sensitive signaling pathways like JNK and NF-κB, which, as discussed above, activate serine phosphorylation of IRS proteins and inflammatory gene expression (Houstis et al., 2006). This results in a self-sustaining cycle where insulin resistance gives rise to hyperglycemia, which further generates oxidative stress and inflammation that worsen insulin resistance. Table 2 illustrates the key mediators of hyperglycemia-induced damage and their sequelae.

Table 2: Key Mediators of Hyperglycemia-Induced Damage and Their Sequelae

Mediator/Pathway	Mechanism of Formation/Activation	Pathophysiological Consequences
Advanced Glycation End-Products (AGEs)	Non-enzymatic glycation and cross-linking of proteins/lipids/nucleic acids by chronic hyperglycemia.	Alters protein function; increases tissue stiffness; activates pro-inflammatory RAGE signaling.
Reactive Oxygen Species (ROS)	Overproduction via mitochondrial overload, glucose auto-oxidation, and polyol pathway flux.	Oxidizes cellular components; activates stress kinases (JNK, IKK, PKC); promotes apoptosis.
Protein Kinase C (PKC) Isoforms	Activated by *de novo* synthesis of DAG from hyperglycemia-induced glycolytic intermediates.	Increases vascular permeability, cytokine expression, and pro-coagulant activity; impairs signaling.
Hexosamine Biosynthesis Pathway	Diverts fructose-6-phosphate from glycolysis to produce UDP-GlcNAc, leading to O-GlcNAcylation of proteins.	Alters transcription factor function and insulin signaling components.
Polyol Pathway	Shunts glucose to sorbitol using aldose reductase, consuming NADPH.	Depletes NADPH (an antioxidant cofactor); increases osmotic stress.

Emerging Players: Gut Microbiota and Epigenetics

Aside from the conventional pathways, recent studies have highlighted the role of the gut microbiome and epigenetic modifications. The gut microbiota, through its metabolites, can influence host metabolism. Short-chain fatty acids like butyrate typically increase insulin sensitivity and intestinal barrier function (Canfora et al., 2015). A saturated fat diet, by contrast, can alter the microbiota, leading to increased circulating lipopolysaccharide (LPS) from Gram-negative bacteria—a state known as "metabolic endotoxemia"—causing systemic inflammation and insulin resistance (Cani et al., 2007).

Epigenetic modifications, such as DNA methylation and histone acetylation, provide a pathway by which environmental factors such as diet and obesity induce long-lasting modifications in gene expression that render a person susceptible to insulin resistance. Hyperglycemia, for example, can alter the methylation pattern of genes involved in β-cell function and insulin signaling (Nilsson et al., 2014).

Conclusion and Therapeutic Perspectives

The molecular pathogenesis of insulin resistance is a complex intertwinement of inflammatory signaling, lipotoxicity, organelle stress, and genetic susceptibility. The initial defect, often triggered by excess nutrients, is inhibitory serine phosphorylation of IRS proteins, defiling the unmarred tyrosine kinase signal of the insulin receptor. This leads to an avalanche of metabolic derangements in key tissues. The following hyperglycemia then produces its own injury by chemical formation of AGEs and ROS, setting up a vicious cycle of disease acceleration.

Understanding of these molecular intricacies is important for therapy development. The present attempts, such as metformin (which increases hepatic insulin sensitivity and suppresses gluconeogenesis) and thiazolidinediones (which activate PPARγ to increase adipose tissue function and suppress lipotoxicity), trace their beginnings in therapeutic targeting of these pathways. More contemporary drug classes like the SGLT2 inhibitors, while their main effect is in the kidney, also affect fuel metabolism and may reduce ectopic lipid accumulation. Therapies of the future might include selective inhibitors of the serine kinases (JNK, IKK), ceramide synthetic enzymes, or RAGE signaling. Additionally, dietary and lifestyle interventions reducing inflammatory and lipotoxic burdens remain the cornerstone of treatment and prevention.

For the biomedical and chemical research community, the opportunity and challenge lie in further delineating the chemical structures of the toxic lipid intermediates, the structural biology of inhibitory protein complexes, and the design of highly selective molecular modulators. By persisting in dissecting the chemistry of insulin resistance, we are bringing about a future where not only can T2DM be treated, but it can be prevented and eventually reversed.

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