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REVIEW

SH2B1 regulation of energy balance, body weight, and glucose metabolism

Liangyou Rui

Liangyou Rui, Department of Molecular and Integrative Physiology, University of Michigan Medical School, Ann Arbor, MI 48109, United States
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Correspondence to: Liangyou Rui, PhD, Department of Molecular and Integrative Physiology, University of Michigan Medical School, 1137 Catherine Street, Ann Arbor, MI 48109, United States. ruily@umich.edu
Telephone: +1-734-6157544 Fax: +1-734-6479523
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Abstract

The Src homology 2B (SH2B) family members (SH2B1, SH2B2 and SH2B3) are adaptor signaling proteins containing characteristic SH2 and PH domains. SH2B1 (also called SH2-B and PSM) and SH2B2 (also called APS) are able to form homo- or hetero-dimers *via* their N-terminal dimerization domains. Their C-terminal SH2 domains bind to tyrosyl phosphorylated proteins, including Janus kinase 2 (JAK2), TrkA, insulin receptors, insulin-like growth factor-1 receptors, insulin receptor substrate-1 (IRS1), and IRS2. SH2B1 enhances leptin signaling by both stimulating JAK2 activity and assembling a JAK2/IRS1/2 signaling complex. SH2B1 promotes insulin signaling by both enhancing insulin receptor catalytic activity and protecting against dephosphorylation of IRS proteins. Accordingly, genetic deletion of SH2B1 results in severe leptin resistance, insulin resistance, hyperphagia, obesity, and type 2 diabetes in mice. Neuron-specific overexpression of SH2B1β transgenes protects against diet-induced obesity and insulin resistance. SH2B1 in pancreatic β cells promotes β cell expansion and insulin secretion to counteract insulin resistance in obesity. Moreover, numerous SH2B1 mutations are genetically linked to leptin resistance, insulin resistance, obesity, and type 2 diabetes in humans. Unlike SH2B1, SH2B2 and SH2B3 are not required for the maintenance of normal energy and glucose homeostasis. The metabolic function of the SH2B family is conserved from insects to humans.

Key words: Obesity; Type 2 diabetes; Leptin resistance; Insulin resistance; Glucose intolerance; Hypothalamus; Energy balance; Food intake; Hyperphagia; Nonalcoholic fatty liver disease

Core tip: The Src homology 2B (SH2B) family members mediate cell signaling in response to a variety of hormones, cytokines, and growth factors. In the brain, SH2B1 enhances leptin signaling and leptin's anti-obesity action. In peripheral tissues, SH2B1 cell-autonomously enhances insulin signaling. In pancreatic islets, SH2B1 is required for compensatory β cell expansion in response to insulin resistance and β cell stress. SH2B1-deficiency results in severe leptin resistance, energy imbalance, obesity, and type 2 diabetes. SH2B1 mutations are linked to leptin resistance, insulin resistance, obesity, and type 2 diabetes in humans. Thus, SH2B1 is a critical metabolic regulator in mammals.

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INTRODUCTION

The Src homology 2B (SH2B) family contains three members (SH2B1, SH2B2 and SH2B3) in mammals. All members contain a characteristic pleckstrin homology (PH) domain and SH2 domain. SH2B1 (also called SH2-B and PSM) was initially identified as a high affinity

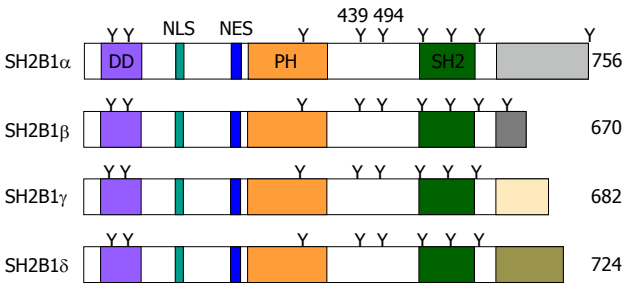

Figure 1 A schematic representation of SH2B1 isoforms. DD: Dimerization domain; PH: PH domain; SH2: SH2 domain; Y: Tyrosine; Numbers: Amino acid numbers.

immunoglobin E receptor (Fc RI) binding protein in the yeast tribrid screen in 1995[1]. SH2B2 (also called APS) was identified as a c-Kit-binding protein by the yeast two-hybrid system in 1997[2]. SH2B3 (also called Lnk) was identified as a SH2 domain-containing, tyrosyl phosphorylated protein in rat lymph node lymphocytes in 1995[3]. The SH2B family is evolutionarily conserved from insects through humans. Unlike mammals, insects have only one *SH2B* gene (also called Lnk)[4,5]. Deletion of SH2B1, but not SH2B2 or SH2B3, results in obesity and metabolic diseases in mice, whereas deletion of either SH2B2 or SH2B3, but not SH2B1, impairs immune function[6-11]. Therefore, individual SH2B1 family members have distinct function in mammals. In this review, I will mainly discuss mammalian SH2B1 and SH2B2.

METABOLIC FUNCTION OF SH2B1

Structure, subcellular localization, posttranslational modification, and tissue distribution of SH2B1

The *SH2B1* gene generates four SH2B1 isoforms (α, β, γ, and δ) through mRNA alternative splicing[1,12-14]. All isoforms have an identical N-terminal region (amino acids 1-632), but differ at their C-termini after the SH2 domain (Figure 1).

SH2B1 structure: All four isoforms have identical dimerization (DD), PH, and SH2 domains (Figure 1). The DD domain mediates SH2B1 homodimerization or its heterodimerization with SH2B2[15-17]. The SH2 domain binds to the phospho-tyrosine motifs of its binding partners (*e.g.*, JAK2 and insulin receptors)[12,18]. The function of the central PH domain remains unclear.

SH2B1 subcellular localization: SH2B1 is located mainly in the cytoplasm, but a subset shuttles between the cytoplasm and the nucleus[19]. SH2B1 contains a nuclear localization sequence (NLS) (KLK^{150}KR) which is required for its nuclear translocation[20]. SH2B1 also contains a nuclear export sequence (NES) (GERWTHRFERL^{231}RLSR) (Figure 1), and replacement of the conserved Leu^{231} and Leu^{233} with Ala increases its nuclear localization[19]. SH2 domain-defective SH2B1β(*R555E*) mutant is also excluded from the nucleus[20]. Therefore, the NLS, NES, and SH2 domain all are involved in the regulation of SH2B1 trafficking between the cytoplasmic and nuclear compartments. SH2B1 is also translocated to the plasma membrane[21]. A N-terminal polybasic region (S^{145}KPKLKKRF), which overlaps the NLS, is required, but not sufficient, for SH2B1β translocation to the plasma membrane[22].

SH2B1 posttranslational modification: SH2B1α and SH2B1β contain nine Tyr residues, and SH2B1γ and SH2B1δ have eight (Figure 1). Tyr^{439} and Tyr^{494} are conserved in all four isoforms, and are able to be phosphorylated by JAK1 and JAK2[23]. Src tyrosine kinases also phosphorylate all four isoforms[24]. Additionally, insulin, insulin-like growth factor (IGF-1), and nerve growth factor (NGF) also stimulate tyrosine phosphorylation of SH2B1 *via* their cognate receptor tyrosine kinases[14,18,25].

SH2B1 contains numerous Ser and Thr residues. NGF stimulates SH2B1 phosphorylation on multiple Ser/Thr residues[21]. Mitogen-activated protein kinase (MAPK) directly phosphorylates Ser^{96}[21], and protein kinase C phosphorylates both Ser^{161} and Ser^{165} residues[22,26]. However, the physiological consequence of SH2B1 phosphorylation remains unknown.

SH2B1 tissue distribution: SH2B1 is ubiquitously expressed in both peripheral tissues and the central nervous system, including adipose tissue, skeletal muscle, liver, pancreas, heart, spleen, hypothalamus, and other brain areas[27]. SH2B1 expression is regulated by neuronal, hormonal, and nutritional signals. The mRNA levels of hypothalamic SH2B1 are 20-fold higher in fed mice than in fasted mice[28]. The expression of hypothalamic SH2B1 in rats is downregulated by high fat diet (HFD) feeding[29]. Chronic overexpression of bovine growth hormone (GH) increases the levels of hepatic SH2B1 protein in GH transgenic mice[30]. The molecular steps, which control the activity of the SH2B1 promoter and the stability of SH2B1 mRNA and protein, remain completely unknown.

SH2B1 regulates cell signaling in response to multiple hormones, growth factors, and cytokines

In cultured cells, SH2B1 acts as an adaptor to couple upstream activators to downstream effectors, to assemble a multiple-protein signaling complex, and/or to enhance the catalytic activity of its bound enzymes.

SH2B1 mediates/modulates leptin signaling: Leptin is an adipose hormone identified by Friedman and his colleagues using positional cloning[31]. Leptin deficiency results in morbid obesity in *ob/ob* mice[31], and recombinant leptin fully corrects obesity and metabolic disorders in *ob/ob* mice[32-34]. Leptin exerts its biological action by binding to and activating its long form receptors (called LEPRb)[35-38]. LEPRb binds to JAK2, a cytoplasmic tyrosine kinase which also mediates GH, prolactin, erythropoietin (EPO), and other cytokine signaling[39,40]. Leptin stimulates tyrosine phosphorylation and activation of JAK2 which activates multiple downstream signaling

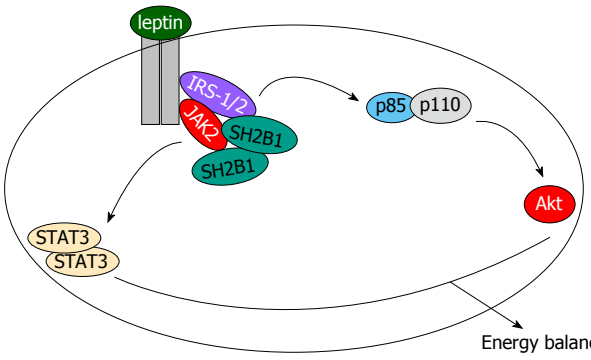

Figure 2 A model of Src homology 2B1 regulation of leptin signaling. The Src homology 2B1 (SH2B1) homodimers bind to JAK2, IRS1, and/or IRS2. SH2B1-JAK2 interaction increases JAK2 kinase activity, thus globally enhancing leptin signaling. JAK2 phosphorylates STAT3 which subsequently homodimerizes, translocates into the nucleus, and activates its target genes. SH2B1-IRS1/2 interaction allows JAK2 to phosphorylate IRS proteins which subsequently activate the PI 3-kinase pathway. Both the STAT3 and the PI 3-kinase pathways are required for leptin to control energy balance and body weight. JAK2: Janus kinase 2; IRS1: Insulin receptor substrate-1; STAT3: Signal transducer and activator of transcription 3.

pathways, including the signal transducer and activator of transcription 3 (STAT3) and the PI 3-kinase pathways[39,40]. Both the STAT3 and the PI 3-kinase pathways are required for leptin's anti-obesity action[39,40]. Impaired leptin signaling and action (leptin resistance) are believed to be the primary risk factor for obesity[39,40].

We reported that leptin stimulates activation of JAK2 which subsequently autophosphorylates on Tyr^{813}[41]. SH2B1 binds *via* its SH2 domain to phospho-Tyr^{813}[41]. This physical interaction markedly increases JAK2 catalytic activity, thus enhancing activation of leptin signaling pathways downstream of JAK2[41-43]. In agreement, leptin-stimulated activation of hypothalamic JAK2 is dramatically attenuated in SH2B1 knockout mice[10]. Leptin sensitivity has been well documented to be negatively regulated by protein tyrosine phosphatase 1B (PTP1B) and SOCS3[39,40]. Overexpression of SH2B1 reverses PTP1B-induced inhibition of leptin stimulation of tyrosine phosphorylation of STAT3[10]. Therefore, cellular leptin sensitivity is likely to be determined, at least in part, by the ability of endogenous SH2B1 to counteract negative regulators such as PTP1B and SOCS3.

Leptin stimulates tyrosine phosphorylation of insulin receptor substrate-1 (IRS1) and IRS2, and IRS proteins subsequently bind to the p85 regulatory submit of PI 3-kinase and activate the PI 3-kinase pathway[39,40,44]. Genetic deletion of IRS2 in LEPR-expressing cells results in leptin resistance and obesity in mice[45]. SH2B1 directly binds to both IRS1 and IRS2 in addition to JAK2[46]. In response to leptin, SH2B1 recruits IRS proteins to JAK2, thus allowing JAK2 to phosphorylate IRS proteins on tyrosine residues[46]. Accordingly, in SH2B1 knockout mice, leptin is unable to stimulate tyrosine phosphorylation of hypothalamic IRS2[10]. SH2B1 is likely to mediate leptin stimulation of the PI 3-kinase pathway by coupling JAK2 to IRS proteins (Figure 2).

SH2B1 C-terminal SH2 domain binds to phospho-Tyr^{813} in JAK2 as discussed above; in contrast, its N-terminal region binds to different sites on JAK2 in a tyrosine phosphorylation-independent manner[43]. Similarly, SH2B1 binds to phospho-tyrosine(s) of IRS1 or IRS2 *via* its SH2 domain, and binds to other sites on IRS proteins *via* its PH domain-containing regions in a tyrosine phosphorylation-independent fashion[46]. SH2B1 forms homodimers or oligomers *via* its N-terminal domains[15-17]. Each individual SH2B1 molecule is able to bind to JAK2 and/or IRS proteins; therefore, SH2B1 dimers or oligomers are predicted to assemble a large signaling complex containing multiple copies of JAK2 and IRS proteins (Figure 2). Physical proximity allows JAK2 to transphosphorylate and activate each other in this complex, contributing to SH2B1 stimulation of JAK2 activation and leptin signaling. Additionally, this highly-organized SH2B1/JAK2/IRS complex may also provide a permissive condition for JAK2 to efficiently phosphorylate IRS proteins and activate the PI 3-kinase pathway in response to leptin.

SH2B1 enhances insulin and IGF-1 signaling: SH2B1 was reported to bind to insulin receptors (IRs) *via* its SH2 domain[18]. Insulin stimulates the binding of SH2B1α to phospho-Tyr^{1158}, Tyr^{1162} and/or Tyr^{1163} within the IR activation loop, and IRs subsequently tyrosyl phosphorylate SH2B1α[13,47]. Overexpression of SH2B1β markedly enhances the ability of insulin to stimulate tyrosine phosphorylation of IRS1 and IRS2[9]. In contrast, SH2B1β(R555E), which has a defective SH2 domain, acts as a dominant negative mutant to inhibit insulin signaling[9]. Moreover, deletion of SH2B1 impairs insulin signaling in the skeletal muscle, adipose tissue, and livers of SH2B1 knockout mice[9].

Mechanistically, SH2B1-IR interaction markedly increases IR catalytic activity and IR-mediated tyrosine phosphorylation of IRS proteins[48]. Replacement of IR Tyr^{1158} with Phe disrupts IR binding to SH2B1, and completely blocks the ability of SH2B1β to stimulate IR kinase activity[48]. SH2B1α similarly increases IR catalytic activity[49]. Additionally, SH2B1β directly binds to tyrosyl phosphorylated IRS1 and IRS2 and protects IRS proteins against dephosphoarylation, thus prolonging the ability of IRS proteins to activate their downstream pathways[48]. Accordingly, overexpression of SH2B1α delays dephosphorylation of IRS proteins in cells[50]. SH2B1 homodimers and oligomers are predicted to simultaneously bind to both IRs and IRS proteins and assemble a large, highly-organized signaling complex, thereby increasing insulin signaling specificity and efficiency.

SH2B1 also binds *via* its SH2 domain to IGF-1 receptors[14], and is predicted to promote IGF-1 signaling in a similar fashion.

SH2B1 enhances TrkA, TrkB and TrkC signaling: Amino acid sequence analysis reveals that like IRs, Trk family members (TrkA, TrkB and TrkC) contain potential SH2B1-binding site(s) within their activation loops. NGF

stimulates both the binding of SH2B1 to NGF receptor TrkA and phosphorylation of SH2B1 on Tyr/Ser/Thr residues in PC12 cells[21,25]. NGF also stimulates the binding of TrkA to both SH2B1 and SH2B2 in primary neurons[51]. SH2B1-TrkA interaction is mediated by the SH2 domain of SH2B1 and phospho-Tyr^{679}, -Tyr^{683} and/or -Tyr^{684} within TrkA activation loop[21,25,51]. Additionally, SH2B1α binds *via* its proline rich regions (amino acids 394-504 between the PH and SH2 domains) to Grb2, contributing to NGF-stimulated activation of the MAPK pathway[51]. Overexpression of SH2B1β also enhances NGF-stimulated activation of Akt in PC12 cells[52].

Brain-derived neurotrophic factor (BDNF) or neurotrophin-3 (NT-3) similarly stimulates the binding of SH2B1 to TrkB or TrkC, respectively, and they also stimulate tyrosine phosphorylation of SH2B1[51,53,54]. Unlike JAK2 and IRs, TrkB kinase activity is not enhanced by SH2B1[53].

SH2B1 regulates GH, prolactin, and EPO signaling: JAK2 binds to GH receptors and mediates GH signaling[55]. GH stimulates the binding of SH2B1 to JAK2 and robust tyrosine phosphorylation of SH2B1 by JAK2 in 3T3-F442A fibroblasts[12]. GH stimulates JAK2-mediated phosphorylation of SH2B1 on Tyr^{439} and Tyr^{494} residues[56]. Like leptin, GH stimulates phosphorylation of JAK2 on Tyr^{813} which binds to the SH2 domain of SH2B1[57]. SH2 domain-phospho-Tyr^{813} interaction markedly increases JAK2 activity, thus enhancing GH signaling (*e.g.*, phosphorylation and activation of STAT5B)[42,43].

JAK2 also mediates prolactin signaling[58]. Like GH, prolactin stimulates tyrosine phosphorylation of SH2B1[59]. Overexpression of SH2B1β enhances prolactin signaling, including tyrosine phosphorylation of JAK2[59].

Unlike GH, EPO stimulates the binding of SH2B1 to EPO receptors rather than to JAK2[60]. SH2B1 constitutively binds to unphosphorylated EPO receptors under basal conditions, and EPO stimulates phosphorylation of EPO receptors on Tyr^{343} and Tyr^{401} which subsequently bind to the SH2 domain of SH2B1[60]. EPO rapidly stimulates phosphorylation of SH2B1 on Ser/Thr residues[60]. Knockdown of SH2B1 increases EPO-stimulated tyrosine phosphorylation of EPO receptors, JAK2, and ERK1/2, raising the possibility that SH2B1 may negatively regulate EPO signaling[60].

SH2B1 binds to JAK1, JAK2 and JAK3, but it only stimulates JAK2, but not JAK1 and JAK3, kinase activity[61]. Both JAK1 and JAK2 are able to phosphorylate SH2B1 on Tyr^{439} and Tyr^{494}, but Tyr^{439}/Tyr^{494} phosphorylation does not affect the ability of SH2B1 to stimulate JAK2[23]. The JAK family members mediate cell signaling and action in response to numerous hormones and cytokines in addition to GH, prolactin, and EPO, so it is conceivable that SH2B1 may mediate or modulate cellular responses to these hormones and cytokines through interacting with JAK family members.

SH2B1 regulates additional receptor tyrosine kinase signaling: SH2B1 binds *via* its SH2 domain to tyrosyl phosphorylated platelet-derived growth factor (PDGF) receptors in response to PDGF-BB stimulation[62]. PDGF-BB stimulates phosphorylation of SH2B1 on Tyr/Ser/Thr residues[62]. PDGF-BB is able to stimulate tyrosine phosphorylation of all four isoforms of SH2B1[14]. PDGF receptors directly phosphorylate SH2B1 on Tyr^{439} residue[23].

Glial cell line-derived neurotrophic factor (GDNF) stimulates the binding of SH2B1β to GDNF receptor RET through SH2B1β SH2 domain and RET phospho-Tyr^{981} motifs[63,64]. This interaction increases RET kinase activity, RET autophosphorylation, and RET-mediated tyrosine phosphorylation of STAT3[64].

SH2B1 directly interacts with fibroblast growth factor receptor 3 (FGFR3) and is tyrosyl phosphorylated by FGFR3[65]. The SH2 domain of SH2B1 binds to phospho-Tyr^{724} and phospho-Tyr^{760} of FGFR3, and the interaction increases the ability of FGFR3 to phosphorylate and activate STAT5[65].

SH2B1 regulates multiple cellular responses

In cultured cells, SH2B1 has been demonstrated to regulate multiple cellular processes, including migration, proliferation, and differentiation.

SH2B1 regulates actin cytoskeletal reorganization and cell motility: SH2B1 is able to regulate cell morphology, adhesion, and motility through modifying actin cytoskeletal reorganization in cultured cells. SH2B1β is detected in membrane ruffles, filopodia, and focal adhesions[26,59], and is colocalizated with filamentous actin (F-actin) in membrane ruffles[66]. SH2B1β binds *via* both its N-terminal (amino acids 150-200) and C-terminal regions (amino acids 615-670) to F-actin, and promotes actin filament cross-link[59]. SH2B1 directly binds *via* its amino acids 200-260 to the actin-binding protein filamin A[67]. Additionally, SH2B1 binds *via* its amino acids 85-106 to Rac, a critical regulator of actin cytoskeletal reorganization[68].

SH2B1 mediates GH regulation of cell adhesion and migration. GH increases the cycling of SH2B1 into and out of focal adhesions[26], and promotes SH2B1 colocalization with F-actin in membrane ruffles[66]. Overexpression of SH2B1β, but not SH2 domain-defective SH2B1β(R555E), enhances the ability of GH to stimulate both membrane ruffles in 3T3-F442A fibroblasts[59,66] and macrophage migration[56]. In fact, SH2B1β(R555E) blocks GH-induced lamellipodia dynamics in 3T3-F442A cells[68]. Both the N-terminal region (amino acids 85-106) and the SH2 domain of SH2B1β are required for GH stimulation of cell motility[68]. Additionally, SH2B1β mutants lacking Tyr^{439} and Tyr^{494} phosphorylation sites are unable to enhance GH-stimulated membrane ruffling in 3T3-F442A fibroblasts[23] and GH-stimulated motility of RAW264.7 macrophages[56]. SH2B1-Rac interaction is involved in mediating GH-promoted actin cytoskeletal reorganization and cell motility[68].

Overexpression of SH2B1β similarly enhances prolactin-stimulated membrane ruffling[59]. SH2B1 directly binds to filamin A, which appears to mediate prolactin stimulation of membrane ruffling and cell motility[67].

SH2B1 promotes neuronal survival and neuronal differentiation: Overexpression of SH2B1β markedly enhances the ability of NGF to stimulate neurite outgrowth in PC12 cells[25], and both SH2B1α and SH2B2 are able to promote NGF/TrkA-induced neuronal differentiation[51]. In contrast, overexpression of SH2 domain-defective SH2B1(R555E) blocks NGF-induced neuronal differentiation of PC12 cells[25]. SH2B1β mutants lacking either the NES or the NLS also are unable to enhance NGF-induced neuronal differentiation[19,20]. Overexpression of a N-terminal (amino acids 1-499) truncated SH2B1 mutant, which lacks both NES and NLS, induces axon degeneration in NGF-treated primary sympathetic neurons[51]. Moreover, neutralization of endogenous SH2B1 with anti-SH2B1 antibody decreases the survival of primary sympathetic neurons[51]. These observations suggest that the SH2 domain, NES, and NLS all are required for SH2B1 to mediate NGF stimulation of neuronal differentiation and survival.

SH2B1β also enhances GDNF/RET-induced neuronal differentiation of PC12 cells[63,64]. However, the molecular mechanisms, by which SH2B1 promotes neuronal survival, differentiation, and neurite outgrowth, remain largely unknown.

SH2B1 promotes mitogenesis and transformation: All four SH2B1 isoforms are able to increase the mitogenic response to epidermal growth factor, IGF-1, and PDGF-BB[14,69]. SH2B1 increases the ability of RET to promote transformation of NIH 3T3 cells[64]. SH2B1 is abnormally expressed in non-small cell lung cancer (NSCLC) tissues and NSCLC cell lines[70]. SH2B1 overexpression is associated with increased tumor grade, tumor size, lymph node metastasis in NSCLC patients[70].

Neuronal SH2B1 regulates body weight and nutrient metabolism in mice

We reported that genetic deletion of SH2B1 results in severe obesity and type 2 diabetes in mice[9,10].

Central SH2B1 regulates energy balance and body weight: We disrupt the *SH2B1* gene to generate SH2B1 knockout (KO) mice by DNA homologous recombination[9]. Exons 1-6, which encode the N-terminal region of all four isoforms of SH2B1, are replaced by a neo cassette[9]. SH2B1-null mice are hyperphagic and morbidly obese[10]. Both *SH2B1* KO males and females gain more body weights than wild type (WT) littermates after 7 wk of age[10,71]. White adipose tissue mass and fat content are much higher in *SH2B1* KO mice in either C57BL/6 or 129Sv/C57BL mixed congenic background, and the size of individual white adipocytes is also larger in *SH2B1* KO mice[10].

SH2B1 KO mice are extremely hyperphagic, causing obesity[10]. Surprisingly, energy expenditure, as estimated by O_2 consumption and CO_2 production, is also higher in *SH2B1* KO mice than in WT littermates[10]. Accordingly, in the pair-feeding paradigm in which each individually-housed mouse is fed the identical amount of food daily, *SH2B1* KO mice gain less body weights and become leaner than WT littermates[10].

Food intake is controlled largely by the brain, particularly the hypothalamus[72], so we generate SH2B1 transgenic (Tg) mice in which a rat SH2B1β transgene is expressed specifically in neurons under the control of neuron-specific enolase promoter[27]. SH2B1β Tg mice are crossed with *SH2B1* KO mice to generate TgKO mice which lack endogenous SH2B1 in all cell types but express recombinant SH2B1β specifically in neurons[27]. Neuron-specific restoration of SH2B1β into *SH2B1* KO mice fully rescues the hyperphagic and obese phenotypes in TgKO mice[27]. Energy expenditure, which is abnormally higher in *SH2B1* KO mice, is normal in TgKO mice[27]. Furthermore, SH2B1β Tg mice, which contain homozygous SH2B1β transgenes and overexpress recombinant SH2B1β in the brain, resist HFD-induced obesity[27]. These observations indicate that central SH2B1 is a key regulator of energy balance and body weight. Multiple brain areas and neural circuits are involved in the control of energy metabolism and body weight[72]; however, SH2B1 target neural circuits remain unknown.

Surprisingly, Ohtsuka *et al*[11] reported that disruption of SH2B1 did not cause obesity, insulin resistance, and glucose intolerance; however, their subsequent studies show that their *SH2B1* KO mice indeed display insulin resistance and glucose intolerance as we observed in our *SH2B1* KO mice[9,73]. Since *SH2B1* KO mice have high energy expenditure[10], a slight disturbance of food intake is expected to lead to reduction in body weight. Thus, variations in house conditions and other environmental factors may contribute to body weight discrepancy between these studies.

SH2B1 KO mice have relatively normal somatic growth, indicating that SH2B1 is not required for GH stimulation of body growth[9,11,71]. Nonetheless, it is still possible that SH2B1 may modulate GH regulation of metabolism and/or other physiological processes.

Central SH2B1 regulates glucose and lipid metabolism: Obesity is the primary risk factor for insulin resistance and type 2 diabetes[39]. As expected, obese *SH2B1* KO mice develop hyperglycemia, hyperinsulinemia, glucose intolerance, and insulin resistance[9,71]. Insulin signaling is impaired in the skeletal muscle, adipose tissue, and livers of *SH2B1* KO mice[9]. *SH2B1* KO male mice display frank type 2 diabetes after 7 mo of age[9]. Moreover, *SH2B1* haploinsuffiency predisposes to HFD-induced insulin resistance[9]. *SH2B1* KO mice develop the symptoms of metabolic syndrome, including hyperlipidemia, hepatic steatosis, and lipid accumulation in skeletal mus-

cle[10]. Moreover, neuron-specific restoration of SH2B1β reveres obesity, type 2 diabetes, and metabolic syndrome in TgKO mice[27]. These observations indicate that central SH2B1 is absolutely required for the maintenance of normal glucose and lipid homeostasis in mice.

Central insulin and leptin are able to regulate systemic glucose and lipid metabolism independently of their action on energy balance and body weight[39,40,74-77]. SH2B1 positively regulates both leptin and insulin signaling, so central SH2B1 may regulate peripheral glucose and lipid metabolism independently of its action on energy balance and body weight.

Central SH2B1 positively regulates hypothalamic leptin sensitivity: Central SH2B1 controls food intake and body weight at least in part by enhancing leptin sensitivity in the brain. SH2B1 cell-autonomously enhances leptin signaling by promoting JAK2 activity and activation of pathways downstream of JAK2[41]. SH2B1 also mediates leptin-stimulated activation of the PI 3-kinase pathway by binding to IRS1/2 and recruiting IRS proteins to JAK2[46]. *SH2B1* KO mice display severe hyperleptinemia, a hallmark of leptin resistance[10]. Hyperleptinemia develops prior to the onset of obesity, suggesting that leptin resistance is a causal factor for obesity progression in *SH2B1* KO mice[10]. In agreement, exogenous leptin is unable to suppress food intake and weight gain in *SH2B1* KO mice, and has reduced ability to stimulate phosphorylation of hypothalamic JAK2, STAT3 and IRS2 in these mice[10]. Furthermore, neuron-specific expression of recombinant SH2B1β in SH2B1-null mice reverses hyperleptinemia, leptin resistance, hyperphagia, and obesity in TgKO mice[27]. However, neuron-specific expression of SH2B1β(R555E) is unable to rescue leptin resistant, hyperphagic, and obese phenotypes in SH2B1-null mice[78], suggesting that the SH2 domain of SH2B1 is required for its anti-obesity action. Like *SH2B1* KO mice, SH2B1β(R555E) transgenic mice develop obesity, insulin resistance, hyperglycemia, and glucose intolerance[78], suggesting that SH2B1β(R555E) blocks the action of endogenous SH2B1 as a dominant negative mutant.

Orexigenic agouti-related protein (AgRP) neurons and anorexigenic proopiomelanocortin (POMC) neurons in the arcuate nucleus are key leptin targets[39]. Leptin suppresses the expression of AgRP and neuropeptide Y (NPY) but stimulates POMC expression[72]. The expression of hypothalamic AgRP and NPY is higher in *SH2B1* KO mice[10], and neuron-specific expression of SH2B1β in *SH2B1* KO mice normalizes AgRP and NPY expression[27]. By contrast, the expression of hypothalamic POMC is normal in *SH2B1* KO mice[10]. Since *SH2B1* KO mice develop severe hyperleptinemia[10], leptin-stimulated expression of POMC may still be impaired in SH2B1-null mice.

Leptin promotes energy expenditure[39]; therefore, increased energy expenditure in *SH2B1* KO mice cannot be explained by leptin resistance. It is likely that central SH2B1 regulates energy metabolism by an additional leptin-independent mechanism. SH2B1 is able to mediate or modulate cell signaling in response to multiple factors as described above. These pathways may be involved in central regulation of energy balance and body weight. For instance, SH2B1 enhances BDNF signaling[51,54]. Central administration of BDNF suppresses food intake and weight gain; conversely, haploinsufficiency of BDNF or TrkB leads to hyperphagia and obesity in mice[79-83]. Mutations in either BDNF or TrkB are associated with obesity in humans[82,84]. Therefore, neuronal SH2B1 may regulate energy metabolism and body weight by enhancing TrkB signaling in addition to LEPRb signaling in the brain.

Peripheral SH2B1 regulates glucose and lipid metabolism in mice

SH2B1 is expressed in both central and peripheral tissues[27], and peripheral SH2B1 also regulates nutrient metabolism.

Peripheral SH2B1 regulates insulin sensitivity and glucose metabolism: TgKO mice, which lack endogenous SH2B1 in all tissues but express SH2B1β transgenes in the brain, have relatively normal blood glucose, plasma insulin, and glucose tolerance[27]. These observations suggest that peripheral SH2B1 is not required for the maintenance of insulin sensitivity and glucose metabolism in mice fed a normal chow diet. We feed TgKO mice a HFD for 16 wk to induce metabolic stress. TgKO mice develop more severe HFD-induced hyperglycemia, hyperinsulinemia, insulin resistance, and glucose intolerance, even though they have similar body weight and fat content as WT mice[48]. Insulin signaling in skeletal muscle, adipose tissue, and the liver is impaired to a greater extent in HFD-fed TgKO mice[48], and these mice display more severe hepatic steatosis[85]. Thus, peripheral SH2B1 promotes insulin signaling and glucose and lipid metabolism under obesity conditions.

SH2B1 in pancreatic β cells promotes β cell expansion and insulin secretion: Pancreatic β cells express high levels of several SH2B1 isoforms[86]. To examine the role of β cell SH2B1, we generate pancreas-specific *SH2B1* KO (PKO) mice, using the *Pdx1-cre*/loxp system[86]. PKO mice have normal body weight, blood glucose, insulin sensitivity, and glucose tolerance; however, they develop more severe HFD-induced glucose intolerance[86]. Pancreatic insulin content, β cell mass, and glucose-stimulated insulin secretion are significantly lower in PKO than control mice fed a HFD, and PKO islets have more apoptotic cells and less mitotic cells[86]. These observations indicate that SH2B1 in β cells is required for HFD-induced compensatory β cell expansion to counteract insulin resistance in obesity.

SH2B1 appears to directly promote β cell expansion by both promoting proliferation and inhibiting apoptosis[86]. In a rat INS-1 832/13 β cell line, silencing of SH2B1 decreases, whereas overexpression of SH2B1β

increases, β cell toxin streptozotocin (STZ)-induced apoptosis[86]. In line with these findings, PKO mice are more susceptible to STZ-induced β cell destruction, insulin deficiency, and glucose intolerance[86]. Mechanistically, SH2B1 directly enhances insulin and IGF-1 signaling in β cells[86], and both insulin and IGF-1 potently increase β cell survival and proliferation[87-91]. Therefore, β cell SH2B1 cell-autonomously promotes β cell survival, proliferation, and expansion under stress conditions at least in part by enhancing insulin and IGF-1 signaling in β cells.

Hepatic SH2B1 regulates liver triacylglycerol content and very low-density lipoprotein secretion: SH2B1 is also highly expressed in the liver[27], so we generate hepatocyte-specific *SH2B1* KO (HKO) mice using the *albumin-cre*/loxP system[85]. Surprisingly, somatic growth, body weight, insulin sensitivity, and glucose metabolism are similar between HKO and control mice fed either a normal chow diet or a HFD[85]. Adult-onset deletion of SH2B1 in the liver also does not alter insulin sensitivity and glucose metabolism in mice fed a HFD[85]. These data indicate that hepatic SH2B1 is dispensable for the maintenance of systemic insulin sensitivity and glucose metabolism in mice. However, adult-onset deletion of liver SH2B1 decreases liver triacylglycerol content in mice fed a HFD[85], suggesting that hepatic SH2B1 regulates hepatocyte lipid metabolism. Liver-specific deletion of SH2B1 alone does not alter very low-density lipoprotein (VLDL) secretion; however, deletion of liver SH2B1 in SH2B2 knockout mice decreases VLDL secretion[85]. These observations suggest that liver SH2B1 and SH2B2 act redundantly to promote VLDL secretion.

SH2B1 regulates reproduction in mice

SH2B1 is highly expressed in testes and ovaries, and systemic deletion of SH2B1 severely impairs fertility in both male and female mice[11]. Ovary size and follicle number are lower in *SH2B1* KO females; similarly, testis size and sperm number are also lower in *SH2B1* KO males[11]. SH2B1 deficiency impairs both follicle-stimulating hormone and IGF-1 signal transduction in ovaries, which may contribute to impaired fertility in *SH2B1* KO mice[11].

Metabolic function of SH2B1 in humans

SH2B1 rs7498665, the first human *SH2B1* single nucleotide polymorphism (SNP), was reported in 2007[92]. It is associated with hyperleptinemia, increased body weight, increased total fat, and increased waist circumference in a United Kingdom white female cohort[92].

Human SH2B1 is a candidate obesity gene: In 2009, two groups independently reported that *SH2B1* rs7498665 is genetically linked to human obesity in genome-wide association studies (GWAS) on large populations[93,94]. Since then, *SH2B1* rs7498665 has been reported to be associated with human obesity in Swedish adults[95], Belgian adults[96], children of European ancestry[97], Chinese women[98], Hong Kong Chinese[99], Japanese adults[100], the MONIKA/KORA cohort[101], a Mexican cohort[102], and a African-American cohort[103]. *SH2B1* rs7498665 risk allele is associated with increased visceral adiposity in Japanese[104] and German[105]. *SH2B1* rs7498665 is also associated with increased fat intake in Dutch females[106].

Several additional *SH2B1* SNPs have been described since 2009. In GWAS, *SH2B1* rs7359397 is associated with obesity in 249796 adult individuals of European ancestry[107] and in Danish adults[108]. *SH2B1* rs4788102 is associated with obesity in Chinese girls[109] and in Japanese populations[100]. *SH2B1* rs4788099 is associated with increased body mass index (BMI) in individuals of European ancestry[110], and is linked to more servings of dairy products[111]. *SH2B1* rs8055982 is associated with severe obesity in children of European ancestry[97].

Aside from *SH2B1* SNPs, chromosomal 16p11.2 deletion is associated with severe obesity in European cohorts[112-115]. The deleted region contains the *SH2B1* gene. In contrast, chromosomal 16p11.2 duplication is associated with underweight in humans[116].

Several *SH2B1* non-synonymous variants have been identified. *SH2B1* rs7498665 risk allele encodes a non-synonymous substitution of Thr484Ala[92]. However, Thr484Ala substitution alone is not sufficient to cause obesity[117], raising the possibility that other unidentified *SH2B1* mutations, which co-segregate with rs7498665, may increase risk for obesity. Several *SH2B1* missense mutations (P90H, T175N, P322S and F344LfsX20) were reported to be genetically linked to obesity and insulin resistance in mixed European descents[118]. *F344LfsX20A* mutation causes a frameshift, resulting in production of a C-terminally-truncated SH2B1 variant lacking the entire SH2 domain[118]. A separate study reported that *SH2B1* g.9483(C/T) missense mutation, but not Thr175Asp non-synonymous variant (rs147094247), is linked to obesity[119]. *SH2B1* g.9483(C/T) mutation results in generation of non-synonymous SH2B1β(Thr656Ile) and SH2B1γ(Pro674Ser) variants[119]. Four additional rare non-synonymous variants (G131S, V209I, L293R, M465T, and W649G) have been identified in Chinese populations[120]. V209I and M465T variants are detected in obese children, whereas G131S, L293R and W649G variants are observed in lean children[120].

None of the above human SH2B1 variants has been verified in animal models to be a causal factor for obesity or obesity-associated metabolic syndrome. We reported that neuron-specific expression of SH2 domain-defective SH2B1β(R555E), which is functionally similar to F344LfsX20A variant, is sufficient to cause obesity and insulin resistance in mice[78]. These findings raise the possibility that F344LfsX20A non-synonymous variant may be a causal factor for obesity in humans.

***SH2B1* mutations increase risk for type 2 Diabetes in humans:** Obesity is the primary risk factor for insulin resistance and type 2 diabetes[39], so *SH2B1* risk alleles

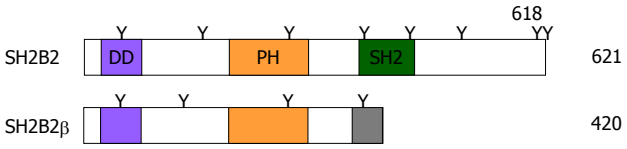

Figure 3 A schematic representation of SH2B2 isoforms. DD: Dimerization domain; PH: PH domain; SH2: SH2 domain; Y: Tyrosine.

are expected to be associated with type 2 diabetes in humans. *SH2B1* rs7498665 is associated with type 2 diabetes in both United Kingdom[92] and French populations[121]. Heterozygous carriers of a P90H, T175N, P322S, or F344LfsX20 non-synonymous variant develop severe early-onset obesity as well as insulin resistance and type 2 diabetes[118].

We reported that peripheral SH2B1 regulates insulin sensitivity and glucose metabolism independently of its action on body weight in mice[48]. SH2B1 in pancreatic β cells directly promotes β cell expansion and insulin secretion in mice[86]. Hepatic SH2B1 regulates liver lipid levels and VLDL secretion[85]. In agreement, *SH2B1* rs4788102 is associated with type 2 diabetes after adjustment for BMI in Japanese[100]. *SH2B1* rs7498665 is associated with increased risk for type 2 diabetes independently of BMI in middle aged Danes[122]. *SH2B1* rs7359397 is associated with insulin resistance after adjustment of BMI in Sweden men at 71 years of age[123]. Thus, SH2B1 also regulates nutrient metabolism by a body weight-independent mechanism.

SH2B1 may regulate multiple physiological processes in humans: Chromosomal 16p11.2 deletion, which results in loss of *SH2B1*, is associated with cognitive deficits, developmental delays[112-115], and autism[115]. Chromosomal 16p11.2 deletion is also linked to abnormal renal and enteric development in humans[124]. *SH2B1* rs4788102 (G/A) is associated with increased circulating triacylglycerol levels in the Northern Swedish Population Health Study cohort[125], and is linked to myocardial infarction[126]. *SH2B1* rs7498665 G allele is linked to increased bone mineral density in Japanese women[127]. However, none of these potential functions have been verified in animal models.

Metabolic function of SH2B1 is evolutionarily conserved

We reported that insulin stimulates the binding of *Drosophila* SH2B (also called Lnk) to Chico, a homologue of mammalian IRS proteins[5]. Almudi *et al*[128] showed that Drosophila SH2B binds to both Chico and insulin receptors in Drosophila cells. SH2B-deficient flies display defects in insulin/IGF signaling, developmental delay, small size, and female sterility[4,5]. Like SH2B1 null mice, SH2B-deficient flies accumulate abnormally-high levels of lipids in their fat bodies[4,5,129].

Interestingly, loss of SH2B increases resistance to oxidative stress as well as lifespan in flies, suggesting that SH2B may regulate aging and longevity[5,129]. However, SH2B1-null mice have a shorter lifespan compared with WT littermates[5]. Obesity and obesity-associated diseases may contribute to early death of SH2B1-null mice. Thus, the role of mammalian SH2B family members in aging remains unclear.

METABOLIC FUNCTION OF SH2B2

SH2B2 was originally identified in 1997[2], and the amino acids of its SH2 and PH domains are 78% and 63% identical to that of SH2B1, respectively.

SH2B2 structure

Crystal structure analysis reveals that the N-terminal region of SH2B2 mediates its homodimerization *via* a Phe zipper[15]. The C-terminal SH2 domain is also able to form a dimer[130]. SH2B2 dimerization is predicted to induce and/or stabilize dimerization of its binding proteins, including JAK2, insulin receptors, or IGF-1 receptors, thus promoting activation of these kinases[15,130].

The *SH2B2* gene also generates an additional C-terminally-truncated isoform (named SH2B2β) through alternative mRNA splicing[131]. SH2B2β contains N-terminal DD and PH domains but lacks C-terminal SH2 domain (Figure 3). SH2B2β binds to both SH2B1 and SH2B2 *via* its DD domain and acts as an endogenous dominant negative variant to inhibit SH2B1 and SH2B2 signaling[131].

SH2B2 regulates insulin signaling and glucose metabolism

Like SH2B1, SH2B2 binds *via* its SH2 domain to phospho-Tyr^{1158} in the activation loop of insulin receptors[130,132,133]. Insulin stimulates phosphorylation of SH2B2 on Tyr^{618} residue in adipocytes[132-134]. Insulin stimulates tyrosine phosphorylation of SH2B2 to a higher level than that of SH2B1[50]. IGF-1 and IGF-Ⅱ also stimulate tyrosine phosphorylation of SH2B2[135]. Additionally, insulin also stimulates Akt-mediated phosphorylation of SH2B2 on Ser^{588} residue[136].

The role of SH2B2 in insulin action is complex. SH2B2 overexpression prolongs insulin-stimulated tyrosine phosphorylation of insulin receptors and IRS proteins[50]. Phospho-Tyr^{618} binds to the tyrosine kinase-binding domain of c-Cbl and promotes c-Cbl phosphorylation by insulin receptors[134,137,138]. Accordingly, knockdown of SH2B2 inhibits insulin-stimulated tyrosine phosphorylation of c-Cbl[139]. SH2B2 also enhances insulin-stimulated phosphorylation of Cbl-b on Tyr^{665} and Tyr^{709} residues[140]. SH2B2 directly binds to SHIP2 and increases SHIP2 activity, and SHIP2 in turn negatively regulates insulin-stimulated tyrosine phosphorylation of SH2B2 and its interaction with c-Cbl[141]. Furthermore, SH2B2 mediates insulin-stimulated plasma membrane translocation of both c-Cbl and Cbl-b in adipocytes[140]. SH2B2 also binds to CAP[134,139] and mediates the activation of the CAP/Cbl/Crk/C3G/TC10 pathway in adipocytes[142]. The SH2B2/CAP/Cbl/Crk/C3G/TC10 pathway is believed to be required for insulin stimulation of GLUT4 trafficking and glucose uptake in adipocytes[142];

consistently, overexpression of SH2B2(Y618F) inhibits insulin-stimulated GLUT4 trafficking[134]. However, SH2B2 also promotes c-Cbl-mediated ubiquitination and internalization of insulin receptors, thus inhibiting insulin signaling[138,143]. Additionally, SH2B2 binds to Asb6, a SOCS family member that may negatively regulate insulin signaling[144].

Deletion of SH2B2 increases insulin sensitivity in mice[6]. We reported that deletion of SH2B2 does not affect HFD-induced insulin resistance and glucose intolerance in *SH2B2* KO mice in either 129Sv/C57BL mixed or C57BL congenic background[71]. Deletion of SH2B2 in *SH2B1* KO mice also does not further exacerbate obesity and insulin resistance in *SH2B1* and *SH2B2* double KO mice relative to *SH2B1* KO mice[71]. The metabolic function of SH2B2 remains unclear.

SH2B2 regulates cytokine signaling and immune response

Like SH2B1, SH2B2 binds *via* its SH2 domain to JAK1, JAK2 and JAK3, and is tyrosyl phosphorylated by these kinases[61,145]. SH2B2 binds *via* both its SH2 domain and non-SH2 domain regions to JAK2, and its SH2 domain binds to phospho-Tyr^{813} of JAK2[16,146]. Unlike SH2B1, SH2B2 is unable to activate, or only slightly activates, JAK2[61,146]. Multiple cytokines, including interferon-γ, EPO, leukemia inhibitor factor, granulocyte-macrophage colony stimulating factor, interleukin-5 (IL-5) and IL-3, stimulate tyrosine phosphorylation of SH2B2, presumably through JAK family members[135,145,147]. Stem cell factor stimulates the binding of SH2B2 *via* its SH2 domain to phospho-Tyr^{568} and -Tyr^{936} of c-Kit and subsequent tyrosine phosphorylation of SH2B2[2,148]. SH2B2 binds *via* its SH2 domain to phospho-Tyr^{343} of EPO receptors[145] , and it also binds *via* its phospho-Tyr^{618} motif to c-Cbl and recruits c-Cbl E3 ligase to EPO receptors, thereby inhibiting the JAK2/STAT5 pathway in hematopoietic cell lines[145]. SH2B2 is colocalized with B cell antigen receptors (BCRs) and negatively regulates BCR signaling, and it is tyrosyl phosphorylated in response to BCR activation[2,149,150].

SH2B1 and SH2B2 play different roles in regulating immune cell function. Deletion of *SH2B1* does not affect the development of T and B lymphocytes and mast cells in mice[11]. In contrast, SH2B2-deficient mast cells display augmented degradulation after cross-linking FcRI[151]. SH2B2 is expressed in B cells but not in T cells[150]. Overexpression of SH2B2 in lymphocytes impairs BCR-induced B cell proliferation and reduces B-1 and B-2 cell number in SH2B2 transgenic mice[150]. Conversely, *SH2B2* KO mice have increased B-1 cell number, and SH2B2-deficient B cells display enhanced response to trinitrophenol-Ficoll, a thymus-independent type 2 antigen[149]. SH2B2 appears to be a negative regulator of a subset of immune cells.

SH2B2 regulates multiple signaling pathways in cultured cells

Like SH2B1, SH2B2 binds *via* its SH2 domain to phospho-Tyr^{679}, -Tyr^{683} and/or -Tyr^{684} of TrkA in response to NGF[51]. BDNF and NT-3 also stimulate the binding of SH2B2 to TrkB and TrkC, respectively[51]. NGF, BDNF and NT-3 stimulate tyrosine phosphoryation of SH2B2[51]. SH2B2 promotes NGF-induced neuronal differentiation of PC12 cells[51].

PDGF-BB stimulates the binding of SH2B2 *via* its SH2 domain to phospho-Tyr^{1021} of PDGFRβ, and SH2B2 in turn inhibits PDGF-stimulated phosphorylation of PLC-γ by competing for phospho-Tyr^{1021} site with PLC-γ[135]. Additionally, PDGF-BB stimulates phosphorylation of SH2B2 on Tyr^{618} which binds to c-Cbl, which recruits c-Cbl E3 ligase to PDGFR complex to negatively regulate PDGFR signaling and PDGFR-promoted mitogenesis[135].

FUTURE DIRECTION

Study of the SH2B family is in its early stages, and many important questions remain unaddressed. Central SH2B1 is required for the maintenance of normal energy balance, body weight, and nutrient metabolism; however, SH2B1 target neurons and neural circuits are unknown. It is unclear whether and how central SH2B1 regulates nutrient mobilization, utilization, and metabolism by a body weight-independent mechanism, and whether and how SH2B1 regulates neuronal activity by a leptin- and insulin-independent mechanism. Numerous *SH2B1* mutations are associated with obesity and type 2 diabetes in humans; however, it is unclear whether these mutations are causal factors for the diseases. Does central SH2B1 regulate higher brain function independently of its action on body weight and metabolism? Do posttranslational modifications affect SH2B1 function? Do SH2B2 and SH2B3 play a role in nutrient metabolism? Can we treat obesity and type 2 diabetes by targeting SH2B family members?

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