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Growth hormone signaling pathways

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Abstract

Over 20 years ago, our laboratory showed that growth hormone (GH) signals through the GH receptor-associated tyrosine kinase JAK2. We showed that GH binding to its membrane-bound receptor enhances binding of JAK2 to the GHR, activates JAK2, and stimulates tyrosyl phosphorylation of both JAK2 and GHR. The activated JAK2/GHR complex recruits a variety of signaling proteins, thereby initiating multiple signaling pathways and cellular responses. These proteins and pathways include: 1) Stat transcription factors implicated in the expression of multiple genes, including the gene encoding insulin-like growth factor 1; 2) Shc adapter proteins that lead to activation of the grb2-SOS-Ras-Raf-MEK-ERK1,2 pathway; 3) insulin receptor substrate proteins implicated in the phosphatidylinositol-3-kinase and Akt pathway; 4) signal regulatory protein α, a transmembrane scaffold protein that recruits proteins including the tyrosine phosphatase SHP2; and 5) SH2B1, a scaffold protein that can activate JAK2 and enhance GH regulation of the actin cytoskeleton. Our recent work has focused on the function of SH2B1. We have shown that SH2B1β is recruited to and phosphorylated by JAK2 in response to GH. SH2B1 localizes to the plasma membrane, cytoplasm and focal adhesions; it also cycles through the nucleus. SH2B1 regulates the actin cytoskeleton and promotes GH-dependent motility of RAW264.7 macrophages. Mutations in SH2B1 have been found in humans exhibiting severe early-onset childhood obesity and insulin resistance. These mutations impair SH2B1 enhancement of GH-induced macrophage motility. As SH2B1 is expressed ubiquitously and is also recruited to a variety of receptor tyrosine kinases, our results raise the possibility that effects of SH2B1 on the actin cytoskeleton in various cell types, including neurons, may play a role in regulating body weight.

Keywords

Growth hormone; JAK2; SH2B1; Signal transduction

1. Introduction

For many years, growth hormone (GH) has been known to be the primary hormone responsible for body growth. The tallest man on record (http://

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Conflict of interest

There are no conflicts of interest.

www.guinnessworldrecords.com/world-records/tallest-man-ever/), Robert Wadlow, had an untreated pituitary tumor that secreted abnormally high levels of GH [7]. He grew throughout life, achieving a height of 8 ft., 11 in. at the time of his death. Even today, the tallest people on record tend to achieve their great heights due to untreated pituitary tumors. The reverse is also true. Individuals who, for whatever reason, do not make normal levels of GH as children or have defective GH receptors, are short statured [14]. GH has also been recognized to regulate carbohydrate, protein and lipid metabolism. For example, GH decreases fat and increases lean body mass [16].

2. GH binding to its receptor activates the tyrosine kinase JAK2

In the mid 1980s, we asked the question of how GH acted at the level of the cell to bring about its diverse responses on body growth and metabolism. The GH receptor had been shown to be a membrane receptor that migrated as an ~ 110 kDa protein [11]. It was also known that defective GH receptors (patients with Laron Syndrome) resulted in short stature [20]. However, nothing was known about the signal transduction events that enabled GH binding to its plasma membrane-bound receptor to direct cellular responses. Around that time, a number of growth factors had been shown to bind to membrane receptors that had intrinsic tyrosine kinase activity. Since GH promoted growth, we hypothesized that GH might similarly bind to a membrane receptor with intrinsic tyrosine kinase activity or activate a tyrosine kinase. In support of this hypothesis, we showed that highly purified GH-GH receptor complexes co-purified with a tyrosine kinase [12]. Initial studies suggested that the GH receptor and the tyrosine kinase were the same protein since we saw essentially one band on sodium dodecyl sulfate polyacrylamide gels of highly purified and kinase-active GH receptor preparations. However, Leung et al. [33] cloned a GH receptor, which did not have tyrosine kinase activity. We solved the apparent discrepancy when we purified a truncated form of the GH receptor and saw that the truncated GH receptor co-purified with a tyrosine kinase the size of the full-length GH receptor [63]. This led us to search for a ~110 kDa tyrosine kinase, which in turn led us to the JAK family of tyrosine kinases. JAK1 and JAK2 were of the appropriate size, had been recently identified, and had no known function [67]. We showed that GH binding to its receptor increased the binding of JAK2 to GH receptor, activated JAK2, and increased phosphorylation of tyrosines within both JAK2 and GH receptor [3] (Fig. 1). This was an exciting finding because for the first time, it suggested a mechanism by which GH signal transduction was initiated – activation of JAK2. This finding was published back-to-back in *Cell* with an article by James Ihle's group showing that erythropoietin similarly activated JAK2 [68]. These two publications were paradigm-shifting, since JAK family members have since been found to be activated in response to ligand binding to all members of the cytokine superfamily of receptors [6], a family numbering over 25 members. These ligands regulate such diverse and important physiological functions as satiety, immune function, milk production, hematopoiesis, and nerve function [23].

3. JAK2 activation initiates signaling via multiple pathways

Having identified JAK2 as a critical and initiating cell signaling event for GH, we set out to determine the signaling events that are initiated as a consequence of JAK2 activation (Fig.

1). The first protein that caught our attention was p91, a transcription factor that had been identified in the context of the immune system. P91 was an intriguing candidate because of the finding that interferon (IFN)γ and IFNα, both of which were known to activate p91 [21,28,48,49] had recently been shown to activate members of the JAK family of tyrosine kinases (JAK2 and Tyk2 respectively) [62,64]. By investigating how GH regulates gene transcription, we were able to show that GH stimulated the tyrosyl phosphorylation of p91 [subsequently named Signal Transducer and Activator of Transcription 1 (Stat1)] and binding of p91 to the c-*Sis*-inducible element of the c-*fos* promoter [36]. Subsequently, we were among the first to show that GH also activates Stat3, Stat5a and Stat5b and promotes the accumulation of the activated form of Stats in the nucleus [9,25,50,51]. Stats 5a and 5b have been implicated in the synthesis of a variety of GH-sensitive genes, including insulin-like growth factor 1 (IGF-1), and acid labile subunit (ALS) which is a critical component of IGF binding protein complex (IGF1–IGFBP 3-ALS) [29]. They have been implicated in the transcription of a variety of GH regulated Cyp genes in the liver of mice [65]. Subsequent gene deletion studies [59] and human mutation identification [27] provide strong evidence that Stat5b is critical for GH's effect on body height. These and other findings form the basis for the current canonical paradigm for GH signaling [31]: GH binding to its receptor activates JAK2, which in turns phosphorylates GH receptor on multiple tyrosines. These phosphorylated tyrosines, or tyrosines within JAK2, recruit various Stat proteins, which in turn are phosphorylated by JAK2 on a critical tyrosine. The phosphorylated Stat proteins are then released from the GH receptor/JAK2 complex, dimerize, move to the nucleus, and bind to Stat binding sites in GH-regulated genes. Stat proteins can also dimerize with other transcription factors, affecting the ability of those factors to bind to DNA and regulate gene transcription.

Although we recognized that Stat proteins are important for many actions of GH, we considered it likely that GH activation of JAK2 would initiate signaling pathways in addition to the Stat transcription factors. Over the years, we established that GH activates a number of additional signaling pathways. These include 1) the MAP kinase pathway; 2) insulin receptor substrate (IRS) proteins implicated in the activation of the phosphatidylinositol-3-kinase (PI3K) and Akt pathway; 3) signal regulatory protein α (SIRPα/SHPS1), a transmembrane scaffold protein that recruits proteins including the tyrosine phosphatase SHP2; and 4) SH2B1, a scaffold protein that can activate JAK2 and enhance GH regulation of the actin cytoskeleton.

Because JAK2 is a tyrosine kinase, we thought it likely that GH would be found to regulate the MAP kinases Erks 1 and 2. We showed that GH promotes the binding of the SH2 domain of Shc adapter protein to JAK2-GHR complexes, the tyrosyl phosphorylation of the 3 forms of Shc, and the binding of the adapter protein grb2 to Shc [60,61]. Further, we showed that GH stimulates association of the guanine nucleotide exchange factor SOS with Shc, and the activation of Ras, Raf, MEK and Erks 1 and 2 with a time course consistent with Erks 1 and 2 being activated via a Shc-grb2-SOS-Ras-Raf-MEK-Erk1/2 pathway. Erks have been shown to regulate a number of different types of molecules, including protein kinases, cytoskeletal proteins, phospholipases, and transcription factors [69]. Thus, GH activation of this pathway would be expected to regulate multiple responses in GH targeted cells.

The third pathway that we investigated was the IRS–PI3K pathway. Because under certain conditions, GH stimulates glucose transport in adipocytes [10], we hypothesized that GH might activate some of the pathways implicated in insulin regulation of glucose transport. Insulin and IGF-1 had been shown to activate IRS proteins, and activation of IRS proteins had been shown to recruit multiple PI3K proteins [56], which had been implicated in insulin stimulation of glucose transport [13]. We therefore hypothesized that GH activation of JAK2 would stimulate the tyrosyl phosphorylation of IRS proteins, which would recruit PI3K, leading to regulation of glucose transport and most likely other cellular responses. We demonstrated that indeed, GH stimulated that tyrosyl phosphorylation of both IRS1 and 2, as well as binding of the p85 regulatory subunit of PI3K to IRS1 and 2 and of the tyrosine phosphatase SHP2 to IRS2 [4,5]. These findings provide one possible mechanism by which GH causes the transient increase in glucose transport in adipocytes observed following a period of GH deprivation [10]. Longterm and in vivo, GH is considered diabetogenic and decreases insulin-sensitivity [1], which is likely to occur by a different mechanism. GH activation of IRS proteins also suggests a pathway by which GH could activate the transcription factor C/EBPβ. Activation of PI3K converts phosphatidylinositol (3,4)-bisphosphate (PIP_2) lipids to phosphatidylinositol (3,4,5)-trisphosphate (PIP_3). PIP_3 recruits Akt to the plasma membrane, which enables the kinase PDK1 to access and phosphorylate T308 in Akt, leading to partial Akt activation [2]. Akt phosphorylation of glycogen synthase kinase 3 (GSK3) inhibits GSK3 activity. Decreased GSK3 activity results in decreased phosphorylation of a GSK3 phosphorylation site in C/EBPβ, and increased binding of a form of C/EBPβ, designated liver activating protein or LAP, to the c-*fos* promoter [44].

Because GH activates multiple pathways, we questioned whether multiple GH pathways might act together to regulate GH responses. One example of multiple pathways working together is GH regulation of expression of the c-*fos* gene (Fig. 2). We have shown that maximal expression of c-*fos* requires input from multiple GH signaling pathways. The promoter region of c-*fos* contains a binding site for Stat1 and Stat3 hetero or homodimers whose binding promotes c-*fos* gene expression [9,36,52]. The c-*fos* promoter also contains a serum response element that binds both serum response factor and ternary complex transcription factors, such as Elk1 [26,34,37]. GH stimulates the serine phosphorylation of Elk-1 via the MEK/Erk pathway, thereby enabling Elk-1 to mediate transcriptional activation. CREB and C/EBPβ, whose activity is also stimulated by phosphorylation by Erks 1 and/or 2 [17] but inhibited by phosphorylation by GSK3 [43,44], also bind to the promoter region of c-*fos* gene. Thus, c-*fos* gene expression in response to GH depends upon the balance of GH regulation of Stats, the MAPK pathway, the PI3K pathway and perhaps other pathways.

While trying to identify the tyrosine phosphatase(s) that dephosphorylate the GH receptor and/or JAK2, we identified signal regulatory protein α (SIRPα) as a JAK2 substrate [53,54]. SIRPα is a transmembrane glycoprotein that had been identified previously as a substrate of insulin receptor that recruits multiple SHP2 proteins. We found that in response to GH, JAK2 highly phosphorylates SIRPα1 and recruits SHP2 tyrosine phosphatases (Fig. 1). Recruitment of SHP2 to SIRPα1 appears to negatively regulate GH-JAK2 signaling.

4. JAK2 interacts with the scaffold protein SH2B1

To identify novel GH signaling proteins that are activated as a consequence of GH activation of JAK2, we performed a yeast 2-hybrid assay using the C-terminal amino acids of JAK2, which contains the kinase domain. When expressed in yeast, this portion of JAK2 is constitutively active. Of the potential JAK2 binding proteins identified in this assay, the adapter protein SH2B1 (SH2-B, PSM) was the most intriguing [47]. We pulled out the C-terminal 143 amino acids of a previously unidentified isoform of SH2B1. We designated this new isoform the β isoform. This isoform contains unique C-terminal 39 amino acids that lie just downstream of the SH2 domain. SH2B1 was originally cloned from mast cells because of its ability to bind in a yeast tribrid system to the tyrosyl-phosphorylated gamma subunit of the high-affinity immunoglobulin E (IgE) receptor [41]. Nothing else was known about the structure or function of SH2B1. This made it quite a challenge to identify the cellular function of SH2B1.

We established that SH2B1β is recruited to tyrosine (Tyr) 813 in activated JAK2 in response to GH and is phosphorylated on tyrosines 439 and 494 by JAK2 [30,39,47], suggesting that JAK2 phosphorylation of SH2B1β may recruit SH2 domain-containing signaling proteins to GH receptor/JAK2 complexes. We also showed that when overexpressed with JAK2, SH2B1β is a potent activator of JAK2 [46]. SH2B1β is also recruited to other members of the JAK family of tyrosine kinases, including JAK1 and JAK3 [40]. In the case of JAK1, SH2B1 is recruited to JAK1 and is phosphorylated by JAK1 but does not activate JAK1. In the case of JAK3, SH2B1 is recruited to Tyr785, the equivalent of Tyr813 in JAK2 [30]. However, we did not find that JAK3 phosphorylates SH2B1 nor did we find that SH2B1 activates JAK3. We hypothesized that SH2B1 was likely to bind additional proteins in a JAK3 independent manner, which would be recruited to JAK3 complexes when SH2B1 bound to JAK3.

5. SH2B1 regulates the actin cytoskeleton and cell motility

We have identified several other functions of SH2B1. When we observed the subcellular localization of GFP-tagged SH2B1, we found that SH2B1β localizes to membrane ruffles in cultured fibroblasts [24]. Membrane ruffles are formed at the leading edge of motile cells. This led us to hypothesize that SH2B1 interacts with and regulates the actin cytoskeleton. In support of this, we found that overexpressing SH2B1β increases membrane ruffling and cell motility in response to GH [18,24]. We next investigated whether GH acts as a chemoattractant to stimulate macrophage migration using a transwell migration assay. GH has been implicated in the migration of human monocytes [66] and both resting and activated human T cells [58]. We first showed that GH stimulates the migration of cultured RAW264.7 and bone marrow-derived mouse primary macrophages [55]. We then showed that overexpression of SH2B1β enhances GH-stimulated migration of RAW macrophages whereas reducing levels of SH2B1 using shRNA greatly impaired the GH-stimulated migration of RAW macrophages. As discussed above, we had previously shown that JAK2 phosphorylated SH2B1 on Tyr 439 and 494 [39]. We found that phosphorylation of these tyrosines appear to be required for SH2B1 to enhance GH-dependent macrophage motility since mutating them singly or together greatly impairs SH2B1 enhancement of GH-

dependent macrophage motility [55]. Based on these and other migration studies using various truncated and mutated forms of SH2B1β, we speculate that SH2B1 regulates the actin cytoskeleton by recruiting proteins up to the plasma membrane where they are in close proximity to the actin cytoskeleton (Fig. 3). Some of these proteins are recruited by binding to tyrosines that are phosphorylated by JAK2 while others (e.g. Rac, [18]) bind constitutively to SH2B1β.

Cell migration relies, in part, on regulation of focal adhesion dynamics. Focal adhesions are large integrin-based macromolecular complexes that mediate cell-extracellular-matrix (ECM) attachment, facilitate direct signaling between the ECM and the cell and facilitate cell anchorage and motility (reviewed in [22]). We therefore looked to see if SH2B1β localizes to focal adhesions. Using confocal microscopy, we showed that SH2B1β colocalizes with vinculin, a focal adhesion protein [32]. Further, GH increases cycling of SH2B1β in and out of focal adhesions. Thus, SH2B1 may contribute to cell motility not only by interacting with and recruiting proteins to the actin cytoskeleton at the plasma membrane and in membrane ruffles, but also by serving as a scaffold protein for proteins in focal adhesions.

Because SH2B1 is recruited to JAK2 via its SH2 domain, we hypothesized that SH2B1 might be recruited to other cytokine receptors–JAK2 complexes or to activated receptor tyrosine kinases. In fact, we and others showed that SH2B1 is recruited to other receptors implicated in body growth, energy balance, and cell motility, including leptin receptor–JAK2 complexes and receptors for insulin, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and IGF-1 [35,42]. Variants in SH2B1 have been associated with obesity in genome wide association studies and gene deletion studies [8]. In addition, $SH2B1^{-/-}$ mice are obese [45]. Recently, individuals with point mutations in SH2B1 were identified among patients in the Genetics of Obesity Study (GOOS) [19]. These patients exhibit severe early onset childhood obesity, insulin resistance, hyperphagia and reduced height as adults. The $SH2B1^{-/-}$ mice similarly exhibit severe obesity, insulin resistance and hyperphagia. Some of the patients also exhibit maladaptive behavior, including social isolation, speech and language delay, and aggression.

We examined whether the human obesity mutations in SH2B1 impair SH2B1β-enhancement of GH-mediated macrophage migration. We found that overexpression of SH2B1β containing any of the three human obesity mutations tested, P90H, A175N and P322S completely blocked GH-stimulated macrophage migration [19]. These results raise the possibility that effects of SH2B1 on the actin cytoskeleton in other cell types, including neurons, and perhaps during development, may play a role in regulating body weight.

6. Growth hormone signaling pathways implicated in humans

Among the GH signaling proteins identified in these in vitro studies, only the GH receptor and Stat5b have been shown by human mutations to be associated with short stature in humans [20,27]. However, it is interesting to note that individuals with mutations in the IRS-1/PI3K pathway are short [15] as are individuals with RASopathies, which are diseases due to mutations in proteins in the MAP kinase pathway [57]. Some of the latter individuals

are GH-deficient. Whether impaired GH signaling due to the mutations in these proteins contributes to the observed short stature or other altered phenotypes in these individuals is not known. However, GH has been shown to increase phosphorylation of Erk and PI3K in addition to Stat5 in cultured human fibroblasts [38], indicating that GH activates multiple pathways in cultured human cells, in addition to the cultured rodent cell lines used in our studies.

7. Summary

We have shown that GH binding to its receptor activates the GH receptor associated JAK2 tyrosine kinase. JAK2 in turn phosphorylates tyrosines within the GH receptor and within itself. These phosphorylated tyrosines can then recruit signaling proteins to GH receptor–JAK2 complexes in the plasma membrane. Proteins recruited to GH receptor-JAK2 complexes and phosphorylated by JAK2 include the transcription factors Stats 1, 3, 5a, and 5b that regulate GH sensitive genes including genes encoding c-Fos and IGF-1; IRS 1 and 2 which recruit PI3K and lead to activation of Akt and other proteins; Shc adapter proteins that initiate the Shc/grb2/SOS/Ras/Raf/MEK pathway leading to activation of Erks 1 and 2; SIRPα1 that recruits a tyrosine phosphatase that appears to be a negative regulator of JAK2 activity; and SH2B1, a scaffold protein that enhances GH-induced changes in the cytoskeleton leading to enhanced motility of cells, including macrophages. These pathways work together, presumably with other signaling proteins, to lead to a variety of responses to GH, including body growth, regulation of metabolism, and the ever-emerging actions of GH throughout the body.

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Abbreviations:

GH	growth hormone
IGF1	insulin-like growth factor 1
IFN	interferon
IRS	insulin receptor substrate
PI3K	phosphatidylinositol-3-kinase
SIRPα	signal regulatory protein α
ALS	acid labile subunit
GSK3	glycogen synthase kinase 3
ECM	extracellular matrix
Tyr	tyrosine

Stat	Signal Transducer and Activator of Transcription
TCF	ternary complex factors
SRF	serum response factor
C/EBP	CCAAT enhancer binding protein

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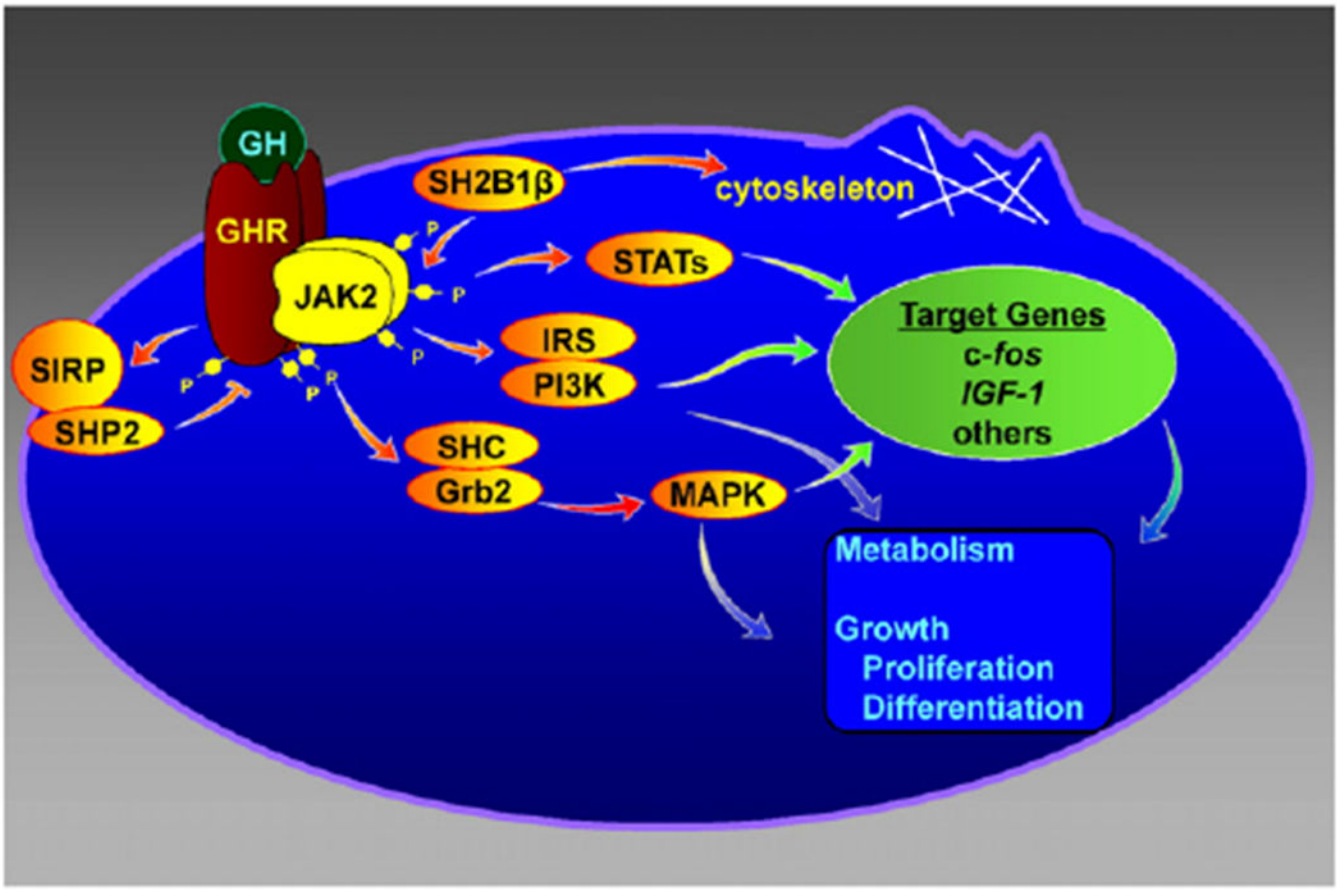

Fig. 1.

GH acts via a variety of signal transduction pathways. GH: growth hormone; GHR: growth hormone receptor; JAK2, Janus kinase 2; STAT: Signal Transducer and Activator of Transcription; MAPK: mitogen-activated protein kinase; IRS: insulin receptor substrate; PI3K: phosphatidyl inositol 3 kinase. Figure adapted from C Carter-Su, L Rui, J Herrington, M Stofega and M Diakonova, 2001, Targets for Growth Hormone and IGF-1 Action, pp31–43 © Bioscientifica Ltd. Adapted by permission.

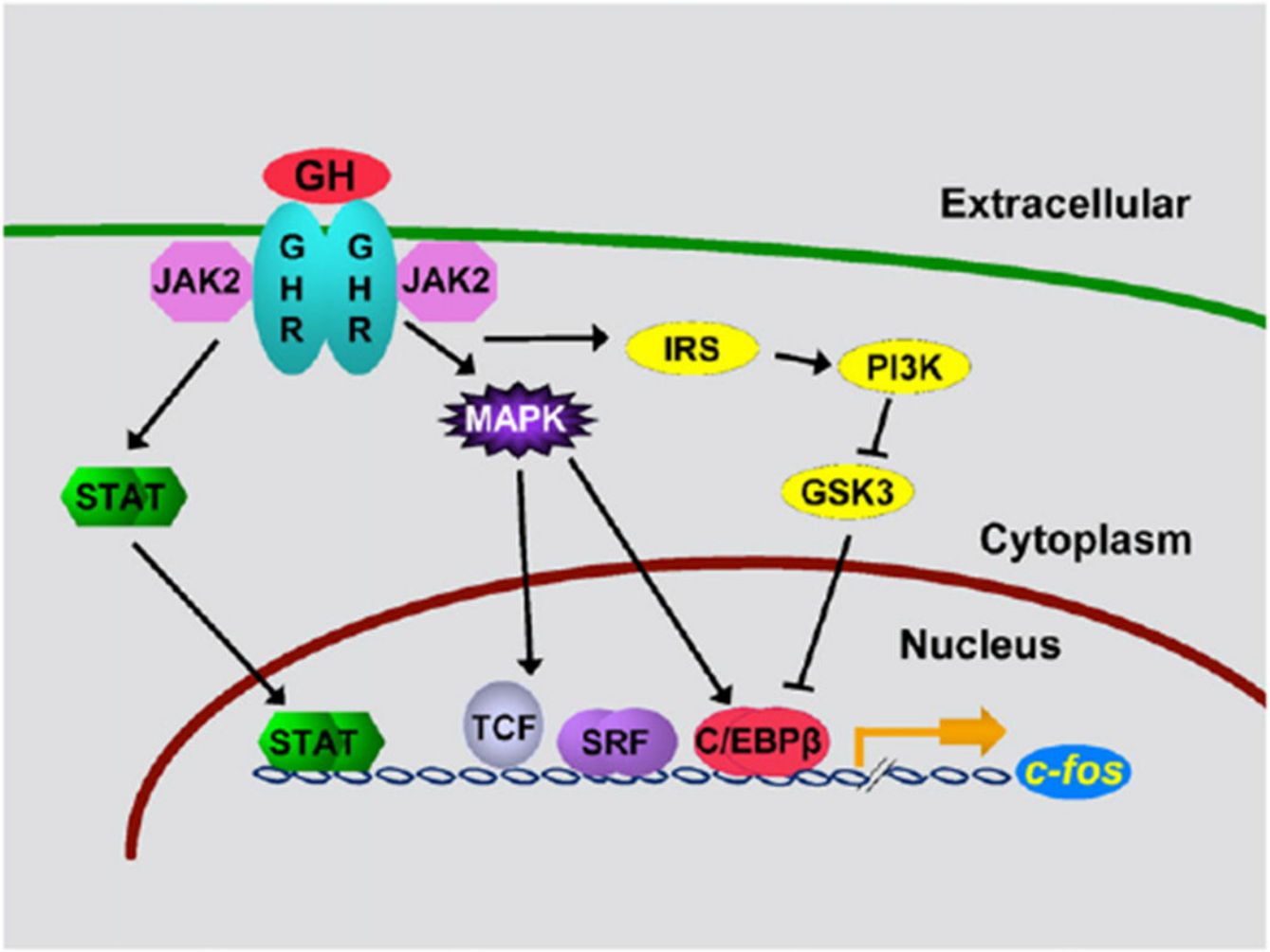

Fig. 2.

Multiple GH signaling pathways can contribute to specific GH responses. GH: growth hormone; GHR: growth hormone receptor; JAK2, Janus kinase 2; STAT: Signal Transducer and Activator of Transcription; MAPK: mitogen-activated protein kinase; IRS: insulin receptor substrate; PI3K: phosphatidyl inositol 3 kinase; GSK-3: glycogen synthase kinase-3; TCF: ternary complex factors; SRF: serum response factor; C/EBP: CCAAT enhancer binding protein. Figure adapted from Cesena et al., Molecular Genetics and Metabolism, 2007, 90, 126–133 © Bioscientifica Ltd (2007). Adapted by permission.

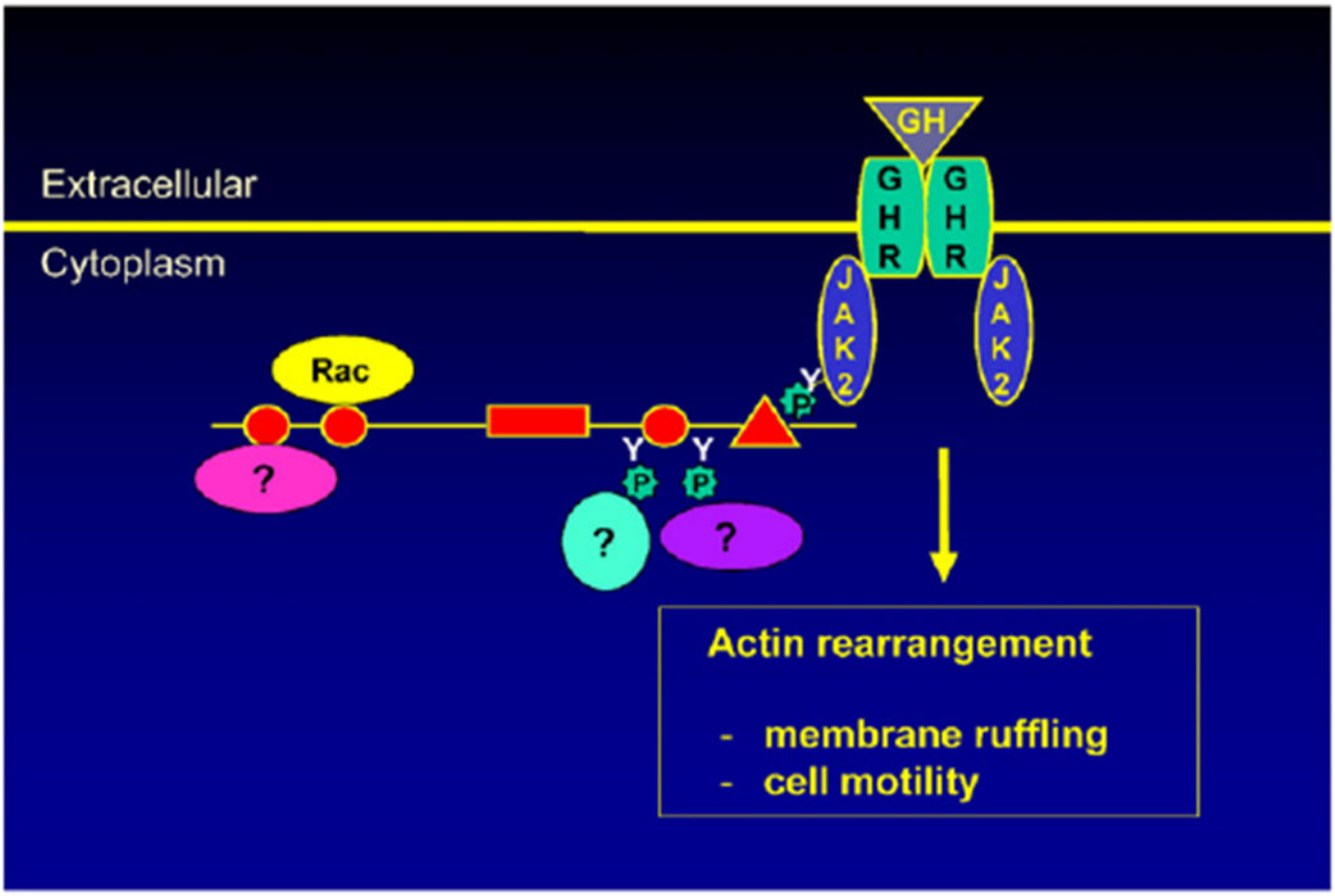

Fig. 3.

SH2B1β regulates the actin cytoskeleton and cell motility at least in part by serving as a scaffold protein for actin cytoskeleton-regulating proteins.