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Research Progress on Molecular Mechanisms of Insulin and Insulin-like Growth Factor

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In recent years, insulin and insulin-like growth factor have been widely used in the diagnosis, condition evaluation, treatment monitoring, and prognosis judgment of various clinical diseases. It has important clinical potential value to study the molecular mechanism related to insulin and insulin-like growth factor. It has been proved that insulin and insulin-like growth factor are closely related to the occurrence and development of cancer, diabetes, and aging. In this paper, the research progress of insulin and insulin-like growth factor is further elaborated, and the mechanism of action of insulin and insulin-like growth factor and the prospect of clinical application in the future are discussed. (Anal Quant Cytopathol Histpathol 2021;43:493–497)

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Insulin is the body's main anabolic hormone, which participates in cellular metabolism, exerts pleiotropic effects by acting on the liver, skeletal muscle, and adipose tissue, while insulin-like growth factor I (IGF-I) regulates growth, differentiation, and life. In the human body, insulin sensitivity increases with age, which constitutes a risk factor for various diseases, such as hypertension, diabetes, obesity, and other diseases. From the perspective of epidemiology and molecular research, there is more and more evidence that there is a connection between these diseases. The study of such associations may not only be of great significance to the discovery of disease mechanisms, but also provide a new research direction to find a new way of treatments.[1]

With the aging of populations around the world,

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the increasing number of metabolic diseases such as cancer and diabetes have caused great challenges to human society. Studies have shown that metabolic diseases are closely related to insulin and insulin-like growth factors. Therefore, its related mechanism of action has become very meaningful. This article focuses on the biological characteristics of the insulin and insulin-like growth factor (IGF) systems, as well as the research progress in diabetes, cancer, and aging.

Biological Characteristics of Insulin and Insulin-like Growth Factor (IGF) Systems

Ligands and Binding Proteins

The insulin/IGF system has multiple components including ligands, binding proteins, receptors, and downstream proteins. Insulin is a key hormone β islet cells, mainly in several tissues can regulate blood sugar and glucose uptake, while promoting the synthesis of lipids in the liver.[2] IGFs (IGF1 and IGF2) are peptides similar in structure to insulin and are produced in the liver and tissues, mainly in the autocrine and paracrine pathways. IGF is an important medium for cell growth, differentiation, and metabolism. In addition to the IGF and insulin responsible for triggering the signaling cascade, there are 6 high-affinity IGF-binding proteins (IGFBPs) in a family that regulate the interactions between these ligands and their receptors. IGFBP plays a key role in the effective utilization of ligands by regulating its half-life, blocking the interaction with receptors, and even promoting signal activation by controlling the release of ligands.[3] Studies suggest that IGFBP may have insulin/IGF-dependent functions, which is closely related to tumorigenesis and development.

Receptor

The main receptors of the insulin/IGF system are IGF1 receptor (IGF1R), IGF2 receptor (IGF2R), and insulin receptor (INSR). Splice variants can also produce 2 additional subtypes, INSR-INSR-A (short isomers) and INSR-B (long isomers). The interaction of the IGF1R isoform can also produce hybrid receptor A (HR-A) and hybrid receptor B (HR-B). In addition to the monomeric IGF2R, the other 5 receptors can also form heterotetrameric structures consisting of 2 subunits of α and 2 subunits of β. The α subunit is extracellular and responsible for ligand binding, while the β subunit has an intracellular segment where the transmembrane and tyrosine kinase domains are located. IGF1R binds to the ligand after autophosphorylation. In order to activate the kinase, phosphorylation of 3 major tyrosine residues (Tyr1131, Tyr1135, and Tyr1136) is required. Full activation of INSRs requires phosphorylation of tyrosine polymers (Tyr1146, Tyr1150, Tyr1151). These receptors are regulated by posttranslational modification of subunits, where the α subunit may be N-glycosylated and the β subunit may be modified by both N- and O-glycosylation. In adipocytes, glucose deprivation results in abnormal glycosylation of INSR, inhibits oligomerization, and regulates insulin-dependent tyrosine kinase activity.[4]

Downstream Protein

Insulin/IGF receptor activation triggers intracellular signaling through the insulin receptor substrate (IRS) protein, which is a family of adaptor molecules (IRS1-IRS4) consisting of 4 closely related members and 2 distant relatives IRS5 and IRS6, also known as docking proteins (DOK4 and DOK5, respectively),[5,6] link receptor activation to downstream kinase cascades, such as the RAS/MEK/ERK or PI3K/AKT1 pathway. IRS protein has 2 common expression forms in humans: IRS1 and IRS2, both of which are highly regulated by phosphorylation (Tyr, Ser, and Thr) and ubiquitination. Although the structures of IRS1 and IRS2 are very similar, the triggering signal mechanisms are different from each other. Mice lacking IRS1 show insulin resistance and stunted growth but do not develop diabetes because hyperinsulinemia may make up for this resistance, and destruction of IRS2 can impair insulin secretion from islet β cells, leading to type 2 diabetes. IRS3 is a human pseudogene, but IRS4 induces excessive activation of the constitutive PI3K/AKT1 pathway in breast cancer cells.[7]

Advances in the Molecular Mechanism of Insulin/IGF in Clinical Research

Insulin/IGF System and Type II Diabetes Mellitus

Type II diabetes mellitus is a chronic metabolic disorder with a complex etiology. At the molecular level, type II diabetes mellitus due to dysregulation of multiple signaling pathways leads to insulin resistance, changes in blood glucose and triglyceride levels, and islet β-cell failure and gluconeogenesis. Studies have found that regulating PFKFB3 activity or glycolysis affects insulin signal transduction, indicating that there is an im-

portant link between glycolysis and growth factor signaling. These diseases are mainly characterized by severe obstacles to metabolism and growth factor signaling.[8] Experiments have confirmed that the occurrence of diabetes is related to abnormal insulin and IGF signals. At the same time, the latest research found that serum levels of IGF-I in patients with type II diabetes mellitus are significantly reduced. Therefore, serum IGF-I levels are likely to be clinical markers for predicting and monitoring treatment options for patients with type 2 diabetes in the future.[9]

Insulin resistance refers to the insensitivity or non-response of peripheral tissues (liver, skeletal muscle, and fat) to the biological reactivity of physiological concentrations of insulin. Rome et al[10] used DNA chip technology to find that insulin regulates the expression of about 800 genes in skeletal muscle of healthy subjects, indicating that insulin plays a major role in controlling gene expression. The physiological relevance of insulin-dependent gene regulation has been confirmed: in insulin resistance and T2DM, the expression levels of 82 transcription factor genes have significantly changed (65 upregulated and 17 downregulated).[11] In addition, Muka et al[12] proposed that further large-scale clinical studies will be needed in the future to determine whether changes in epigenetic markers, including multiple histone acetylation, may cause insulin resistance and increase the risk of T2DM.

Insulin/IGF System and Tumor

In the progress of cancer research, the insulin/IGF system is involved in cancer metabolism, the acquisition of cancer resistance, and the tumor stem cell (CSC) phenotype, all of which highlight the importance of the system in the development of cancer.[13] Several possible mechanisms lead to insulin/IGF signaling network imbalances in cancer, including increased ligand bioavailability, signal protein imbalance, and receptor overexpression.[14] Recently, more and more studies have shown that insulin/IGF signaling is involved in the acquisition of malignant phenotypes by regulating the epithelial-mesenchymal transition (EMT) process, thereby negatively affecting proliferation, invasion, migration, and apoptosis.[15-18] EMT related to the loss of intercellular adhesions will mainly lead to cancer cell migration and the acquisition of invasive phenotypes. Experiments have confirmed that the EMT process produces so-called cancer stem cells (CSCs), which promotes metastasis and drug resistance.[19]

However, only IGF2 is involved in the self-renewal process, and the increase in differentiation is related to the downregulation of insulin and IGF receptors. In breast cancer cells, a proven positive feedback mechanism is that when IGF2 and IGF1 receptors are bound, they trigger the PI3K/AKT1 signal, leading to the activation of the DNA-binding protein inhibitor ID1. ID1 is a transcription factor that not only has the maintenance of stem cells, but also plays a positive role in regulating IGF2.[20] Changes in the insulin/IGF system may also be involved in acquiring an aggressive cancer phenotype. In gastric cancer patients, elevated IGF1R levels are associated with lymph node metastasis. In triple-negative breast cancer cells, studies have also shown that overexpression of IGF1R induces migration and invasive behavior through activation of the focal adhesion kinase (FAK) signaling cascade, which can be inhibited using pharmacological inhibitors of FAKs.[21] The occurrence and development of breast cancer are affected by insulin-like growth factor 1 (IGF1R) and insulin receptor (InsR) signals, which drive cancer phenotypes such as cell growth, proliferation, and migration. IGF1R and InsR form the IGF1R/InsR hybrid receptor (HybR), which consists of an IGF1R molecule and an InsR molecule. In view of the overexpression of HybR in breast cancer cell lines and tumors, in the future research direction of cancer, strategies to inhibit the action of IGF1 and insulin can consider blocking this form of the receptor, so as to control the occurrence and development of tumors.[22-24] In summary, considering the effect of the insulin/IGF pathway on the mechanism of cancer drug resistance, the regulation of this pathway may be an attractive strategy to reverse the resistance of various cancer treatments.

Insulin/IFF System and Aging

New research finds that from single-cell yeast to more complex mammals, insulin and IGF-I signaling pathways (IIS) play key roles in controlling biological aging.[25] IIS is the earliest sensing pathway affecting the aging process, which is highly conserved and most studied in different organisms. Although reducing insulin signaling in the central nervous system can prolong lifespan, IIS has been shown to have neuroprotective effects and is essential for the development and sur-

vival of neurons. Reduced insulin receptor signal in rat brain extends lifespan by 18%.[26]

Although lower species have only 1 insulin/IGF signaling, it is divided into 2 different hormonal pathways in mammals: growth hormone (GH)/IGF axis and glucose/insulin system. Bartke et al[27] proposed that during biological evolution, INS and IGF signals regulate pathways that affect carbohydrate metabolism. As a result, an anti-aging regulatory switch that switches between slowing metabolic pathways and GH/INS/IGF signals has been produced. Both pathways have similar functions and can interact. Delaying animal aging by disrupting GH/IGF signals may be due to the following mechanisms: inhibition of cell proliferation, reducing the risk of cancer; various favorable metabolic regulation; enhancing anti-stress capabilities; and reducing inflammation.[28-32] All of these mechanisms have a relevant role in the aging process. In particular, superficial chronic inflammation, known as "inflammation," is considered an important mechanism of aging and has been linked to the risk of multiple age-related diseases.[33] There is a positive correlation between telomere length and lifespan in different animal models.[34] IGF-1 inhibited cellular aging via Nrf2/Sirt3-dependent activation of mitophagy. Thus, activation of IGF-1 signaling is a novel potential strategy to activate mitophagy and slow cellular aging.[35] The mechanism of insulin resistance, serum IGF-I concentration, and telomere length in leukocytes is unknown. Recent research shows[36] that by using highly specific inhibitors to target GH/INS/IFF signaling, we may be able to develop new, effective, and side-effect-free treatments that can extend human life and health.

Concluding Remarks and Prospects

In summary, analyzing the complex signaling pathways mediated by the insulin/IGF system and clarifying its specific mechanism of action may help find a way to regulate the biological feedback between the insulin/IGF system and thus control the occurrence of related diseases and development. Targeting the signal-regulating network of the insulin/IGF system as a target may be a novel treatment for cancer, diabetes, and delaying aging. With the further development of more research, new mechanisms of insulin/IGF need to be discovered in the future, which will be beneficial to the early diagnosis of related diseases, condition evaluation, treatment monitoring, and prognosis evaluation, which have great clinical application value.

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