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

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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) was initially identified as a high affinity receptor for insulin and other cytokines. 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.

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...
immunoglobulin 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[4,5]. Deletion of \(SH2B1\), but not \(SH2B2\) or \(SH2B3\), results in obesity and metabolic disorders 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 (\(\alpha, \beta, \gamma, \) and \(\delta\)) through mRNA alternative splicing[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[18,19]). 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) (KJK[19]KR) which is required for its nuclear translocation[15]. \(SH2B1\) also contains a nuclear export sequence (NES) (GERWTHRERL[20]RLSR) (Figure 1), and replacement of the conserved Leu[21] and Leu[22] with Ala increases its nuclear localization[19]. \(SH2B1\) domain-defective \(SH2B1\β(R553E)\) mutant is also excluded from the nucleus[23]. Therefore, the NLS, NES, and SH2 domain all are involved in the regulation of \(SH2B1\)

SH2B1 posttranslational modification: \(SH2B1\) contains numerous Ser and Thr residues. NGF stimulates \(SH2B1\) phosphorylation on multiple Ser/Thr residues[24]. Mitogen-activated protein kinase (MAPK) directly phosphorylates Ser[25], and protein kinase C phosphorylates both Ser[26] and Ser[27] residue[28]. 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[32], and recombinant leptin fully corrects obesity and metabolic disorders in \(ob/ob\) mice[23,34]. Leptin exerts its biological action by binding to and activating its long form receptors (called LEPBr)[35-38]. LEPBr binds to JAK2, a cytoplasmic tyrosine kinase which also mediates GH, prolactin, erythropoietin (EPO), and other cytokine signaling[39-41]. Leptin stimulates tyrosine phosphorylation and activation of JAK2 which activates multiple downstream signaling

Figure 1 A schematic representation of \(SH2B1\) isoforms. DD: Dimerization domain; PH: PH domain; SH2: SH2 domain; Y: Tyrosine; Numbers: Amino acid numbers.
SH2B1 C-terminal SH2 domain binds to phospho-Tyr in JAK2 as discussed above; in contrast, its N-terminal region binds to different sites on JAK2 in a tyrosine phosphorylation-independent manner. 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 PI domain-containing regions in a tyrosine phosphorylation-independent fashion. SH2B1 forms homodimers or oligomers via its N-terminal domains. 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. Insulin stimulates the binding of SH2B1α to phospho-Tyr, Tyr and/or Tyr within the IR activation loop, and IRSs subsequently tyrosyl phosphorylate SH2B1α. Overexpression of SH2B1β markedly enhances the ability of insulin to stimulate tyrosine phosphorylation of IRS1 and IRS2. In contrast, SH2B1β(R555E), which has a defective SH2 domain, acts as a dominant negative mutant to inhibit insulin signaling. Moreover, deletion of SH2B1 impairs insulin signaling in the skeletal muscle, adipose tissue, and livers of SH2B1 knockout mice.

Mechanistically, SH2B1-IR interaction markedly increases IR catalytic activity and IR-mediated tyrosine phosphorylation of IRS proteins. Replacement of IR Tyr with Phe disrupts IR binding to SH2B1, and completely blocks the ability of SH2B1β to stimulate IR kinase activity. SH2B1α similarly increases IR catalytic activity. Additionally, SH2B1β directly binds to tyrosyl phosphorylated IRS1 and IRS2 and protects IRS proteins against dephosphorylation, thus prolonging the ability of IRS proteins to activate their downstream pathways. Accordingly, overexpression of SH2B1α delays dephosphorylation of IRS proteins in cells. 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, 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
SH2B1 regulates GH, prolactin, and EPO signaling: JAK2 binds to GH receptors and mediates GH signaling. GH stimulates the binding of SH2B1 to JAK2 and robust tyrosine phosphorylation of SH2B1 by JAK2 in 3T3-F442A fibroblasts. GH stimulates JAK2-mediated phosphorylation of SH2B1 on Tyr and Tyr residues. Like leptin, GH stimulates phosphorylation of JAK2 on Tyr, which binds to the SH2 domain of SH2B1. SH2 domain-phospho-Tyr interaction markedly increases JAK2 activity, thus enhancing GH signaling (e.g., phosphorylation and activation of STAT5). JAK2 also mediates prolactin signaling. Like GH, prolactin stimulates tyrosine phosphorylation of SH2B1. Overexpression of SH2B1 enhances prolactin signaling, including tyrosine phosphorylation of JAK2.

Unlike GH, EPO stimulates the binding of SH2B1 to EPO receptors rather than to JAK2. SH2B1 constitutively binds to unphosphorylated EPO receptors under basal conditions, and EPO stimulates phosphorylation of EPO receptors on Tyr and Tyr residues which subsequently bind to the SH2 domain of SH2B1. EPO rapidly stimulates phosphorylation of SH2B1 on Ser/Thr residues. 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.

SH2B1 binds to JAK1, JAK2 and JAK3, but it only stimulates JAK2, but not JAK1 and JAK3, kinase activity. Both JAK1 and JAK2 are able to phosphorylate SH2B1 on Tyr and Tyr residues, but Tyr phosphorylation does not affect the ability of SH2B1 to stimulate JAK2. 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. PDGF-BB stimulates phosphorylation of SH2B1 on Tyr/Ser/Thr residues. PDGF receptors directly phosphorylate SH2B1 on Tyr residues.

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

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

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, and is colocalized with filamentous actin (F-actin) in membrane ruffles. SH2B1 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. SH2B1 directly binds via its amino acids 200-620 to the actin-binding protein filament A. Additionally, SH2B1 binds via its amino acids 85-106 to Rac, a critical regulator of actin cytoskeletal reorganization.

SH2B1 mediates GH regulation of cell adhesion and migration. GH increases the cycling of SH2B1 into and out of focal adhesions, and promotes SH2B1 colocalization with F-actin in membrane ruffles. Overexpression of SH2B1β, but not SH2B1-domain-defective SH2B1β(R555E), enhances the ability of GH to stimulate both membrane ruffles in 3T3-F442A fibroblasts and macrophage migration. In fact, SH2B1β(R555E) blocks GH-induced lamellipodia dynamics in 3T3-F442A cells. Both the N-terminal region (amino acids 85-106) and the SH2 domain of SH2B1 are required for GH stimulation of cell motility. Additionally, SH2B1β mutants lacking Tyr and Tyr phosphorylation sites are unable to enhance GH-stimulated membrane ruffling in 3T3-F442A fibroblasts and GH-stimulated motility of RAW264.7 macrophages. SH2B1-Rac interaction is involved in mediating GH-promoted actin cytoskeletal reorganization and cell motility.
Overexpression of SH2B1β similarly enhances prolactin-stimulated membrane ruffling [9]. SH2B1 directly binds to filamin A, which appears to mediate prolactin stimulation of membrane ruffling and cell motility [10].

**SH2B1 promotes neuronal survival and neuronal differentiation:** Overexpression of SH2B1β markedly enhances the ability of NGF to stimulate neurite outgrowth in PC12 cells [20], and both SH2B1α and SH2B2 are able to promote NGF/TrkA-induced neuronal differentiation [21]. In contrast, overexpression of SH2 domain-defective SH2B1(R555E) blocks NGF-induced neuronal differentiation of PC12 cells [22]. SH2B1β mutants lacking either the NES or the NLS also are unable to enhance NGF-induced neuronal differentiation [23,24]. 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 [30]. Moreover, neutralization of endogenous SH2B1 with anti-SH2B1 antibody decreases the survival of primary sympathetic neurons [31]. 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 [60,61]. 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 [25,26]. SH2B1 increases the ability of RET to promote transformation of NIH 3T3 cells [27]. 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 [71].

**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 [28]. SH2B1-null mice are hyperphagic and morbidly obese [30]. Both SH2B1 KO males and females gain more body weight than wild type (WT) littersmates after 7 wk of age [29,72]. 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 [30].

SH2B1 KO mice are extremely hyperphagic, causing obesity [10]. Surprisingly, energy expenditure, as estimated by O2 consumption and CO2 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 [73], so we generate SH2B1 transgenic (Tg) mice in which a rat SH2B1 transgene is expressed specifically in neurons under the control of neuron-specific enolase promoter [74]. 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 [75]. Neuron-specific restoration of SH2B1β into SH2B1 KO mice fully rescues the hyperphagic and obese phenotypes in TgKO mice [76]. Energy expenditure, which is abnormally higher in SH2B1 KO mice, is normal in TgKO mice [75]. Furthermore, SH2B1β Tg mice, which contain homozygous SH2B1 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 [76]; 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 [77]. Since SH2B1 KO mice have high energy expenditure [30], 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 [9,11,73].** 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 [78]. As expected, obese SH2B1 KO mice develop hyperglycemia, hyperinsulinemia, glucose intolerance, and insulin resistance [80,81]. 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 haploinsufficiency predisposes to HFD-induced insulin resistance [67]. SH2B1 KO mice develop the symptoms of metabolic syndrome, including hyperlipidemia, hepatic steatosis, and lipid accumulation in skeletal mus-
Moreover, neuron-specific restoration of SH2B1β reverses 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[19,40,74-77]. 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[41,48]. 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[9]. Leptin suppresses the expression of AgRP and neuropeptide Y (NPY) but stimulates POMC expression[78]. The expression of hypothalamic AgRP and NPY is higher in SH2B1 KO mice[80], and neuron-specific expression of SH2B1β in SH2B1 KO mice normalizes AgRP and NPY expression[80]. By contrast, the expression of hypothalamic POMC is normal in SH2B1 KO mice[80]. 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[90]; 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[79,80]. Mutations in either BDNF or TrkB are associated with obesity in humans[80,84]. 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[77], 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[80]. Insulin signaling in skeletal muscle, adipose tissue, and the liver is impaired to a greater extent in HFD-fed TgKO mice[80], and these mice display more severe hepatic steatosis[80]. 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[80]. 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[80]. 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[80]. 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[80]. In a rat INS-1 832/13 β cell line, silencing of SH2B1 decreases, whereas overexpression of SH2B1β

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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[11], so we generate hepatocyte-specific SH2B1 KO (HKO) mice using the albumin-cre/loxP system[89]. 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[88]. Adult-onset deletion of SH2B1 in the liver also does not alter insulin sensitivity and glucose metabolism in mice fed a HFD[80]. 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[83], 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[89]. 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 an 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 rs7359379 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[110]. SH2B1 rs4788099 is associated with increased body mass index (BMI) in individuals of European ancestry[109], and is linked to more servings of dairy products[111]. SH2B1 rs805982 is associated with severe obesity in children of European ancestry[111].

Aside from SH2B1 SNPs, chromosomal 16p11.2 deletion is associated with severe obesity in European cohorts[112-116]. 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[119]. 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, 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[99]. 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[99], so SH2B1 risk alleles
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, and autism[112-115]. Chromosomal 16p11.2 deletion is also linked to abnormal renal and enteric development in humans[114]. SH2B1 rs4788102 (G/A) is associated with increased circulating triacylglycerol levels in the Northern Swedish Population Health Study cohort[112], and is linked to myocardial infarction[124]. 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[43]. Like SH2B1 null mice, SH2B-deficient flies accumulate abnormally-high levels of lipids in their fat bodies[43,129].

Interestingly, loss of SH2B increases resistance to oxidative stress as well as lifespan in flies, suggesting that SH2B may regulate aging and longevity[43,128]. 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 SH 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[13]. The C-terminal SH2 domain is also able to form a dimer[13], 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[13,136].

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 residues in the activation loop of insulin receptors[130-132,133]. Insulin stimulates phosphorylation of SH2B2 on Tyr618 residue in adipocytes[132,134]. Insulin stimulates tyrosine phosphorylation of SH2B2 to a higher level than that of SH2B1[89,135]. SH2B2 directly binds to SHIP2 and increases SHIP2 activity, and SHIP2 in turn negatively regulates tyrosine phosphorylation of SH2B2[133]. Additionally, insulin also stimulates Akt-mediated phosphorylation of SH2B2 on Ser688 residue[136].

The role of SH2B2 in insulin action is complex. SH2B2 overexpression prolongs insulin-stimulated tyrosine phosphorylation of insulin receptors and IRS proteins[49]. Phospho-Tyr1158 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 Tyr60 and Tyr709 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[131]. 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].

Figure 3 A schematic representation of SH2B2 isoforms. DD: Dimerization domain; PH: PH domain; SH2: SH2 domain; Y: Tyrosine.
consistently, overexpression of SH2B2(Y618F) inhibits insulin-stimulated GLUT4 trafficking\(^\text{[134]}\). However, SH2B2 also promotes c-Cbl-mediated ubiquitination and internalization of insulin receptors, thus inhibiting insulin signaling\(^\text{[138,144]}\). Additionally, SH2B2 binds to Asb6, a SOCS family member that may negatively regulate insulin signaling\(^\text{[144]}\).

Deletion of SH2B2 increases insulin sensitivity in mice\(^\text{[28]}\). 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\(^\text{[93]}\). 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\(^\text{[93]}\). 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\(^\text{[61,146]}\). SH2B2 binds via both its SH2 domain and non-SH2 domain regions to JAK2, and its SH2 domain binds to phospho-Tyr\(^\text{913}\) of JAK2\(^\text{[146]}\). Unlike SH2B1, SH2B2 is unable to activate, or only slightly activates, JAK2\(^\text{[61,146]}\). Multiple cytokines, including interferon-\(\gamma\), 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\(^\text{[135,144,147]}\). Stem cell factor stimulates the binding of SH2B2 via its SH2 domain to phospho-Tyr\(^\text{368}\) and -Tyr\(^\text{596}\) of c-Kit and subsequent tyrosine phosphorylation of SH2B2\(^\text{[2,148]}\). SH2B2 binds via its SH2 domain to phospho-Tyr\(^\text{341}\) of EPO receptors\(^\text{[144]}\), and it also binds via its phospho-Tyr\(^\text{418}\) motif to c-Cbl and recruits c-Cbl E3 ligase to EPO receptors, thereby inhibiting the JAK2/STAT5 pathway in hematopoietic cell lines\(^\text{[189]}\). SH2B2 is colocalized with B cell antigen receptors (BCRs) and negatively regulates BCR signaling, and it is tyrosyl phosphorylated in response to BCR activation\(^\text{[2,149,190]}\).

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\(^\text{[11]}\). In contrast, SH2B2-deficient mast cells display augmented degradation after cross-linking Fc\(R\)\(^\text{155}\). SH2B2 is expressed in B cells but not in T cells\(^\text{[193]}\). Overexpression of SH2B2 in lymphocytes impairs BCR-induced B cell proliferation and reduces B-1 and B-2 cell number in SH2B2 transgenic mice\(^\text{[190]}\). 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\(^\text{[190]}\). 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 phos-}

A reference for the image: It is unclear whether these mutations are causal factors for the disease. Does central SH2B1 regulate higher brain function independently of its action on body weight and metabolism? Do posttranslational modifications affect SH2B1 function? Do SH2B1 and SH2B2 play a role in nutrient metabolism? Can we treat obesity and type 2 diabetes by targeting SH2B family members?

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