Sci. Bull.
DOI 10.1007/s11434-016-1058-2

www.scibull.com
www.springer.com/scp

Review

Life & Medical Sciences

Adapter proteins regulate insulin resistance and lipid metabolism in obesity

Zheng Chen

Received: 20 November 2015 / Revised: 2 February 2016 / Accepted: 6 February 2016

Abstract Insulin resistance and dysregulated lipid metabolism are major causes of type 2 diabetes. Insulin and inflammatory signal pathways play key roles in insulin resistance and fat accumulation. Specifically, adapter proteins transduce signals from insulin or cytokine receptors to the downstream pathways and may contribute to insulin resistance and disordered lipid metabolism in obesity and type 2 diabetes. Here, the recent advances in understanding the roles of adapter proteins in insulin resistance and lipid homeostasis are discussed.

Keywords Adapter protein · Insulin resistance · Lipid metabolism · Inflammation · Obesity

1 Introduction

Obesity and type 2 diabetes are mainly derived from abnormal fat accumulation and insulin sensitivity. Insulin is a primary driver for fat accumulation [1]. During feeding, elevated blood glucose stimulates insulin secretion from pancreatic β cells. Insulin binds to the insulin receptor (IR) in the liver, muscle, and white adipose tissue (WAT), leading to the activation of downstream signaling pathways that function to increase glucose uptake, glycogen synthesis, lipogenesis, and adipogenic pathways [2]. Excess nutrients and higher circulating insulin levels will lead to increased fat accumulation, and ultimately obesity [1]. In obesity, cells cannot respond to insulin leading to an insulin resistant state. Meanwhile, cytokine expression is increased, causing chronic inflammation, which further exacerbates insulin resistance [3]. Therefore, insulin and inflammatory signal pathways play important roles in insulin resistance and lipid metabolism in the setting of obesity.

In insulin and inflammatory signaling pathways, adapter proteins are required to integrate insulin or cytokine receptor-mediated signals to intracellular effector systems [4]. Adapter proteins characteristically lack enzymatic or transcriptional activity, but contain several modular binding domains (e.g. SH2-, SH3-, PTB-, PH-, TRAF-, RING Finger-, SOCS-domains) or a tyrosine based signaling motif [5–7]. These functional domains are summarized in Table 1. Src homology 2 (SH2) domains are protein domains of about 100 amino-acid residues that recognize phosphotyrosine (pTyr) peptide motifs [6]. SH3 domains are small protein modules of about 50 amino acid residues which recognize proline-rich and hydrophobic amino acids [6]. The pTyr-binding (PTB) domains are protein modules of about 160 amino acids that bind to the Asn–Pro–Xaa–Tyr(p) motifs found in many tyrosine-phosphorylated proteins including insulin receptors [6]. Pleckstrin homology (PH) domains are small protein motifs of about 120 amino acids that bind to phosphatidylinositol lipids within biological membrane, and proteins such as protein kinase C (PKC) [6]. PH domains play a role in recruiting proteins to plasma membranes, allowing the transduction of signals to downstream effector systems [6]. Tumor necrosis factor receptor-associated factor (TRAF) domains are protein domains of about 150 amino acids that bind to the cytosolic domains of cytokine receptors, and to other TRAF proteins [5]. RING finger domains are protein domains containing a characteristic pattern of cysteines and histidines which mediate DNA binding, protein–protein interactions, and ubiquitin ligases [5] thereby contributing to the activation of downstream

SPECIAL TOPIC: Lipid Metabolism and Human Metabolic Disorder

Z. Chen (✉)
School of Life Sciences, Northeast Normal University, Changchun 130024, China
e-mail: chenz100@nenu.edu.cn

Published online: 09 May 2016

Table 1 Functional domains of adapter proteins

Domains	Biological functions
SH2	Recognizes phosphorylated tyrosine residues on other proteins
SH3	Recognizes proline-rich and hydrophobic amino acids
PTB	Bind to the Asn–Pro–Xaa–Tyr(p) motifs
PH	Binds to phosphatidylinositol lipids and proteins
TRAF	Binds to cytosolic domains of cytokine receptors
RING finger	Mediates DNA binding, protein–protein interaction, and ubiquitin ligases
SOCS	Mediates ubiquitination and degradation of targeted substrates
TIR	Mediates protein–protein interaction via homotypic TIR interactions
DD	Mediates protein–protein interaction homotypic DD interactions

signaling complexes. SH2-domain-containing proteins of the suppressor of cytokines signaling (SOCS) box domains are protein domains of about 50 amino acids which couple proteins to the ubiquitination or proteasomal compartments [7]. The Toll/interleukin-1 receptor (TIR) domain is a protein–protein interaction domain consisting of 125–200 amino acids [8]. The death domain (DD) is a protein–protein interaction domain containing six alpha-helices [9]. These domains enable adapter proteins to mediate constitutive or inducible protein–protein or protein–lipid interactions with other signaling complex components.

During the last 20 years, a variety of adapter proteins have been identified that mediate insulin signaling, obesity-induced chronic inflammation, and lipid metabolism (Table 2). Here, the recent advances of adapter proteins in insulin resistance and lipid metabolism are discussed.

2 Adapter proteins in insulin signaling pathway regulate insulin resistance and lipid metabolism

Insulin exerts its action by binding to IR on cell plasma membrane, which induces IR dimerization and tyrosine autophosphorylation on its intracellular β-subunit [2]. Phosphorylated tyrosine residues recruit different substrate adapter proteins such as insulin receptor substrate (IRS) proteins, Src homology 2 domain containing (SHC) transforming protein 1 (SHC1), growth factor receptor-bound (Grb), and SH2B proteins [10]. These adapter proteins mediate insulin signaling from IR to the downstream PI3Kinase/Akt. From biochemical, cellular, and transgenic animal studies, it has been demonstrated that these adapter proteins are associated with insulin resistance and lipid metabolism.

2.1 IRS proteins regulate insulin resistance and lipid metabolism

IRS proteins are key components of insulin signaling that couple IR activation to phosphoinositide 3-kinase (PI3K) signaling. IRS proteins contain PH and PTB domains, which are essential for signal transduction [10]. IRS proteins also have a variety of tyrosine phosphorylation residues, which are responsible for signal amplification by acting as docking sites for several effector proteins. Conversely, phosphorylation at serine residues of IRS proteins serve as inhibitory mechanisms, which account for insulin resistance [11]. Chronic hyperglycemia or hyperlipidemia, and several adipokines such as TNFα activate serine/thrine protein kinase such as JNK, IKK, PKC, which induce serine phosphorylation of IRS proteins and inhibit their tyrosine phosphorylation, leading to insulin resistance [3, 11]. Another major mechanism for insulin resistance is IRS proteasome degradation. Chronic hyperinsulinemia, a compensatory response to insulin resistance, is one of the factors that increases IRS proteasomal degradation [12]. Several E3 ubiquitin ligases (SOCS1/3, Fbw8, GSK3β, or MG53) target IRS protein for ubiquitination and degradation [13–15]. IRS proteins are major targets for nutrient and chronic inflammation induced insulin resistance.

IRS proteins contain at least six members (IRS1–6) [16]. Among these, IRS1 and IRS2 have been extensively studied. Deletion of either IRS1 or IRS2 causes insulin resistance and growth retardation in mice [17–19]. IRS1 deficient brown adipocytes show reduced cytosolic lipid content indicating that IRS1/PI3K/Akt signaling pathway is an essential requirement for lipid synthesis in brown adipocytes [20]. IRS1 deficiency reduces lipoprotein lipase activity [21], and increases lipolysis via increasing the expression of hormone-sensitive lipase (HSL) in white adipocytes [22], resulting in increased plasma TG level [21]. Liver-specific deletion of IRS1 and IRS2 reduces the expression of SREBP1c and SREBP2, and decreases lipogenesis in the liver, which leads to lower plasma TG and total cholesterol (TC) levels [23]. These data indicate that IRS proteins are key regulators for insulin resistance, lipid synthesis, lipolysis, and plasma TG and TC levels.