Insulin Resistance and Adipogenesis: Role of Transcription and Secreted Factors

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Abstract—Insulin stimulates carbohydrate uptake by cells and induces their conversion into lipids as a more efficient form of energy storage. Insulin resistance is associated with a decrease in glucose uptake by muscle and adipose cells and also with a decrease in glycogen synthesis on retention of glucose synthesis by liver cells. Disorders in the insulin signaling cascade on development of insulin resistance can be caused by both changes in functioning of transcriptional factors and in the secretion profile of hormone-like substances. Diacylglycerols and ceramides responsible for activation of some kinases and phosphatases can directly trigger these changes in muscle and liver cells. In adipose tissue, insulin mainly stimulates adipogenesis (adipocyte differentiation) and lipogenesis (lipid accumulation in the cells). Thus, studies on the action mechanisms of factors influencing adipogenesis can be of help for understanding the molecular mechanisms of insulin resistance.

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The frequency of such diseases as obesity, type II diabetes, and heart insufficiency is significantly increased in modern society. The development of these diseases can be caused by disorders in insulin sensitivity of systems responsible for synthesis and transport of glucose. Insulin resistance is the designation of a disturbed metabolic response to exogenous or endogenous insulin.

This disturbance is usually associated with increased levels of insulin and glucose in blood plasma. The increased concentration of insulin strengthens its influence on cell division and differentiation, protein synthesis, and lipid accumulation. The insulin-dependent increased blood concentration of glucose is associated with increased glycation and glycosylation of blood and vascular wall proteins, which leads to disorders in the system of blood circulation. Insulin-dependent systems of glucose transport are especially developed in the liver and in muscle and adipose tissues. Especially these tissues determine the glucose level in blood. We will consider mechanisms of insulin resistance in each of these tissues. But initially we will consider the molecular mechanisms of the action of insulin on cells and similarity and differences in the insulin signaling pathways in different tissues.

**SIGNALING PATHWAY OF INSULIN**

Insulin is a polypeptide with molecular weight of 5808 Da consisting of two polypeptide chains. The two insulin chains (A- and B-chains) contain, respectively, 21 and 30 amino acids and are connected with disulfide
bonds. The insulin molecule can bind with the insulin receptor (IR) and also with the insulin-like growth factor 1 receptor (IGF1R), each of which can phosphorylate a number of protein substrates, which in their turn can interact with regulatory subunits of phosphoinositide-3-kinase (PI3K) (Fig. 1) [1].

Upon binding with an insulin molecule, the receptor is autophosphorylated due to the presence of a tyrosine kinase catalytic domain [1]. As differentiated from other receptor tyrosine kinases, the insulin signaling cascade has additional mediators, such as insulin receptor protein substrates (IRS). The IRS are activated by tyrosine phosphorylation and inhibited by tyrosine phosphatases and serine phosphorylation. Moreover, their expression is regulated through ligands.

The activity of the insulin receptor is regulated very precisely because an increased or decreased activity can result in fatal metabolic consequences for the organism. This activity is regulated by proteins – tyrosine phosphatases, and among them protein tyrosine phosphatase 1B (PTP1B) is the best studied. This phosphatase directly interacts with the insulin receptor and dephosphorylates tyrosine residues, thus recovering the inactive state of the receptor [2-4]. Other proteins, such as SOCS1, SOCS3, or Grb10 decrease the function of the insulin receptor by sterically preventing its interaction with the IRS proteins or changing its kinase activity [5]. The insulin receptor can also lower its expression through a ligand-mediated internalization and degradation. This process occurs during the development of insulin resistance of cells [6].

At least 11 intracellular substrates of the insulin receptor and of the insulin-like growth factor receptor are now known. Six of these belong to the family of IRS-proteins and are called IRS1-IRS6 [7-10]. These proteins contain both pleckstrin-homologous domains (PH domains) and phosphotyrosine-binding domains (PTB domains), which determine the high affinity of these substrates for the insulin receptor.

The central and N-terminal parts of these proteins contain to 20 possible sites for tyrosine phosphorylation. Upon phosphorylation by the insulin receptor, these sites bind to proteins containing SH2 domains, e.g. with regulatory subunits of PI3K kinase or with SH2-containing phosphatases such as SHP-2 [11]. Dephosphorylation with these phosphatases can lower signal transduction from the receptor and is often observed under conditions of insulin resistance. Molecules of insulin receptor substrates can also be phosphorylated by serine residues, which inhibit their ability to transduce the receptor signal. This inhibitory mechanism has not been studied in detail. The substrate serine phosphorylation degree correlates with the degree of insulin resistance [12]. Insulin resistance can be also associated with the level of IRS expression: hyperinsulinemia was shown to lower the expression of IRS1 and IRS2 [13].

Despite a high degree of homology, different substrates of IRS compensate each other in their functions [14]. Thus, mice with Irs1 knockout display a defect in transduction of the insulin signal mainly in muscles, whereas in Irs2-knockout mice the signal transduction is difficult mainly in liver [15-17]. Irs1-knockout preadipocytes have difficulties in their differentiation to mature adipocytes, whereas the differentiation of Irs2-knockout cells is normal, although glucose transport in them is affected [18, 19]. Decrease in Irs1 expression in liver induces a decrease in expression of genes responsible for glucose synthesis but concurrently promotes an increase in the expression of genes related to lipogenesis [20].

PI3K kinase is a necessary link in the insulin signal cascade, and it forms PIP3 from PIP2 on plasma membranes of the cells. Regulatory subunits of PI3K bind with phosphorylated residues of IRS. On formation of heterodimers with the catalytic domain of the kinase, PI3K catalyzes the formation of PIP3 from PIP2 on plasma membranes of cells. Proteins containing PH-domains can bind with PIP3 and occur in the same region of the membranes, which is a prerequisite for their activation. PDK1, or serine-threonine kinase, is one of these proteins. This kinase phosphorylates AKT kinase on Thr308 [21] and PKCζ kinase on Thr410 [22], which increases their activities. To completely activate AKT kinase, it must be also phosphorylated on Ser473, but this cannot be catalyzed by PDK1 kinase. It can be catalyzed by the mTOR complex with its associated protein Rictor [23].

The activation of AKT kinase influences a number of crucially important processes in the cell (Fig. 2):