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Molecular Mechanism of Insulin Resistance and Type 2 Diabetes

Nirubama.K
Saveetha Dental College and Hospitals
Saveetha Institute of Medical and Technical Sciences (SIMATS)
Saveetha University
Chennai- 600077,
India.
Email Id- 151801045.sdc@saveetha.com

Dr.Raghu Nandhakumar
Associate Professor
Department of Pharmacology

Saveetha Dental College and Hospitals
Saveetha Institute of Medical and Technical Sciences (SIMATS)
Saveetha University
Chennai-600077,
India.
Email Id- ragunandhakumars.sdc@saveetha.com

Dr.Ezhilarasan,
Associate Professor,
Department of Pharmacology
Saveetha Dental College and Hospitals,
Saveetha Institute of Medical and Technical Sciences (SIMATS)
Saveetha University
Chennai-600077,
India.
Email Id- ezhilarasand.sdc@saveetha.com

Dr.Lakshmi Thangavelu
Associate Professor
Department of Pharmacology
Saveetha Dental College and Hospitals
Saveetha Institute of Medical and Technical Sciences (SIMATS)
Saveetha University
Chennai-600077,
India.
Email Id- lakshmi@saveetha.com

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Corresponding Author
Dr.Raghu Nandhakumar,
Associate Professor,
Department of Pharmacology,
Saveetha Dental College and Hospitals,
Saveetha Institute of Medical and Technical Sciences (SIMATS)
Saveetha University
Chennai-600077,
India.
Email Id- ragunandhakumars.sdc@saveetha.com
Phone: 9790270479

ABSTRACT:

Aim: To analyze the relationship between the molecular mechanism of insulin resistance and its associated type-2 diabetes.

Method: Relevant articles were identified via PUBMED, GOOGLE SCHOLAR MeSH, Cochrane, bioRxiv, Semantic scholar search engines using the keywords Insulin receptor, Insulin resistance, signaling, Insulin receptor substrate proteins, Type 2 diabetes mellitus. Period of duration considered was from 1980 to till date.

Discussion: Insulin resistance is a major risk factor for developing type 2 diabetes caused by insulin-target tissue's inability to respond properly to insulin and contributes to obesity morbidity. Insulin action involves a series of signaling cascades initiated by insulin binding to its receptor, causing autophosphorylation of the receptor and activation of the tyrosine kinase receptor, resulting in tyrosine phosphorylation of the insulin receptor substrates (IRSs). Phosphorylation of IRSs contributes to phosphatidylinositol 3-kinase (PI3K) activation and subsequent activation of Akt and its downstream mediator AS160, both of which are critical measures to promote insulin-induced glucose transport.

Conclusion: Identifying signals and understanding the complex relationship of the various factors that modulate insulin sensitivity are important prerequisites for developing new and more specific antidiabetic compounds.. By elucidating the cellular and molecular mechanisms responsible for insulin resistance, these studies provide potential new targets to treat and prevent type 2 diabetes mellitus. This review focuses on the molecular basis of insulin resistance to skeletal muscles and type 2 diabetes.

keywords: Insulin receptor, Insulin resistance, signaling, Insulin receptor substrate proteins, Type 2 diabetes mellitus

INTRODUCTION:

Type 2 DM soon appears as one of 21st century's biggest public health threats. The pathogenesis of Type 2 diabetes includes irregularities in the activity of insulin as well as secretion.(Wild *et al.*, 2004). The relationship between insulin resistance and type-2 diabetes is not only the most

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powerful predictor of future development of type-2 diabetes, it is also a therapeutic target once hyperglycemia is present. The natural activity of insulin is begun by establishing its layer receptor that triggers various flagging processes for intercession. Because of the importance of metabolic guidelines and advancing elements of cell development and expansion, insulin activity is exceptionally controlled in order to advance the appropriate balance of metabolic work and vitality. This can prompt a condition known as insulin resistance, which is the result of insufficient insulin flagging caused by transformations or post translational alterations of receptor or effector atoms found downstream. Translocation of glucose transporter 4 (Glut4) the main insulin controlled glucose transportation network, from intracellular vesicles to the plasma membrane and transverse tubules, facilitates the capacity of Insulin to improve glucose transfer in skeletal muscles (2). On a cellular level, it defines the inadequate strength of insulin signaling from the insulin receptor downstream to the final substrates of insulin action involved in various metabolic and mitogenic aspects of cellular function (Kraemer and Ginsberg, 2014). The type 2 pathogenesis involves anomalies in both the action of insulin and its secretion(Saltiel, 2001). Although the precise pathophysiological sequence leading to insulin resistance is still largely unknown, recent studies have contributed to a deeper understanding of the molecular mechanisms. Also expected to trigger a steep rise in complications associated with diabetes, such as ischemic heart disease, stroke, neuropathy, retinopathy, and nephropathy. Besides β cell failure, the major pathophysiological event which is contributing to the development of type 2 DM is target tissues resistance to insulin, which is usually associated with abnormal insulin secretion. necessitates the need to develop new drugs for its effective management. Plants and their bioactive compounds are found to be an alternative therapeutic approach. The *C. fimbriata* extract showed potent inhibitory activity on enzymes of glucose metabolism in a dose-dependent manner(Anitha and Ashwini, 2017; Ashwini, Ezhilarasan and Anitha, 2017). This review discusses the molecular mechanisms of insulin resistance in type 2 diabetes. Azadirachta indica is an evergreen tree having potential medicinal values and it has anti mutagenic values(Lakshmi *et al.*, 2015). A detailed understanding of these basic pathophysiological mechanisms is critical to developing novel therapeutic strategies for diabetes.Our team has rich experience in research and we have collaborated with numerous authors over various topics in the past decade (Ariga *et al.*, 2018; Basha, Ganapathy and Venugopalan, 2018; Hannah *et al.*, 2018; Hussainy *et al.*, 2018; Jeevanandan and Govindaraju, 2018; Kannan and Venugopalan, 2018; Kumar and Antony, 2018; Manohar and Sharma, 2018; Menon, Ks, R, *et al.*, 2018; Nandakumar and Nasim, 2018; Nandhini, Babu and Mohanraj, 2018; Ravinthar and Jayalakshmi, 2018; Seppan *et al.*, 2018; Teja, Ramesh and Priya, 2018; Duraisamy *et al.*, 2019; Gheena and Ezhilarasan, 2019a; Hema Shree *et al.*, 2019; Rajakeerthi and Ms, 2019; Rajendran *et al.*, 2019; Sekar *et al.*, 2019; Sharma *et al.*, 2019; Siddique *et al.*, 2019; Janani, Palanivelu and Sandhya, 2020; Johnson *et al.*, 2020; Jose, Ajitha and Subbaiyan, 2020).

RETRIEVAL OF LITERATURE DATA:

Relevant articles were referred by PUBMED, GOOGLE SCHOLAR MeSH, Cochrane, bioRxiv, Semantic scholar search engines using the keywords Insulin receptor, Insulin resistance, Insulin signaling, Insulin receptor substrate proteins and type 2 diabetes mellitus. Period of duration considered was from 1980 to till date. Out of searched article, 28 articles were selected, out of which 25 are with known concept and 3 articles with recent concept.Our institution is passionate about high quality evidence based research and has excelled in various fields ((Pc, Marimuthu

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and Devadoss, 2018; Ramesh *et al.*, 2018; Vijayashree Priyadharsini, Smiline Girija and Paramasivam, 2018; Ezhilarasan, Apoorva and Ashok Vardhan, 2019; Ramadurai *et al.*, 2019; Sridharan *et al.*, 2019; Vijayashree Priyadharsini, 2019; Chandrasekar *et al.*, 2020; Mathew *et al.*, 2020; R *et al.*, 2020; Samuel, 2021)

Insulin signaling:

Insulin receptor (IR) is a heterotetramer consisting of two α subunits and two β subunits linked by disulphide bonds (Pedersen *et al.*, 1990). Insulin binds to the insulin receptor α subunit and activates the tyrosine kinase in the β subunit. The activation of tyrosine kinase in the insulin receptor promotes autophosphorylation of the β subunit, where phosphorylation of three tyrosine residues (Tyr-1158, Tyr-1162, and Tyr-1163) is needed to amplify kinase activity (White and Ronald Kahn, 1989). Most of insulin metabolism and antiapoptotic effects are mediated by the signaling pathway of phosphorylation of the insulin receptor substrate (IRS) proteins, and the activation of the phosphatidylinositol (PI) 3-kinase, Akt (also known as protein kinase B), the molecular target of rapamycin (mTOR), and p70 S6 kinase (Guesdon, Waller and Saklatvala, 1994). The insulin receptor tyrosine kinase phosphorylates the IRS proteins, and phosphotyrosine residues on IRS proteins become good targets for the p85 regulatory subunit of PI3-kinase (Shepherd, Navé and Siddle, 1995). The activated PI3-kinase generates 3′-phosphoinositides [phosphatidyl - inositol-3,4-bisphosphate (PIP2) and phosphatidyl-inositol-3,4,5-trisphosphate (PIP3)] (Alessi, 2000) which are bound to the phosphoinositide dependent kinase 1 (PDK1) (Balusamy *et al.*, 2018). The PDKs are the protein kinase B (PKB) and also atypical forms of the protein kinase C (PKC) (Kotani *et al.*, 1998).

Mutation in irs proteins:

Insulin initiates its diverse biological effects by binding to the a-subunit of the insulin receptor, resulting in activation of intrinsic tyrosine kinase activity and rapid phosphorylation of tyrosine residues in three domains, including the juxtamembrane domain, the tyrosine kinase domain, and the COOH-terminal domain of its intracellular p-subunit. Insulin receptor kinase-1 is one of the major substrates of insulin receptor tyrosine kinase and mediates various insulin signals downstream. After insulin stimulation, the insulin receptor undergoes autophosphorylation on tyrosine residues, which in turn activates the tyrosine kinase activity of the receptor towards other substrates. IRS-1 played a significant role in insulin-stimulated glucose uptake, suggesting that the IRS-1 gene may be involved in the development of NIDDM. In humans, insulin resistance is associated with rare mutations of the IRS-1 protein (Whitehead *et al.*, 1998). Disruption of the IRS-1 gene in mice results in insulin resistance, mainly of muscle and fat (Yamauchi *et al.*, 1996). The analysis of IRs in knockout mice shows an important phenotype of single allele IRS-1 gene whereas homozygous disruption of the IRS-1 gene results in a mild form of insulin resistance(Erenler and Karan, 2017). IRS-1 homozygous null mice (IRS-$1^{-/-}$) do not show a clear diabetic phenotypic expression, presumably because of pancreatic β cell compensation. By comparison, IRS-$2^{-/-}$ mice developed diabetes as a result of severe insulin resistance paired with β cell failure(Araki *et al.*, 1994).

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Inhibition of IR gene transcription:

The promoter region of the human IR gene has been established and researched by many groups in order to explain the molecular basis for the modulation of IR expression. Two unique AT-rich sequences, C2 and E3, within the IR gene promoter and both sequences are positively regulated by transcription factor HMGA1 (earlier known as HMG1-Y) (23). HMGA1 interacts with the AT rich regions and regulates multiple gene transcriptional activation by modifying DNA conformation that allows transcriptional factor recruitment to the transcription start site(Bustin and Reeves, 1996). HMGA1 induces human IR gene to be transcriptional activation by enabling the recruitment of SP1 and cEBPβ, the ubiquitously expressed transcription factors, to the promoter region. A recent report demonstrates that a genetic defect that reduces the intracellular expression of HMGA1 protein may adversely affect IR expression in cells and tissues from subjects with insulin resistance and type 2 diabetes(Foti *et al.*, 2005). There is also a possibility that activated PKCε phosphorylates HMGA1, which inhibits its mobilization to the promoter region IR gene(Sujatha, Asokan and Rajeshkumar, 2018). It has been shown that phosphorylation of the HMGA1 protein reduces its DNA-binding ability(Reeves and Beckerbauer, 2001). There is no specific transcription factor recruitment for the promoter region of the IR gene and therefore no expression of the IR gene without the mobilization of HMGA1 for the IR promoter.

Mitochondrial dysfunction:

For many years, severe mitochondrial dysfunction can result in diabetes(DiMauro and Rustin, 2009). The observation of abnormal mitochondrial function in vitro in type 2 diabetes(Kelley *et al.*, 2002) was soon followed by in vivo demonstration of this abnormality in insulin-resistant, first-degree relatives of people with type 2 diabetes(Petersen *et al.*, 2004). Further reports of a modest defect in muscle mitochondrial function in type 2 diabetes were published shortly thereafter(Szendroedi *et al.*, 2007; Phielix *et al.*, 2008). These studies raised the question of whether type 2 diabetes could be a primary disorder of the mitochondria. However, the study of first-degree relatives tended to be misinterpreted as having shown a major defect in mitochondrial function in type 2 diabetes, although it had studied nondiabetic groups from the opposite ends of the insulin resistance–sensitivity spectrum. Indeed, other studies showed no defect in mitochondrial function in type 2 diabetes(De Feyter *et al.*, 2008; Ee L. Lim *et al.*, 2011a), which led to further confusion. Mitochondrial function was then shown to be acutely modifiable by changing fatty acid availability(Baker *et al.*, 2006; Ee L. Lim *et al.*, 2011b) and that it was affected by ambient blood glucose concentration(Kelley and Mandarino, 1990). When ambient blood glucose levels were near normal in diabetes, no defect in mitochondrial function was apparent.In a study using $^{13}C/^{31}P$ MRS, it was found that in healthy lean elderly volunteers with severe muscle insulin resistance, there is ~40% reduction in the rates of oxidative phosphorylation activity associated with increased intramyocellular and intrahepatic lipid content(Lee, Sciamanna and Peterson, 1993). This study indicates that the acquired lack of mitochondrial function associated with aging predisposes elderly subjects to intramyocellular lipid accumulation, which results in insulin resistance. Furthermore, mitochondrial density reduced by 38%, intramyocellular lipid content increased by 60% and serine phosphorylation of

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IRS-1 was increased by 50% in the young insulin-resistant offspring of type 2 diabetes. Muscle insulin resistance as determined by the euglycemic-hyperinsulinemic clamp is clearly a risk factor for development of type 2 diabetes(Lillioja *et al.*, 1993). However, the pathophysiology of hyperglycemia in established diabetes relates to hepatic not muscle insulin resistance. This distinction has been elegantly demonstrated in studies of moderate calorie restriction in type 2 diabetes, which resulted in a fall in liver fat, normalization of hepatic insulin sensitivity, and fasting plasma glucose, but no change in muscle insulin resistance(Petersen *et al.*, 2005). More recent work employing severe calorie restriction confirmed previous findings and also demonstrated a longer-term return of normal insulin secretion as intrapancreatic fat content fell(E. L. Lim *et al.*, 2011).

Adipokines:

Insulin has three major target tissues-skeletal muscle, adipose tissue and the liver. Not only is IR overexpressed in these tissues, but they also have three sites where glucose is accumulated and stored, no other tissue may store glucose. About 75% of postprandial insulin-dependent glucose disposal takes place in the skeletal muscle(Klip *et al.*, 1990). Hence, it is a main target organ. Insulin resistance patients with type 2 diabetes frequently display signs of abnormal lipid metabolism, increased circulatory concentration and elevated deposition of lipids in the skeletal muscle. Increase in plasma FFA reduces insulin-stimulated glucose uptake, whereas a decrease in plasma lipid content improves insulin activity in the skeletal muscle cells, adipocytes and liver. Studies have shown that increasing plasma fatty acids in both rodents and humans abolishes insulin activation of IRS-1-associated PI3-kinase activity in skeletal muscle were most prevalent in IRS-1 gene. . Insulin resistance associated with lipid metabolism - has also been shown to be linked to GLUT4 translocation defects. Adipose tissue also acts as an endocrine organ producing adipokines which modulate glucose homeostasis. Many studies are most intensely discussed about the TNF-α, leptin, adiponectin and resistin at the molecular level of insulin resistance and type 2 diabetes mellitus. Recently a study reported thatTNF-α increases serine phosphorylation of IRS-1 and down-regulates GLUT4 expression, thereby activating the insulin resistance. Furthermore, mice without functional TNF-α were protected from obesity-induced insulin resistance(Uysal *et al.*, 1997). The role of leptin in regulating food intake and energy expenditure is well known. Humans with leptin deficiency or leptin receptor mutations are severely obese. It also has direct effects on insulin sensitivity and may also reverse insulin resistance in mice with congenital lipodystrophy. Adiponectin has insulin-sensitizing effects, as it facilitates suppression of the synthesis of hepatic glucose and utilization in muscle and fat . The expression of adiponectin is decreased in obese humans and mice(Stumvoll and Häring, 2002). Adiponectin levels were correlated with insulin sensitivity in humans. Because of its insulin-antagonistic effects, adipokine resistance has drawn considerable attention in preclinical research . Resistin decreases in vitro insulin-dependent glucose transport and improves in vivo high blood glucose levels and hepatic glucose production.

Type-2 diabetes association with cancer and its treatment:

Diabetes and cancer are common diseases with tremendous impact on health worldwide. Epidemiologic evidence suggests that people with diabetes are at significantly higher risk for

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many forms of cancer. Type 2 diabetes and cancer share many risk factors(Giovannucci *et al.*, 2010). Diabetes (primarily type 2) is associated with increased risk for some cancers (liver, pancreas, endometrium, colon and rectum, breast, bladder). Diabetes is associated with reduced risk of prostate cancer. The association between diabetes and some cancers may partly be due to shared risk factors between the two diseases, such as aging, obesity, diet, and physical inactivity. Possible mechanisms for a direct link between diabetes and cancer include hyperinsulinemia, hyperglycemia, and inflammation. Accordingly, new strategies are evolving to control and to treat cancer and one such strategy could be the use of medicinal plants. Previous studies have reported the anticancer efficacy of medicinal plants against several human in vitro cancer cell lines and came out with promising results (Ezhilarasan, Lakshmi, Vijayaragavan, *et al.*, 2017). Coumarin plays a vital role in the drug discovery process against type-2 diabetes due to its diverse biologically active components(Perumalsamy *et al.*, 2018). The ethanol seed extracts of *A. catechu* were found to be cytotoxic at lower concentrations and induced apoptosis in human pancreatic cells (Ezhilarasan, Lakshmi, Nagaich, *et al.*, 2017). Nanotechnology beholds infinite potential and innovative applications which are being continuously explored for detecting, diagnosing, imaging and treating different types of cancers(Rajeshkumar, Venkat Kumar, *et al.*, 2018; Sharma *et al.*, 2019). Nanoparticles play an important role in the target-specific delivery of drugs. In addition, oligonucleotides also are extensively used for gene transfer in the form of polymeric, liposomal and inorganic carrier materials (Rajeshkumar, Agarwal, *et al.*, 2018; Mehta *et al.*, 2019). Selenium nanoparticles can open ways to new regular strategies for treating illnesses like malignancy, and this audit expresses the reasons why these nano measured medications can be the following huge achievement as chemotherapeutic operators(Karthiga, Rajeshkumar and Annadurai, 2018; Menon, Ks, Santhiya, *et al.*, 2018). There is a significant relationship between oxidative stress and different liver pathogenesis induced by drugs and xenobiotics, focusing upon different chronic liver injury induced by alcohol, antitubercular drugs and hyperactivity of drugs in hyperglycemic patients(Ezhilarasan, 2018; Ezhilarasan, Sokal and Najimi, 2018; Gheena and Ezhilarasan, 2019b).Our institution is passionate about high quality evidence based research and has excelled in various fields ((Pc, Marimuthu and Devadoss, 2018; Ramesh *et al.*, 2018; Vijayashree Priyadharsini, Smiline Girija and Paramasivam, 2018; Ezhilarasan, Apoorva and Ashok Vardhan, 2019; Ramadurai *et al.*, 2019; Sridharan *et al.*, 2019; Vijayashree Priyadharsini, 2019; Chandrasekar *et al.*, 2020; Mathew *et al.*, 2020; R *et al.*, 2020; Samuel, 2021)

CONCLUSION:

In this review, we have summarized the recent findings that leads to our understanding of insulin resistance type 2 diabetes pathogenesis . Identifying signals and understanding the complex relationship of the various factors that modulate insulin sensitivity are important prerequisites for developing new and more specific antidiabetic compounds. About 75% of postprandial insulin-dependent glucose disposal takes place in the skeletal muscle. By elucidating the cellular and molecular mechanisms responsible for insulin resistance, these studies provide potential new targets to treat and prevent type 2 diabetes mellitus.

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