THE ROLE OF INTERLEUKIN-6 (IL-6) IN THE PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

Scientific supervisor: ***Karimov R.N.***
Assistant of the Department of Pharmacology and Pathophysiology of TashPMI Completed:
3rd year student of TashPMI ***Omonov Madorbek Oybekovich***
3rd year student of TashPMI ***Kamilova Sevara Abdumuratovna***
3rd year student at ASMI ***Abdullaev Sirozhiddin Oybekovich***

Abstract: Interleukin-6 (IL-6) is a pro-inflammatory cytokine that induces the development of insulin resistance and underlies the pathogenesis of type 2 diabetes mellitus (DM2), through the generation of inflammation by controlling differentiation, migration, proliferation, and apoptosis of cells. The presence of IL-6 in tissues is normal, but its irregular production and prolonged exposure lead to the development of inflammation, which induces insulin resistance. There is a mechanistic relationship between IL-6 stimulation and insulin resistance. IL-6 causes insulin resistance by disrupting the phosphorylation of the insulin receptor and the substrate of the insulin-1 receptor, inducing the expression of SOCS-3, a potential inhibitor of insulin signaling.

Keywords: type 2 diabetes mellitus, IL 6, molecular mechanisms, phosphorylation, insulin, socs3, ri-1.

Introduction: Insulin resistance is the inability of cells to utilize glucose, and the hypoglycemic effects of insulin become abnormal, which leads to the development of hyperglycemia. Insulin resistance is characterized by defective receptors, and glucose uptake in skeletal muscles is impaired due to defective regulation of isoform 4 glucose transporter (GLUT4). With insulin resistance syndrome, insulin levels are elevated, which ultimately increases the risk of developing DM2. With DM2, the metabolism is seriously disrupted, which affects the metabolism of proteins, carbohydrates and fats. The prevalence is projected to be approximately 4.4% (366 million) by 2030. It is assumed that insulin resistance is a reaction of the body in response to increased levels of various local and circulating proinflammatory cytokines. Mitochondrial dysfunction is associated with insulin resistance. The oxidative capacity of mitochondria leads to a decrease in β-oxidation and accumulation of lipids, such as ceramides and diacylglycerides. This accumulation impairs GLUT4 translocation and the insulin signaling pathway. Due to the increase in lipid peroxidation, the formation of reactive oxygen species (ROS) increases. Elevated ROS levels impair the transmission of insulin signals through the involvement of various inflammatory processes. Due to the

stress of the endoplasmic reticulum, unfolded proteins are activated in three ways: by protein kinase RNA-like ER kinase (PERK) activating transcription factor-6 (ATF6) and inositol requiring the enzyme-1-to-X-box binding potein-1 (IRE1/XBP1). Stress kinases are activated by activating unfolded protein reactions, and they interfere with the transmission of insulin signals, such as c-Jun N-terminal kinase (JNK). Transcription factors that regulate the expression of various liver enzymes involved in gluconeogenesis and lipogenesis also lead to abnormal pathways in the development of insulin resistance. Endoplasmic reticulum stress is a long-term chronic hyperglycemia and activated by the JNK pathway, which is further involved in the development of insulin resistance. Receptors that recognize different types of IL-6 cytokines are classified into non-signal α-receptors and signal-transmitting receptors. Non-signal α-receptors contain IL-6Ra, IL-11Ra and CNTFRa, where R stands for the receptor. The receptors transmitting the signal include gp130, LIFR and signal OSMR. Each IL-6 type cytokine has a specific receptor recruitment scheme or figure, which in each case includes at least one gp130 molecule. Firstly, IL-6 binds to a specific α-receptor, the expression of the α-receptor is limited and tightly regulated. An important function of α-receptors is to make cells sensitive to the corresponding cytokine; thus, the cytokine complex and the soluble receptor can work agonistically rather than antagonistically. Dissolved forms of cytokine receptors are produced by limited proteolysis of membrane-bound receptors or translation occurs using spliced mRNA. The situation with IL-6 is more complicated because sIL-6Ra and sgp130 exist in human sera. sIL-6Ra enhances the antagonistic function of sgp130. Thus, the naturally present association of sIL-6Ra and sgp130 works as a buffer for correcting systemic reactions of circulating IL-6. The cytoplasmic component of IL-6Ra acts as a substitute for the production of the receptor complex and signal transmission, which may be necessary for special signaling actions of the receptor. The presence of IL-6 in tissues is a normal consequence, but its irregular production leads to low-temperature inflammation, which is closely associated with many types of inflammatory diseases.IL-6 plays a role in acute and chronic inflammation, interacting with various inflammatory reactions. IL-6 stimulates the production of acute phase proteins in response to stimuli, depending on the nature or localization of inflammation. The nature of cytokine production and acute phase reactions differs in various inflammatory conditions. Acute phase changes reflect the presence and intensity of inflammation, and they have long been used as clinical guidelines for the diagnosis and treatment of various inflammatory diseases.IL-6 also plays a key role in the transition from acute to chronic inflammation. After an acute inflammatory reaction, IL-6 binds to sIL-6R and participates in signaling via gp130, which leads to the recruitment of monocytes. Long – term exposure to IL-6 leads to the development of neutrophilic apoptosis, phagocytosis and mononuclear accumulation at the site of injury. IL-6 also plays a key

role in the induction of inflammatory reactions in the central nervous system. Insulin secretion is mainly affected by the generation of oxidative stress and the induction of inflammation in the islets of the pancreas. They are involved in the induction of oxidative stress and inflammation in the beta cells of the pancreatic islets; among them, IL-6 is also the main factor contributing to the induction of low-temperature tissue-specific inflammation in the pancreatic islets, which ultimately leads to impaired insulin secretion and apparent DM2. Several experimental studies have shown that IL-6 interferes with glucose-stimulated insulin secretion from pancreatic islets in experimental animal models, but some studies have also shown that acute exposure to IL-6 does not seem to affect the normal functioning of beta cells of pancreatic islets. Thus, the effect of IL-6 on organs is contradictory. Despite its contradictory effects, chronic exposure to IL-6 is responsible for inducing tissue-specific and/or systemic inflammation of low severity, which is one of the main causal factors of impaired insulin secretion by beta cells of pancreatic islets.

Conclusion: IL-6 is one of the main pro-inflammatory mediators that make a decisive contribution to the development of tissue-specific and/or systemic inflammation of low severity. The role of IL-6 in development tissue-specific insulin resistance and impaired insulin secretion by beta cells of pancreatic islets is controversial, but experimental studies conducted on various experimental animal models and in vitro studies show that chronic exposure to IL-6 potentiates a decrease in the mass of beta cells and disrupts the normal functioning of the beta cells of the pancreatic islets. In turn, normal insulin secretion, stimulated by glucose, is disrupted. Moreover, tissue-specific and systemic inflammation of low severity induced by IL-6 is also responsible for the development of tissue-specific resistance to insulin and DM2. Prevention of inflammatory disorders by blocking inflammatory reactions is an effective strategy for the treatment of insulin resistance and DM2.

Used Literature

1. Olarescu NC, Bollerslev J. The impact of adipose tissue on insulin resistance in acromegaly. Trends Endocrinol Metab. 2016;27(4):226–37.

2. Martin SD, McGee SL. The role of mitochondria in the aetiology of insulin resistance and type 2 diabetes. Biochim Biophys Acta. 2014;1840(4):1303–12.

3. Casazza K, Willig AL, Gower BA, Nagy TR, Hunter GR, Wallace S, Amaya M, Franklin F, Beasley M, Fernandez JR. The role of European genetic admixture in the etiology of the insulin resistance syndrome in children: Are the effects mediated by fat accumulation? J Pediatrics. 2010;157(1):50–6. e51.

4. Akash MSH, Rehman K, Chen S. Spice plant allium cape: dietary supplement for treatment of type 2 diabetes mellitus. Nutrition (Burbank). 2014;30(10):1128–37.

5. Akash MSH, Rehman K, Chen S. Effects of coffee on type 2 diabetes mellitus. Nutrition (Burbank). 2014;30(7–8): 755–63.