MOLECULAR MECHANISMS OF INSULIN RESISTANCE IN DIABETES

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Abstract: Molecular components of impaired insulin signaling pathway have emerged with growing interest to understand how the environment and genetic susceptibility combine to cause defects in this fundamental pathway that lead to insulin resistance. When insulin resistance is combined with β-cell defects in glucose-stimulated insulin secretion, impaired glucose tolerance, hyperglycemia, or Type 2 diabetes can result. The most common underlying cause is obesity, although primary insulin resistance in normal-weight individuals is also possible. The adipose tissue releases free fatty acids that contribute to insulin resistance and also acts as a relevant endocrine organ producing mediators (adipokines) that can modulate insulin signalling.

This chapter deals with the core elements promoting insulin resistance, associated with impaired insulin signalling pathway and adipocyte dysfunction. A detailed understanding of these basic pathophysiological mechanisms is critical for the development of novel therapeutic strategies to treat diabetes.

INTRODUCTION

The purpose of this chapter is to review the current understanding of molecular factors that cause the impaired insulin signaling pathway in Type 2 diabetes mellitus (T2DM). Diabetes mellitus (DM) is the most common endocrine disorder, currently affecting over 380 million people world-wide and prospectively over 365 million in the year 2030. It is rapidly emerging as one of the greatest global health challenges of the 21st century. T2DM is a complex disease characterized by a combination of
impaired insulin action, increased hepatic glucose production, and insulin secretory defects. Besides β-cell failure, the major pathophysiological event contributing to the development of T2DM is resistance of target tissues to insulin.

Normally, insulin lowers blood glucose levels by facilitating glucose uptake mainly into skeletal muscle and fat tissue and by inhibiting endogenous glucose production by the liver. In insulin resistant states, these organs do not properly respond to insulin, thereby causing hyperglycaemia and a reactive increase in insulin secretion by the pancreatic β cells. Clinically, the term “insulin resistance” implies that higher-than-normal concentrations of insulin are required to maintain normoglycemia. 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 multiple metabolic and mitogenic aspects of cellular function. The elevated insulin levels can compensate for the poor insulin response only for a limited period, but on the other hand impair insulin resistance. This vicious circle finally leads to disturbance of the fragile balance between β-cell function and peripheral insulin resistance which finally results in the clinical manifestation of T2DM.

Thus, insulin resistance is a major contributor to the pathogenesis of T2DM and plays a key role in associated metabolic abnormalities, such as dyslipidemia and hypertension. Indeed, insulin resistance is the initial measurable defect in patients who are destined to develop T2DM. Although the precise pathophysiological sequence which leads to insulin resistance is still largely unknown, recent studies have contributed to a deeper understanding of the underlying molecular mechanisms.

**INSULIN SIGNALING PATHWAY**

Insulin action involves a series of signaling cascades initiated by insulin binding to its receptor, eliciting receptor autophosphorylation and activation of the receptor tyrosine kinases, resulting in tyrosine phosphorylation of insulin receptor substrates (IRSs). Phosphorylation of IRSs leads to activation of phosphatidylinositol 3-kinase (PI3K) and, subsequently, to activation of Akt/protein kinase B (PKB) and atypical protein kinase Cλ and ζ, (PKCλ/ζ), each of which are serine/threonine kinases. Activated Akt phosphorylates its 160 kDa substrate (AS160), which stimulates the translocation of insulin-mediated Glut4 from intracellular vesicles to the plasma membrane (Fig. 1). However, the insulin receptor (IR) is also dephosphorylated and inactivated by protein tyrosine phosphatases (PTPs), which comprise an extensive family of proteins that exert negative effects on insulin action and glucose metabolism. In addition, phosphatase and tension homologue deleted on chromosome 10 (PTEN), a lipid phosphatase, serves as an important negative modulator for the insulin signaling pathway by hydrolyzing phosphatidylinositol 3,4,5-triphosphate to PIP2, antagonizing the PI3K pathway (Fig. 1). Thus, the physiological regulation of insulin action is controlled by the balance between phosphorylation and dephosphorylation (Fig. 1). Most importantly, the PI3K pathway is thought to be a key component of the insulin signaling cascade, which is necessary for the metabolic effects of insulin on glucose transport and Glu4 translocation. Indeed, insulin-stimulated PI3K activity decreases in skeletal muscle of T2DM subjects, providing evidence for a defect in insulin signaling that could contribute to impaired Glut4 translocation and insulin resistance.