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Review Article

Traditional Insulin Resistance Pathways Revisited with Some Novel Determinants

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ABSTRACT

Insulin resistance (IR) is a result of the compromise in the insulin-dependent and insulin-independent pathways in the key metabolic tissues like adipose tissue, liver, and skeletal muscle. The insulin dependent pathway (IDM) includes IRS/PI3K/AKT, RAS/MAPK, AMPK, mTOR pathways, and any disturbance in these interferes with glucose uptake, glycogen storage, and lipid metabolism. The insulin independent pathways (IIDM) relate to pro-inflammatory and stress related pathways i.e. NFκB, JNK, SOCS, TLR, and WNT. These typically lead to excessive amounts of cytokines, oxidative stress and lipotoxicity. The glucose homeostasis is dependent on the coordinated insulin action across different organs. Both the insulin dependent and independent pathways disrupt the insulin receptor function and its further phosphorylation, precipitating metabolic complications leading to severe outcomes due to lost glucose control. Also, the new research postulates the significance of gut microbiota imbalance, circadian rhythm disturbances, and post-translational modifications (PTMs) in glucose homeostasis. This review focusses on the traditional mechanisms and highlights the novel insights into IDM and IIDM pathways, including AI/ML, emphasizing their significance in the molecular interactions that drive IR development.

INTRODUCTION

Insulin is a peptide hormone released from pancreatic β -cell. In adipose tissue, insulin stimulates glucose uptake via GLUT4 translocation, enhances lipogenesis and reduces lipolysis by inhibiting hormone sensitive lipase [1,2]. In skeletal muscle, it promotes 80% postprandial glucose uptake through GLUT4 and increases glycogen synthesis [3]. In liver, insulin supresses gluconeogenesis, promotes glycogen storage and regulates lipid metabolism, reducing circulating glucose level [2]. Disruption of insulin signalling is fundamental to developing (IR), occurring through insulin dependent mechanisms (IDM) and insulin independent mechanisms (IIDM)[4]. IDM includes IRS/PI3/AKT,

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RAS/MAPK/ and AMPK pathway, and IIDM includes NFκB, JNK, Suppressor of cytokines signaling (SOCS), TLR, and WNT signalling pathways. In IR, metabolic tissue fails to respond to insulin, elevating blood glucose and free fatty acids (FFA) [5].

Insulin dysfunction is characterized by the impaired phosphorylation of IR substrates (IRS-1/IRS-2) and the disruption of the IRS/PI3K/AKT signaling pathway, resulting in impaired glucose uptake and irregular glycogenesis [6,7] At the same time, disturbances in the RAS/MAPK pathway hinder cellular growth signaling, while decreased AMPK activation reduces metabolic flexibility. The deregulation of mTOR affects nutrient-sensing processes, and defects in the AKT substrate 160 kDa/TBC1 domain family member 4 (AS160/TBC1D4)-mediated GLUT4 translocation limit cellular glucose entry[8] . IIDM exacerbates IR through metabolic stress, where pro-inflammatory cytokines like TNF-α and IL-6 activate NF-κB and JNK pathways that impair insulin signaling. Endoplasmic reticulum (ER) stress and the resulting unfolded protein response interfere with normal protein folding, while oxidative stress damages essential insulin signaling components [9,10]. Additionally, lipotoxicity and ceramide accumulation inhibit AKT activation, and hypoxic conditions modify metabolic gene expression. Epigenetic changes, including, histone modifications, and DNA methylation, further influence insulin signaling genes, perpetuating IR

Glucose homeostasis is regulated by extensive coordination between several organs, including the pancreas, liver, muscles, and adipose tissues. IR is the result of an impaired insulin signalling network, which can cause metabolic disruptions leading to metabolic syndrome and associated cardiovascular risks. Hyperglycaemia combined with IR put an individual at a greater risk of developing neurodegenerative diseases over time [11,12]. The present work will provide an overview of IDM and IIDM in context with IR, with a particular focus on identifying the effect of IR on different tissues. The discussion will detail the current studies evaluating IR, including the influence of the gut flora and circadian rhythms upon IR and the role of post-translational modifications (PTMs) of insulin functions.

The objective of the literature review of the present study was to uncover significant studies involving both IDM and IIDM, with their significant effects on metabolic tissues. A thorough search was done in the Google Scholar, PubMed, Scopus, and Science Direct databases. The search terms included insulin, IR, insulin-dependent and independent signaling pathways, metabolic complications due to IR in adipose tissues, skeletal muscles, and liver. We excluded papers that were not in English or that had not undergone peer review.

2. OVERVIEW OF INSULIN SIGNALING

Insulin exerts its biological effects through the insulin receptor (IR), which is part of a broad group of receptor tyrosine kinases. After release, insulin travels through the bloodstream and bind to IR located on the target cells. IR is a disulfide linked two extracellular α-subunits and two transmembrane β-subunits ($\alpha_2\beta_2$) tetramer and undergoes a conformational change and autophosphorylates at three specific tyrosine residues (1150, 1148, 1151) within the activation loop on its β-subunits (Yunn et al., 2023). The phosphorylation relives inhibition of the kinase at the β subunit and enhances its activity. Subsequently, additional tyrosine in the juxta membrane (953, 960) and C-terminal regions (1316, 1322) are phosphorylated, creating docking sites for adaptor protein such as IRS and Src

homology and collagen homolog (SHC), initiating downstream signalling cascades [13].

3. INSULIN-DEPENDENT PATHWAYS

3.1 IRS–PI3K–AKT Pathway

IRS-PI3K-AKT pathway is a key signaling cascade mediating metabolic effects of insulin in target tissues like skeletal muscle, liver and adipose tissue. Binding of insulin phosphorylates and activates IRS proteins, which serve as docking sites for the p85 regulatory subunit of PI3K activating its p110 catalytic subunit. PI3K catalyses conversion of phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3) at the plasma membrane. PIP3 recruits phosphoinositide-dependent kinase-1 (PDK1) and AKT to the membrane, where PDK1 phosphorylates AKT at threonine 308 and mTORC2 complex phosphorylates it at serine 473, activating it (18). Activated AKT coordinates downstream effects to regulate metabolic function. In skeletal muscle and adipose tissue, it phosphorylates AS160 (TBC1D4) reducing inhibition of Ras related in brain GTPases (Rab GTPases), which promotes GLUT4 vesicles movement for glucose uptake, AKT deactivated Forkhead box protein-O1 (Foxo1), downregulating gluconeogenic genes and decreasing glucose production. AKT promotes glycogen synthesis by inhibiting GSK-3 and stimulates protein synthesis through mTOR signalling pathway activation [2].

3.2 RAS–MAPK Pathway

RAS-MAPK pathway orchestrates cell growth, proliferation and differentiation. Insulin binding at its receptor phosphorylates SHC protein, forming a docking site for GRB2-SOS (Growth Factor Receptor-Bound Protein 2-Son of Sevenless) complex. GRB2 binds with SOS, a guanine nucleotide exchange factor, facilitating Guanosine Diphosphate (GDP) replacement with GTP on RAS, activating it. RAS requires farnesylation by farnesyltransferase (FTase) to anchor to the plasma membrane. Activated RAS triggers a kinase cascade by activating Rapidly Accelerated Fibrosarcoma (RAF), which activates MEK, leading to Extracellular Signal-Regulated Kinase (ERK1/2 or p44/p42 MAPK) activation. ERK1/2 influences cellular function by phosphorylating cytosolic, cytoskeletal and nuclear targets. Through this, the pathway controls gene transcription, chromatin remodelling and apoptosis. ERK1/2 signaling is essential for adipose tissue, muscle and pancreatic β cells development. This pathway mediates insulin's anabolic effect by promoting cell proliferation, migration and inhibiting apoptosis. Even though, not involved primarily in IR, the defects in the RAS/MAPK pathway affects insulin signaling inducing hyperglycaemia and metabolic complications [14].

3.3 AMPK Pathway

AMPK pathway is an important link between insulin signalling and cellular energy regulation. Besides, increased AMP/ATP ratio AMPK is also phosphorylated by insulin through indirect mechanisms, modulating glucose and lipid metabolism. Through the upstream AMPK regulators such as Liver Kinase B1 (LKB1) and calcium/calmodulin Dependent Protein Kinase β (CaMKKβ), IRS–PI3K–AKT pathway facilitates GLUT4 translocation, glycogen synthesis and inhibits gluconeogenesis. AMPK regulates the translocation of GLUT4 in the skeletal muscles, complementing insulin-mediated glucose uptake. It inhibits acetyl-CoA carboxylase (ACC) and facilitates the fatty acid oxidation by increasing the rate of fatty acid movement in the mitochondria. AMPK downregulates sterol regulatory element

binding protein 1c (SREBP-1c), and inhibits gluconeogenesis and lipogenesis, in addition to the insulin's role in glucose regulation. Insulin and AMPK interaction ensures metabolic adaptability and energy equilibrium facilitating nutrient storage and use. But in states of IR, both insulin signalling and AMPK activation are compromised, disturbing the homeostasis in terms of glucose uptake, glucose production and lipid storage, triggering metabolic syndrome [15,16].

3.4 mTOR Pathway

mTOR pathway is a nutrient responsive serine-threonine kinase with two distinct complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC consists of shared proteins mTOR, mLST8/GβL and Deptor, with unique partners. It controls cell growth, survival and cytoskeleton organization. mTORC1 detects metabolic energy and regulates cellular metabolism and growth. While physiological activation of mTORC1 maintains β-cell homeostasis, excessive activation impairs β-cell function. mTORC1 associates with Raptor, Proline rich AKT substrate (PRAS40), Deptor and MlST8/GβL, while mTORC2 contains Rictor, mammalian Stress Activated Protein Kinase Interacting Protein 1 (mSIN1) and Protein Observed with Rictor (Protor). Both complexes are activated by insulin, IGF-1, amino acid, glucose and cellular energy status, shown by high ATP:AMP ratio [17]

In insulin signalling, phosphorylated AKT inhibits Tuberous Sclerosis Complex (TSC1/2), a suppressor of Rheb. This allows active GTP-bound Rheb to accumulate on lysosomal surface, enhancing mTORC1 activity. Amino acids enable this through Ras related GTP binding protein (Rag GTPases), recruiting mTORC1 to lysosomal membrane for Rheb interaction, promoting protein synthesis, lipid synthesis, mRNA translation and reduced autophagy. AMPK phosphorylates TSC2 and Raptor to limit mTORC1 activity during low energy, maintaining metabolic balance. Chronic mTORC1 activation in nutrient-rich states leads to insulin signalling inhibition via S6 kinase mediated IRS phosphorylation, causing IR. mTORC2, activated by insulin and growth factors, induces AKT phosphorylation at Ser473, enhancing glucose metabolism and cell survival. It regulates Protein Kinases C alpha (PKCα) and Serum and Glucocorticoid Regulated kinase 1 (SGK1), influencing cytoskeletal dynamics and ion transport for cellular homeostasis, crucial for normal insulin [18]). The signalling pathways are represented in Fig. 1.

4. INSULIN-INDEPENDENT PATHWAYS

4.1. NFκB Pathway

The evolutionarily conserved NFκB transcription factor plays a crucial role in the regulation of innate immune responses by modulating the transcription of cytokines. Under basal conditions, dimers remain inactive in association with the inhibitory protein IκB. The pro-inflammatory stimuli, including TNF-α, lipopolysaccharides (LPS), elevated dietary fatty acids, activates the IκB kinase (IKK) complex phosphorylating IκB. This induces the proteasomal degradation of IκB, liberating NFκB to initiate the transcription of pro-inflammatory mediators. Increasing evidence also identifies NFκB as a central regulator in the development of obesity related inflammation and IR. Fatty acids activate Toll -like receptor 4 (TLR4) signaling in adipocytes driving the NFκB dependent expression of inflammatory cytokines in adipose tissue, liver and macrophages, precipitating a state of chronic, low-grade inflammation with metabolic dysfunction. Thus, NFκB acts as a mechanistic link between obesity, adipokine imbalance, chronic inflammation, and

systemic IR, placing NFκB at the intersection of immunity, metabolism and inflammation [19].

4.2 JNK Pathway

c-Jun N-terminal kinase (JNK), a well characterized member of the Mitogen activated protein kinase (MAPK) family, has been extensively investigated for its involvement in obesity-associated IR. JNK primarily regulates the transcriptional activity of activator protein-1 (AP-1) by phosphorylating c-Jun. In obese or IR individuals, inflammation and elevated FFAs promote JNK activation, enhance TNF-α secretion, and impair adipocyte function, thereby reducing cellular insulin sensitivity. FFAs exposure to 3T3 L1-adipocytes insulin signaling is interfered by inhibiting IRS-1 and Akt phosphorylation and GLUT4 translocation.

Peroxisome proliferator-activated receptor (PPARs) are ligand-activated nuclear transcription factors with three isoforms-α, β/δ and γ. Among them, PPARγ is particularly implicated in insulin signaling, and its regulation is closely linked with JNK activity. TNF-α inhibits PPARγ transcriptional activity through activation of both, JNK and ERK pathways in adipose tissues in obesity. Downstream of tyrosine kinase-1 (Dok1), is as an adaptor protein, and it is significantly upregulated in response to a high-fat diets. Dok1 influences obesity by modulating PPARγ phosphorylation, while ERK and JNK suppress PPARγ activity through direct phosphorylation at Ser112. In line with this, demonstrated in a liver-specific PPARγ knockout mouse model that absence of this receptor predisposes animals to fat intolerance and IR, underscoring its pivotal role in maintaining insulin sensitivity [20].

4.3 Cytokines and Adipokines

Cytokines and adipokines are critical mediators that connect adipose tissue dysfunction with systemic metabolic disturbance. Among these, TNF-α and IL-6 are particularly important in obesity-associated IR. In the obese state, enlarged adipocytes and infiltering immune cells releases increased TNF-α, which promotes serine phosphorylation on IRS proteins, impairing PI3K-AKT phosphorylation and glucose uptake in muscle and adipose tissues. TNF-α also enhance lipolysis, elevating circulating FFAs intensifying IR. The cytokine IL-6 has mixed response, while short term release during physical activity improves glucose utilization, while chronic high IL-6 levels exert detrimental effects. In liver, persistent IL-6 signalling effects elevates gluconeogenesis and C-reactive protein (CRP) levels along with activation of SOCS proteins, which further hampers the IRS signalling. Thus, IL-6 signalling in adipose tissues leads to persistent inflammatory state, induing metabolic complications (Gunes et al., 2023). TNF-α and IL-6 communications change the activity of adipose tissues from an energy storage organ to an inflammatory endocrine organ triggering IR and systemic inflammation. This sustained elevation is strongly linked with the type 2 diabetes, cardiovascular and fatty liver complications. Thus, therapeutic interventions should also target to reduce TNF-α, and IL-6 activity to reduce insulin sensitivity and metabolic complications due to obesity [21] .

4.4 SOCS Pathway

SOCS pathway negatively regulates the cytokines and growth factor signaling. Particularly SOCS1 and SOCS3 proteins are induced rapidly in response to cytokine stimulation through JAK/STAT pathway, which binds to JAKs and prevents STAT activation acting as intracellular brakes. This regulates the immune homeostasis

and prevents prolonged inflammatory signaling [22]. SOCS3 also interacts with IRS-1, inducing its ubiquitination and degradation, which further disrupts its downstream insulin signaling. The increased SOCS levels are observed in obesity, where its chronic exposure produces pro-inflammatory mediators TNF-α and IL-6 drives impairing IR function, gluconeogenesis, and glucose uptake in skeletal muscle and adipose tissue

Besides this, SOCS protein regulates immune tolerance by limiting overactivation of immune cells, thus indicating that their dysregulation induces chronic low-grade inflammation. Emerging studies underline excessive SOCS activation with obesity associated inflammation. Consequently, SOCS targeting intervention should be considered to restore insulin sensitivity and improve metabolic health, while preserving the protective role of SOCS in cytokine regulation [20].

4.5 TLR Pathway

TLR signaling pathway recognizes both microbial molecules and metabolic signals and hence acts as a frontline defence mechanism. Bacterial LPS, saturated fatty acid and stress (ER stress, cellular injury, or oxidative stress) associated molecular patterns acts as ligands for the activation of macrophages, adipocytes and hepatocytes [23]. After stimulation, it recruits the adaptor proteins, myeloid differentiation primary response 88 (MyD88) or TIR-domain-containing adaptor-inducing interferon-β (TRIF), which triggers Interleukin-1 Receptor-Associated Kinase (IRAK) and Tumor Necrosis Factor Receptor-Associated Factor (TRAF) kinases. This downstream pathway activates NF-κB and Interferon Regulatory Factors (IRFs) transcription factor, expressing the pro-inflammatory cytokines TNF-α, IL-6 and IL-1β. Even though, this mechanism stands firm in protecting the host from infection, but it also has profound metabolic complications (Chandrasekaran and Weiskirchen, 2024). In obesity, infiltrated FFA acts as TLR4 endogenous ligands, maintaining a state of chronic low-grade inflammation within the liver and adipose tissues (Fig. 2). This pro-inflammatory Miro-environment impedes insulin signaling by amplifying cytokines release and interfering with IRS cascade thereby promoting systemic IR. Prolonged TLR activation has been associated with many complications such as fatty liver disease, atherosclerosis and cardiovascular dysfunction. Thus, although TLR signaling is indispensable for immunity related diseases, but since it impairs insulin sensitivity also, it is identified as a potential therapeutic intervention in IR [24].

4.6 Wnt Signaling Pathway

Wnt signaling pathway is a highly conserved molecular cascade playing a central role in embryonic development, tissue homeostasis and cellular communication. It operates through a group of secreted glycoproteins called Wnt ligands that bind to Frizzled receptor and low-density lipoprotein receptor related protein (LPR5/6) on the cell membrane. This binding signal is transmitted by the Dishevelled and prevents the degradation of β-catenin a key transcriptional regulator. In the absence of Wnt signal, β catenin is continuously degraded by a destruction complex composed of Axin, adenomatous polyposis coli, casein kinase 1(CK1) and glycogen synthase kinase 3β. Once Wnt ligands activates the receptor complex, this degradation is inhibited, leading to accumulation and nuclear translocation of dephosphorylated β–catenin, where it interacts with T-cell factor/lymphoid enhancer factor (TCF/LEF) transcription factor to regulates gene expression[25] .Wnt pathway is broadly classified into the canonical (β-catenin dependent) and non –

canonical (β-catenin independent) types. While the canonical pathway mainly controls cell proliferation and differentiation, the non-canonical pathway regulates planer cell polarity, cytoskeletal rearrangement and calcium signaling. The precise regulation of Wnt signaling is essential, as a both under and over activation are linked to obesity and IR by influencing adipogenesis [26]. Wnt ligands, such as Wnt3a, Wnt10b activate the canonical Wnt signaling pathway and inhibits adipogenesis, while the non-canonical Wnt ligands such as Wnt5a (upregulated under obese conditions) and Wnt5b promote adipogenesis and are linked to obesity-associated inflammation, IR, β-cell dysfunction and metabolic complications in adipose tissues. Furthermore, abnormal Wnt signaling is strongly implicated in tumour initiation and progression. Thus, the Wnt pathway function as a master regulator of cell fate and its disruption has wide ranging implication in development disorder, metabolic dysfunction and oncogenesis [27].

5. TISSUE-SPECIFIC IR

5.1 Hepatic IR

Hepatic IR is a hallmark abnormality in metabolic syndrome and plays a major role in the onset and progression of type 2 diabetes and its associated disorder. Under physiological condition, insulin regulates liver metabolism by suppressing glucose production by inhibiting gluconeogenesis and glycogen breakdown while at the same time encouraging glycogen storage and maintaining lipid balance in states of IR. However, this fine regulation is disrupted, despite elevated insulin levels, liver continues to release glucose due to sustained activation of gluconeogenic enzyme such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase. This uncontrolled hepatic glucose metabolism along with IR, impairs lipid handling in the liver, resulting in dysregulated lipid synthesis and breakdown leading to dyslipidaemia [27,28].

Lipolysis is inhibited by insulin, and hence in IR states, de novo lipogenesis is increased in hepatic cells while the fatty acid oxidation is decreased. This builds up triglyceride leading to atherogenic lipoprotein release. Raised glucose levels and defective lipid metabolism causes hyperglycaemia and hypertriglyceridemia, causing NAFLD. This is followed by a compensatory mechanism where hepatic lipid overload induces lipotoxicity and inflammation inducing IR. Thus, being a central factor, amelioration of hepatic IR is crucial in the treatment of metabolic diseases [29].

5.2 Skeletal Muscle IR

Skeletal muscle remains the primary organ for postprandial glucose uptake, and it remains highly significant in the regulation of insulin sensitivity and systemic glucose homeostasis. Binding of insulin initiates the IRS-1-PI3K-AKT cascade, which leads to the migration of GLUT4 from intracellular vesicles to the plasma membrane for glucose entry. This insulin signaling cascade is compromised in insulin resistance causing defective GLUT4 translocation and impaired glucose disposal, eventually elevating the blood glucose levels. Besides this, mitochondria play a crucial role in the β-oxidation of fatty acids and ATP generation. Thus, defects in mitochondria also contributes significantly to skeletal muscle IR [30].

Mitochondrial biogenesis is compromised in insulin-resistant muscle tissues, building up partially oxidized lipid intermediates, diacylglycerols and ceramides. These metabolic byproducts hinder the insulin signaling via IRS-1 and worsens the metabolic balance through activating JNK and PKC stress kinases. The blunted mitochondrial activity reduces ATP

production impeding the GLUT4 translocation. The restricted GLUT4 activity decreases the utilization of glucose, contributing to systemic IR (Mthembu et al., 2022; Sergi et al., 2019). In addition to the above, hyperglycemia and dyslipidemia, adds up to the worsened condition potentially leading to type 2 diabetes. Thus, improving insulin sensitivity in skeletal muscles ameliorates metabolic disorders [31].

5.3 Adipose Tissue IR

In obesity, the fat accumulating adipose tissue shifts from a protective organ to a contributor of metabolic disorders. In usual conditions, adipocytes store energy and releases the FFAs in a regulated manner in conditions of energy requirement along with the beneficial adipokines such as adiponectin, leptin. Insulin inhibits lipolysis and prevents the excessive spillage of FFAs into the circulation. But in obesity and IR, this balance is disturbed with a loss of control over lipolysis, leading to flooding of FFAs in circulation [32] Overwhelmed FFAs does not remain confined to adipose tissue but moves into the liver, skeletal muscle and pancreas. This causes lipotoxicity and inflammation in the respective organs causing damage to sub-cellular organelles [33]. Particularly in adipose tissues, there is imbalance in the release of adipokines, where the anti-inflammatory mediators decreases and pro-inflammatory mediators increases. Due to a persistent inflammatory state, immune cells like macrophages intensify the inflammation by migrating to the location. FFAs, pro-inflammatory states further deteriorate the metabolic health causing metabolic and cardiovascular complications [34].

5.4 Cardiac IR

Resistance to insulin in the heart represents a major factor that produces cardiac complications, particularly in type 2 diabetes and obesity. Physiologically, insulin provides the energy for the heart, via glucose uptake by IRS-PI3-AKT pathway that leads to GLUT4 translocation to the heart. This helps in the regulation of the energy production between glucose and fatty acids maintaining metabolic homeostasis. In IR, this whole mechanism is compromised, and heart gets more dependent on FFAs for energy source. FFAs provide possible sources of energy, but the situation worsens because of reactive oxygen species (ROS) production. This aggravates lipotoxicity and mitochondrial dysfunction. NO production is also diminished leading to reduced insulin signaling precipitating further complications [35].Stress signalling pathways like PKC, JNK and NF-κB are activated in states of IR, intensifying oxidative stress and inflammation. These pathways lead to the remodelling of the heart, hypertrophy, and fibrosis. Furthermore, due to the reduced AKT activity, insulin action against apoptosis is compromised, causing cardiomyocytes damage. This challenges the heart's ability in states of cardiac ischemia. Thus, in terms of cardiac function, insulin signaling plays a significant role, and addressing cardiac IR becomes essential for safeguarding heart function [36,37].

5.5 Brain IR

IR is responsible for neurological and cognitive disorders, including Alzheimer's and Parkinson's disease, in brain due to metabolic dysfunction due to defective insulin signaling. Insulin regulates neuronal glucose uptake, synaptic plasticity, neuronal survival, which significantly influences memory, and mood, through PI3K–AKT and MAPK pathways. Due to defective insulin signaling, this balance is disrupted, causing reduced neuronal glucose utilization, weakened synaptic activity, and compromised energy

metabolism. Due to this, the neuronal energy is shifted to the alternative substrates, increasing oxidative stress and mitochondrial dysfunction. IR activates JNK and NFκB inflammatory pathways, causing astrocytes to release pro-inflammatory cytokines causing neuroinflammation, which disrupts the tau phosphorylation, causing neurodegeneration and cognitive decline. These effects alter dopamine and serotonin signaling, linking to depression, addictive behaviours, and disordered eating. In the hypothalamus, impaired insulin signaling disturbs appetite regulation and energy expenditure, contributing to systemic IR. Reduced AKT activity diminishes neuroprotection, increasing vulnerability to neuronal apoptosis and synaptic loss [12,38].

6. MOLECULAR MECHANISMS LINKING IR TO DISEASE PROGRESSION

In IR, target tissue responsiveness to insulin is reduced which impairs the ability to inhibit glucose production and stimulate peripheral glucose elimination and often accompanied with hyperinsulinemia to maintain blood sugar levels. This reduced response to insulin is associated with the numerous metabolic disorders including obesity, diabetes, dyslipidaemia, hypertension, metabolic dysfunction-associated fatty liver disease (MAFLD), and endothelial dysfunction which directs towards the atherosclerosis and cardiovascular diseases. It also causes polycystic ovary syndrome (PCOS).

As discussed above, the serine phosphorylation of the IRS proteins located on pancreatic β-cells reduces the insulin release and dysregulates the PI3K/AKT pathway, affecting its downstream functions. Increased hepatic gluconeogenesis occurs due to decreased AKT-mediated phosphorylation and inhibition of Foxo1, the transcription factor that promotes expression of gluconeogenic genes, such as PEPKC, G6PC). The increased FFAs, due to the increased lipolysis, spills to the metabolic tissues, leading to metabolic inflammation, through the serine phosphorylation of IRS proteins via the PKC and JNK signalling pathways. Both, the hepatic DNL and VLDL secretion is enhanced contributing to hyperlipidaemia. The FFAs, also activate the TLR4 that effects the downstream inflammatory targets, such as NF-κB and MAPK, increasing the pro-inflammatory cytokines, which impair PI3K/AKT signalling. The IR impairs the NO signalling in the blood vessels causing hypertension. Hyperinsulinemia, due to IR, activates the insulin receptors in the pituitary gland that promotes the release of androgen from the ovaries and adrenal glands through the pituitary-ovary and adrenal axis, increasing the testosterone levels from the ovarian cells or through LH. The elevated LH production leads to anovulation, and the clinical symptoms such as hirsutism and acne [7,39].Insulin regulates the vascular tone by modulating the production of Nitric oxide (NO), a potent vasodilator, and endothelin-1 (ET-1), a strong vasoconstrictor. Under normal conditions, a balance between NO-mediated vasorelaxation and ET-1-induced vasoconstriction maintains healthy blood pressure and endothelial function. However, in IR, this balance shifts towards vasoconstriction due to decreased NO production and increased ET-1 secretion, contributing to hypertension and endothelial dysfunction. For maintaining the vascular tone, endothelial nitric oxide synthase (eNOS) produces NO from L-arginine in the endothelial cells. But, in IR and oxidative stress, eNOS uncoupling, substrate depletion, and enhanced degradation reduce NO levels, impairing vasodilation. Moreover, inducible and neuronal isoforms of NOS influence inflammation, glucose metabolism, and appetite regulation, linking metabolic and vascular pathways. Renin-angiotensin-aldosterone system (RAAS) activation promotes vasoconstriction, smooth

muscle hypertrophy and Na^+ retention elevating blood pressure. In obesity, excess RAAS activity in visceral adipose tissue, exacerbates IR through ROS generation and impaired glucose uptake. It also diminishes eNOS activity reducing NO bioavailability, enhancing vascular oxidative stress and increasing blood pressure. Hyperglycemia aggravates the deleterious effects of the RAAS by increasing Ang II levels in tissue, producing advanced glycation end products that stimulate Ang II receptors, and decreasing ACE2 activity, thus creating an imbalance exacerbating vascular dysfunction.

Thus, the development of IR is multifactorial, with several key pathological mechanisms such as impaired insulin binding to its receptors, changes in the internal environment of the host, intracellular processes, dysfunctional autophagy, and altered gut flora [40].

Such changes induces activity in the RAS-MAPK pathway, increasing the risk for coronary artery disease and heart failure by causing vascular smooth muscle cell proliferation, stiffening of arteries, and hastening the atheromatous process; in addition, hyperinsulinaemia associated with IR activates the sympathetic nervous system, as well as the RAAS, further contributing to the development of hypertension and ultimately resulting in cardiac hypertrophy and increased vascular resistance.

It is important to note that some of these mechanisms will manifest differently in different tissues as insulin-sensitive tissues, but the early stages of developing IR will be most apparent in adipose tissue. Although IR may arise from these various mechanisms acting in separate tissues and in different sequences, these mechanisms all closely interact with one another and may lead to the development of systemic IR.

7.PHARMACOLOGICAL INTERVENTIONS FOR THE MANAGEMENT OF IR

7.1 Approved therapies and their molecular targets

The approved drugs along with their targets and mechanisms are represented in Table 1.

Table 1: Therapeutic agents for T2DM, their molecular targets and mechanism of action

Therapy	Molecular Target	Mechanism	Therapies	References
Metformin	AMP activated protein kinase	Lower hepatic gluconeogenesis (decreases hepatic glucose output), Improves peripheral insulin sensitivity via AMPK Pathway	First line T2DM, Prediabetes	[41]
Pioglitazone	Peroxisome proliferator activated receptor γ(PPARγ)	PPARγ agonist cause adipocytes changes (increases insulin sensitive adipocytes), Increases peripheral insulin sensitivity (decrease HOMA-IR)	T2DM (insulin resistant patient), NASH (Non-alcoholic Steatohepatitis)	[42]
GLP-1 receptor agonists	GLP-1 receptor (GLP-1R) on β-cells, brain, GI tract	Increases glucose dependent insulin secretion, decreases hepatic steatosis and Reduces appetite or weight which give indirect but clinically improvement in insulin sensitivity	T2DM and Obesity	[43]
SGLT2 Inhibitors	Sodium glucose cotransporter 2 in renal proximal tubule (SGLT2)	Promote glycosuria causes decreases glucose or insulin load and decreases glucotoxicity which have been	T2DM, heart failure, CKD (chronic kidney disease) in some	[44]

		shown to improve peripheral/vascular sensitivity	agent or indication	
Insulin	Insulin receptor on hepatocytes, muscle and adipose tissue	Suppresses hepatic gluconeogenesis and promote glycogen	Type 1 diabetes mellitus and Type 2 diabetes mellitus	[45]
Sulfonylureas	Sulfonylurea receptor 1(SUR1) subunit of ATP-sensitive on pancreatic β-cells	Clinical effect can increase circulating insulin and reduces glycaemia	Type 2 diabetes mellitus	[46]
Sitagliptin	Dipeptidyl peptidase-4(DPP-4) enzyme	By inhibiting DDP-4 enhances insulin secreation	Low hypoglycemic effect	[47]

7.2 Emerging Incretin therapeutic strategies and molecular targets

Table 2 lists the incretin-based therapies, their molecular targets, and mechanistic approaches undergoing clinical trials.

Table 2: Incretin-based therapies (Phase II to Phase III) for the management of IR and metabolic complications

Drug	Molecular Target	Late-stage status (III/Late II to III)	Mechanistic Approaches	References
Retatrutide	GLP-1R/ GIPR/ Glucagon receptor	Phase 2 completed and Phase 3 study ongoing for obesity and T2DM	Potent weight loss and glucagon activity increase energy expenditure	[48]
Tirzepatide	GIP receptor and GLP-1 receptor	Tirzepatide is approved as a dual agonist, and Phase 3 programs continue for obesity and T2DM	More weight loss and betterment in insulin secretion and insulin sensitivity	[44]
Efinopegdutide	GLP-1R and glucagon receptor	Give Positive Phase 2 result for NAFLD and Phase 3 are planned for NASH	GLP-1 effects and glucagon receptor activation reduces liver fat	[49]
Orforgilpron	GLP-1 Receptor	Phase 3 trial is completed	Improve insulin while offer oral dosing and Oral GLP-1 antagonist can give injectable GLP-1R benefits	[50]

8. NOVEL PATHWAYS AND EMERGING DIMENSIONS IN IR

8.1 Gut Microbiome Influences

Gut microbiota and IR relationship is an advancing field of research, revealing insights far beyond genetic and lifestyle factors. Trillions of microbes present in the gut significantly influence the homeostasis in the body. The good bacteria feeds on the dietary fibres and ferment to generate short-chain fatty acids (SCFAs), which are an important regulator of insulin sensitivity, gut barrier integrity, and inflammatory states [51,52]. Dysbiosis, defined as the reduction in good microbes and increase in bad microbes, has emerged as a major contributor in the development of IR, as it leads to the leaky gut, increasing the

intestinal permeability. This permeability causes the infiltration of bacterial toxins in the bloodstream, inducing metabolic endotoxemia i.e., chronic low-grade inflammatory state, after binding with the TLR4. This signalling pathway further inhibits the IRS phosphorylation in the liver, muscle, and adipose tissue, and inhibits the insulin signaling. Furthermore, they also cause the elevation in the circulating levels of pro-inflammatory mediators triggering the NF-κB, TNF-α, and IL-6 pathways, which are strongly associated with IR development by increasing the SOCS proteins [15,53]. The significant role of the gut-liver axis in metabolic health is established by the recent studies, where approximately 15% link is associated with obesity and IR due to the leaky gut barrier [54]. Thus, for reducing metabolic endotoxemia and improving insulin sensitivity, a balanced microbiota is desirable.

With this background, new therapeutic arenas are opened, suggesting interventions such as probiotics, prebiotics, and fecal microbiota transplantation that can restore the dysbiosis and consequently improve the metabolic disorders. Such microbiome-targeted therapies offer fresh opportunities to improve metabolic health and reduce the burden of chronic disease [55].

8.2 Effects of circadian rhythm on insulin signaling

Circadian rhythm is governed by the endogenous biological clock and synchronizes daily oscillations in physiology and metabolism with respect to environmental light-dark cycles. This regulation influences insulin secretion, signaling, and glucose metabolism across tissues, aligning energy storage and expenditure with feeding and activity patterns. Suprachiasmatic nucleus (SCN) is the central pacemaker located in the hypothalamus and synchronizes peripheral clocks in insulin-sensitive organs through neural, hormonal, and metabolic signals. At the molecular level, the core clock machinery comprises transcriptional-translational feedback loops (TTFF) formed by CLOCK and BMAL1, which heterodimerize to activate the transcription of Period (Per 1/2/3) and Cryptochrome (Cry1/2) genes. The PER and CRY proteins inhibit CLOCK:BMAL1 activity, generating self-sustained circadian oscillations [56]. These core clock components rhythmically regulate the peripheral clock-controlled genes (CCGs) influencing glucose transport, lipid metabolism, insulin signaling, and mitochondrial energetics (Fig. 3).

In β-cells of the pancreas, BMAL1 and CLOCK are two essential components of the biological clock driving glucose responsive insulin exocytosis. The loss of BMAL1 function results in reduced activity on the insulin gene transcription, disorganization of the exocytotic machinery, and a diminished capacity to respond to glucose stimuli [57,58]. However, Rev-erbα, also an element of the molecular clock, prevents glucolipotoxicity by inhibiting gene expression for lipogenesis; thus, protecting β-cells from glucolipotoxic stress. Rhythmic expression of ion channels and metabolic enzymes is beneficial to the release of glucose-dependent insulin peaking during the daily active period when glucose is available. Disruption or misalignment of circadian rhythms will damage and reduce β-cell populations, leading to apoptosis and increased hyperglycemia [59].Insulin sensitivity of cells is governed by circadian rhythms; it peaks during the active or daytime and is lowest during the inactive or resting phase of the cycle as determined by circadian rhythms in peripheral tissues that reside far away from the pancreas. For instance, the timed cycle of insulin-induced phosphorylation of IRS-1 and AKT directs GLUT4 translocation to the cell surface in skeletal muscle, while at the same time,

varying expression levels and oxidative capacity of lipolytic enzyme activity will cause the timed cycle of insulin sensitivity in adipose tissue. Therefore, circadian-regulated genes such as AS160/Tbc1d4 and Tbc1d1 provide further evidence of the temporal relationship between the circadian system and glucose uptake and energy metabolism through the modulation of intra-cellular transport systems [60].

The liver produces glucose through glycogen formation and fat metabolism, responding to external cues based on time of day. This process is regulated by several transcription factors, such as PGC-1α, Rev-erbα, and RORα, which control the daily rhythmicity of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) levels. Proper alignment of these enzymatic pathways with fasting and feeding is necessary for successful gluconeogenesis. Loss of the hepatic circadian transcription factor BMAL1 disrupts the daily rhythmic glucose production and leads to impaired glycogen storage, resulting in hyperglycemia. Additionally, AMPK and SIRT1 work together to form feedback loops in the clock system by regulating the stability of PER and regulating the metabolism of NAD+. Therefore, energy availability has a reciprocal relationship with circadian timing [12].

Due to shift work, jet lag, or irregular eating patterns, the circadian synchrony is disrupted causing central and peripheral circadian rhythms to become desynchronized, leading to metabolic inflexibility. Metabolic inflexibility is thought to be more susceptible favouring elevated levels of proinflammatory cytokines and oxidative stress, and endoplasmic reticulum stress, all of which are contributors of IR. Aberrant activation of NF-κB, JNK, and NLRP3 inflammasome pathways under circadian disruption promotes phosphorylation of IRS-1 at serine residues, inhibiting downstream AKT signaling. Due to the disturbed light exposure, melatonin levels fluctuate exacerbating nighttime hyperglycemia followed by adipose tissue inflammation [61].

8.3 Post-Translational Modifications (PTMs) affecting Insulin Signaling

Translation refers to the formation of polypeptide chain viz proteins by the ribosomes from the message received by the mRNA. Reversible or irreversible chemical and structural modifications in the proteins, after their translation process, is referred to as the PTM and it significantly affects their nature, functions, and stability [62]. PTMs are required for converting the immature polypeptides to mature, functional, and dynamic through covalently adding or deleting the phosphate, methyl or other groups to the active amino acid sequences, necessary for maintaining cell viability and biological functions. They also help in responding to the cellular signals appropriately and mediating correct protein folding, and protein-protein interactions. Therefore, PTM is a very significant process for normal cell function, adaptation to environmental hint, and survival, playing critical roles in development, metabolism, and immune responses. But their perturbation leads to dysfunction and disease, underscoring their biological significance.

PTMs play essential roles in regulating insulin secretion, β-cell development, and insulin signaling in the target tissues. Recent studies have highlighted the significance of PTM in IR and DM [63]. Table 3 represents the PTMs in the IR states.

Table 3: List of PTMs and the respective proteins modified by them including their effects that produce IR [63,64]

Sr. no.	PTM	About	Proteins modified	Effects
1	Methylation	Addition of methyl groups to lysine/arginine of DNA/histones. Enzymes: DNA methyltransferases (DNMT1, DNMT3A, DNMT3B) and Histone methyltransferases (SET, EZH2)	Histones (H3K4, H3K9, H3K27), PPARG	Reduced PPARG and GLUT4 expression, impairing adipocyte insulin sensitivity, promoting IR
2	Acetylation	Addition of acetyl groups on lysine residues Enzymes: Histone acetyltransferases (HATs), histone deacetylases (HDACs), SIRT1-7 (sirtuins)	Histones, IRS1, AKT, PPAR-γ	Histone deacetylation suppresses insulin-responsive genes and hyperacetylation of IRS2/FoxO disrupts insulin signaling
3	Ampylation	Covalent addition of AMP to protein residues. Enzymes: FICD (filamentation induced by cAMP domain proteins) and AMPK	AMPK, IRS1/2, IR	Reduced GLUT4 translocation and insulin response
4	Deamidation	Non-enzymatic conversion of asparagine/glutamine to aspartate/glutamate, Enzyme: Peptidyl Asparagine Deamidase	Insulin (A21 variant), islet amyloid polypeptide (IAPP)	Deamidated insulin reduces stability; IAPP deamidation aggregates amyloid, promoting β-cell dysfunction.
5	O-GlcNAcylation	Addition of O-linked N-Acetylglucosamine to Serine/Threonine residues Enzyme: O-GlcNAc transferase (OGT), O-GlcNAcase (OGA)	IRS1, AKT	Impaired PI3K-AKT, reduced insulin secretion, and increased β-cell dysfunction
6	Oxidation	ROS-mediated oxidative changes on amino acid sequences Enzymes: NADPH oxidases, mitochondrial electron transport chain, and antioxidant enzymes (GPX1, SOD, catalase)	Insulin	Impaired IRS1/AKT pathway, inflammation, and reduced insulin signaling.
7	SUMOylation	Addition of SUMO peptides to lysine side chains Enzymes: SUMO E1 (SAE1/SAE2), E2 (Ubc9), E3 ligases (PIAS family)	PPARγ	Impaired lipid metabolism, adipose inflammation, and β-cell dysfunction
8	Phosphorylation	Covalent attachment of phosphate group to Serine /Threonine/Tyrosine residues. Enzymes: IR kinase, AKT, PI3K, mTORC1/2, JNK, AMPK	IR, IRS1, Akt, AMPK	Serine phosphorylation inhibits IRS1, inhibiting GLUT4 translocation
9	Citrullination	Conversion of arginine to citrulline. Enzymes: Peptidyl Arginine Deiminase Enzyme	Glucokinase	Reduced glucose-stimulated insulin secretion
10	Glycation	Non-enzymatic binding of reducing sugars to proteins, forming Advanced Glycation End products.	Insulin	Advanced Glycation End products reduce IR affinity, trigger inflammation & oxidative stress

11	Carbonylation	Non-enzymatic oxidative addition of carbonyl groups	Insulin	Increases oxidative damage, impairing β-cell and insulin function

9. ROLE OF AI/ML IN IR INTERPRETATION

AI/ML is emerging as a powerful tool for finding patterns and connections in big datasets, where ML is a potent tool for forecasting complicated circumstances like IR. In popular machine learning algorithms. the exhaustive Chi-squared automatic interaction detector (E-CHAID), support vector machine (SVM), back propagation neural network (BPNN), LR each with unique benefits were chosen for this investigation, gradient boosted tree (Cat Boost), random forest (RF), neural network E-CHAID is useful for managing categorical data and finding correlations between variables. Because of its excellent nonlinear mapping capabilities and versatility, BPNN may be used with complex datasets. The resilience of SVM is well known high-dimensional spaces and the capacity to manage kernel functions for nonlinear interactions. Conversely, LR offers comprehensible models, which are essential for therapeutic decision-making. Cat Boost are mostly used for ensemble model for classification and regression task in health data. RF are robust model for feature selection and prediction. To determine the best model for clinical application, it is crucial to compare the accuracy of different algorithms in predicting IR due to their varied features. The goal is to offer a more reliable and useful tool for early IR prediction by assessing these models using a comprehensive dataset that includes both basic health information and dietary parameters [65].

Diabetes management has been completely transformed by the incorporation of Artificial Intelligence (AI) into wearable technology and mobile health apps, which offer real-time monitoring and tailored feedback. AI-powered wearables can continuously monitor important health indicators including blood sugar levels, heart rate and physical activity, allowing patients to actively control their disease. Mobile health (mHealth) applications paired with these devices, enhance user engagement by offering insights into lifestyle adjustments and respect for treatment regimens. For example, applications like Glucose Buddy and mySugr use AI to evaluate user data and provide customized recommendations, enhancing self-management and encouraging patients to make right choices. These products are prime examples of how AI can revolutionize the effectiveness and accessibility of diabetes care. A key component of AI-driven diabetes care, Continuous Glucose Monitoring (CGM) systems offer comprehensive glucose trend data, facilitating prompt actions. By analysing glucose swings and anticipating possible hypoglycemic or hyperglycemic episodes, AI algorithms included into CGM systems enable patients and medical professionals to take preventative measures. For instance, AI is used by the FreeStyle Libre and Dexcom G6 devices to produce useful insights like glucose patterns of fluctuation and the effects of food or exercise on blood sugar. AI-powered CGM systems lessen cognitive load by automating data analysis and delivering it in user-friendly ways to improve glycaemic control for patients [66].

10. CONCLUSION

IR is a metabolic condition resulting from disruptions in both insulin-dependent and independent pathways within metabolic tissues such as adipose tissues, skeletal muscle, and liver. The increased phosphorylation of IRS proteins at

serine/threonine sites by kinases like JNK, IKK-β, and PKC isoforms interferes with PI3K/AKT signaling, leading to reduced GLUT4 migration and glucose absorption. Inflammatory cytokines such as TNF-α and IL-6 trigger the NF-κB and JNK pathways, hindering insulin signaling and contributing to obesity-related IR. ER stress and mitochondrial dysfunction worsen IR by generating ROS. Lipotoxicity, due to high fatty acid levels, hampers AKT activation and triggers stress responses. The overall impact of these disturbed signalling communications impairs glycogen production, interfere with gluconeogenesis regulation, and alter lipid metabolism leading to impaired glucose homeostasis. Risk of diabetes, cardiovascular and neurological complications are elevated due to disturbances in the insulin-dependent and independent signalling pathways. Besides these signalling pathways, gut microbiota imbalance, circadian disruption, and PTMs are also significant in the precipitation of defective insulin related complications. Thus, for restoration of insulin sensitivity and metabolic health, it is necessary to comprehend them for achieving the optimized treatments.

ABBREVIATIONS

Glucose Transporter 4 (GLUT4), Insulin Resistance (IR), Insulin Dependent Mechanisms (IDM) and Insulin Independent Mechanisms (IIDM), Free Fatty Acids (FFAs), Insulin Receptor (IR), Src Homology and Collagen Homolog (SHC), Forkhead box protein-O1 (FoxoO1), Mammalian target of rapamycin (mTOR), Guanosine Triphosphate (GTP), Extracellular Signal-Regulated Kinase (ERK1/2 or p44/p42 MAPK), Mitogen activated protein mTORC1kinase (MEK), mTOR complex 1 (mTORC1), mTOR complex 2 (mTORC2), Sterol regulatory element binding protein 1c (SREBP-1c), Regulatory associated protein of mTOR (Raptor), Domain containing mTOR interacting protein (Deptor), Mammalian lethal with Sec protein 8Gβ (MlST8/GβL), Rapamycin–Insensitive Companion of mTOR (Rictor), Insulin like growth factor-1 (IGF-1), Ras homolog enriched in brain (Rheb), IκB kinase (IKK), Toll - like receptor 4 (TLR4), Mitogen activated protein kinase (MAPK), Downstream of tyrosine kinase-1 (Dok1), Suppressor of cytokines signaling (SOCS), Low-density lipoprotein receptor related protein (LPR5/6), Casein kinase 1(CK1), Reactive oxygen species (ROS), Short-chain fatty acids (SCFAs), Liposaccharides (LPS), suprachiasmatic nucleus (SCN), Period (Per) and Cryptochrome (Cry) genes, Clock-controlled genes (CCGs), Rev-erbα (Nuclear receptor subfamily 1 group D member 1), Tbc1d1 (TBC1 Domain family member 1)

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AG did the drafting of the original manuscript, VJ helped in the visual representation, SP conceived the original idea and did the proofreading

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