Chapter 5

Growth Hormone Receptor Signaling Pathways and its Negative Regulation by SOCS2

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http://dx.doi.org/10.5772/64606

Abstract

Growth hormone (GH) is a critical regulator of linear body growth during childhood but continues to have important metabolic actions throughout life. The GH receptor (GHR) is ubiquitously expressed, and deficiency of GHR signaling causes a dramatic impact on normal physiology during somatic development, adulthood, and aging. GHR belongs to a family of receptors without intrinsic kinase activity. However, GH binding to homodimers of GHR results in a conformational change in the receptors and the associated tyrosine kinase Janus kinase 2 (JAK2) molecules. Activated JAK2 phosphorylates the GHR cytoplasmic domain on tyrosine residues, and subsequent JAK2-dependent and JAK2-independent intracellular signal transduction pathways evoke cell responses including changes in gene transcription, proliferation, cytoskeletal reorganization, and lipid and glucose metabolism. JAK2 phosphorylates STAT5b, which is a key transcription factor in GH regulation of target genes associated with body growth, intermediate metabolism, and gender dimorphism; although STAT1, 3, and 5a have also been shown to be recruited by the GHR. In addition, many transcripts are regulated independently of STAT5b as a result of GHR activation of Src, ERK, and PI3K-mTOR signaling pathways. The analysis of molecular mechanisms involved in inactivation of GHR-dependent signaling pathway is also imperative for understanding GH physiology. This is clearly illustrated in the case of hepatic GHR-JAK2-STAT5b activation where signal duration regulates gender differences in liver gene expression. An early step in the termination of GH-dependent signaling is removal of GHRs by endocytosis and ubiquitination. The level of ubiquitin ligase SOCS2 is constitutively low, but its expression is rapidly induced by GH. SOCS2 binding to GHR complex promotes their ubiquitination and subsequent proteasomal degradation, contributing to the termination of the GH intracellular signaling. Clinically relevant, SOCS2 is a key negative regulator of GH-dependent body growth and lipid and glucose homeostasis. Furthermore, several cytokines, growth factors, xenobiotics, and sex hormones can regulate

SOCS2 protein level, which provides a mechanism for cross-talking where multiple factors can regulate GHR signaling during somatic development. A better understanding of this complex regulation in physiological and pathological states will contribute to prevent health damage and improve clinical management of patients with growth and metabolic disorders.

Keywords: GHR, SOCS2, Growth, Metabolism, sexual dimorphism

1. Introduction

Growth hormone (GH) is the main regulator of somatic growth through pleiotropic actions on systemic metabolism and local actions on the bone growth plate [1–4]. GH is predominantly linked to linear growth during childhood but continues to have important metabolic actions throughout life. Secreted from the pituitary gland, GH binds to its receptor (GHR) on the surface of the cells of the target tissues triggering a rapid cascade of intracellular signaling events, which leads to the expression of GH-regulated genes. This set of genes includes positive regulators of GH actions such as the one coding for the growth factor IGF-I, and also genes involved in the negative feedback mechanism responsible for the termination of the GHR intracellular signal, such as the suppressor of cytokine signaling 2 (SOCS2). In this chapter, we will review the current knowledge about the intracellular GH signaling as well as the role of SOCS2 in this regulation and discuss the implications on body growth.

2. Intracellular GH signaling

GH exerts its intracellular actions via the GHR that is ubiquitously expressed (e.g., liver, fat, muscle, bone, and lymphocytes). The GHR belongs to a family of transmembrane cytokine receptors that lack intrinsic enzymatic activity [5]. Instead, in order to activate intracellular signaling, the GHR cytosolic domain associates to the tyrosine kinase Janus kinase 2 (JAK2) [5]. Upon binding, GH promotes the dimerization of two GHR proteins, which results in a conformational change that triggers the activation of the associated tyrosine kinase JAK2 due to the unmasking of their kinase domain [5]. JAK2 activation triggers cross-phosphorylation event on the two adjacent JAK2 proteins and the phosphorylation of tyrosine residues on the cytosolic domain of the GHR. Signal transducer and activator of transcription (STAT) proteins are then recruited to these phosphorylated tyrosines (pY), where they themselves become substrates of JAK2. Although STAT1, STAT3, and STAT5a can also be recruited to the GHR, STAT5b is the main mediator of GH signaling [1, 3, 6]. Phosphorylation by JAK2 releases STAT5b from the receptor and promotes the formation of STAT5b dimer complexes. STAT5b homodimers translocate to the nucleus, bind to their response elements (TTCNNNGAA) on the DNA, and regulate the transcription of GH target genes (e.g., IGF-1, SOCS2, CYP2C12, and HNF6 [7–10]). Studies of human subjects carrying rare inactivation mutations in the GHR, STAT5b, and IGF-I genes have demonstrated the essentiality of this pathway for normal human

http://dx.doi.org/10.5772/64606

growth. Individuals carrying these mutations exhibit severe dwarfisms with very similar growth curves [11–15]. Although STAT proteins are critical for many actions of GH [6], GH activation of JAK2 can initiate signaling pathways in addition to the STAT transcription factors as a result of GHR activation of: (1) the MAPK (Mitogen Activated Protein 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), 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 [6].

3. SOCS2 mediates GHR turnover

The analysis of molecular mechanisms involved in the inactivation of the GHR-dependent signaling pathway is also imperative for understanding GH physiology. This is clearly illustrated in the case of hepatic GHR-JAK2-STAT5b activation where signal duration regulates gender differences in liver gene expression [10]. Studies on primary hepatocytes and several cell lines have shown that GH-induced activation of JAK2-STAT5b is transient, with maximal activation achieved within the first 30 min of stimulation, followed by a period of inactivation. This period is characterized by an inability to achieve maximal JAK2-STAT5b activation by GH in the following 3–4 h, unless GH is withdrawn from the media [16]. Similarly, the male pattern of pituitary GH secretion in rats is episodic with peaks every 3–4 h with unmeasurable basal levels. Consequently, intracellular activation of STAT5b is also episodic and periods with low GH circulating levels are required to achieve maximal activation of STAT5b. On the other hand, female rats, which exhibit a more continuous GH secretion pattern with higher basal levels and smaller, irregular, and intermittent peaks, show reduced STAT5b activation compared with their males counterparts [17].

An early and important step in the termination of GH-dependent signaling is the removal of GHRs from the cell surface by mechanisms of endocytosis, which are dependent on ubiquitination [18]. SOCS2 is part of an E3 ubiquitin ligase complex with a key role in the negative regulation of GHR-JAK2-STAT5b signaling pathway, acting in a classical negative feedback loop manner [19–22]. The transcription of SOCS2 is induced by STAT5b in response to GH stimulation—which leads to elevated SOCS2 protein levels [16]—consistent with the critical role of STAT5b for growth [7] (**Figure 1**). SOCS2 binds to phosphorylated tyrosines at the GHR cytosolic domain through its SH2 domain while recruits Elongin B and C, the scaffold protein Cullin5, and the ring finger protein Rbx2 through its SOCS box domain to assemble an E3 ubiquitin ligase complex that ubiquitinates the GHR and promotes its internalization [23, 24] (**Figure 2**). These GHR-containing early endosomes are later fused to the lysosomes leading to GHR degradation [24]. In addition to SOCS2, the ubiquitin ligase β-TRCP has also been shown to mediate GHR ubiquitination and internalization with the key difference that this process is not GH dependent and the mechanism seems to act independently from SOCS2 [25]. Therefore, the current evidence would suggest that GHR membrane content is controlled by ubiquitin driven endocytosis [18]. The constitutive internalization of GHR is mediated by β-

TRCP, which is further enhanced upon GH induction of SOCS2 expression and function. Furthermore, the SH2 domain of SOCS2 can also bind to other components of the signaling cascade interfering with the propagation of the signal. Particularly, SOCS2 binds the GHR at Tyr487 and Tyr595 to prevent GHR signaling [21, 22]. The activation loop of JAK2 is also a target of SOCS2 that prevents JAK2 tyrosine phosphorylation and activation of STATs [16].

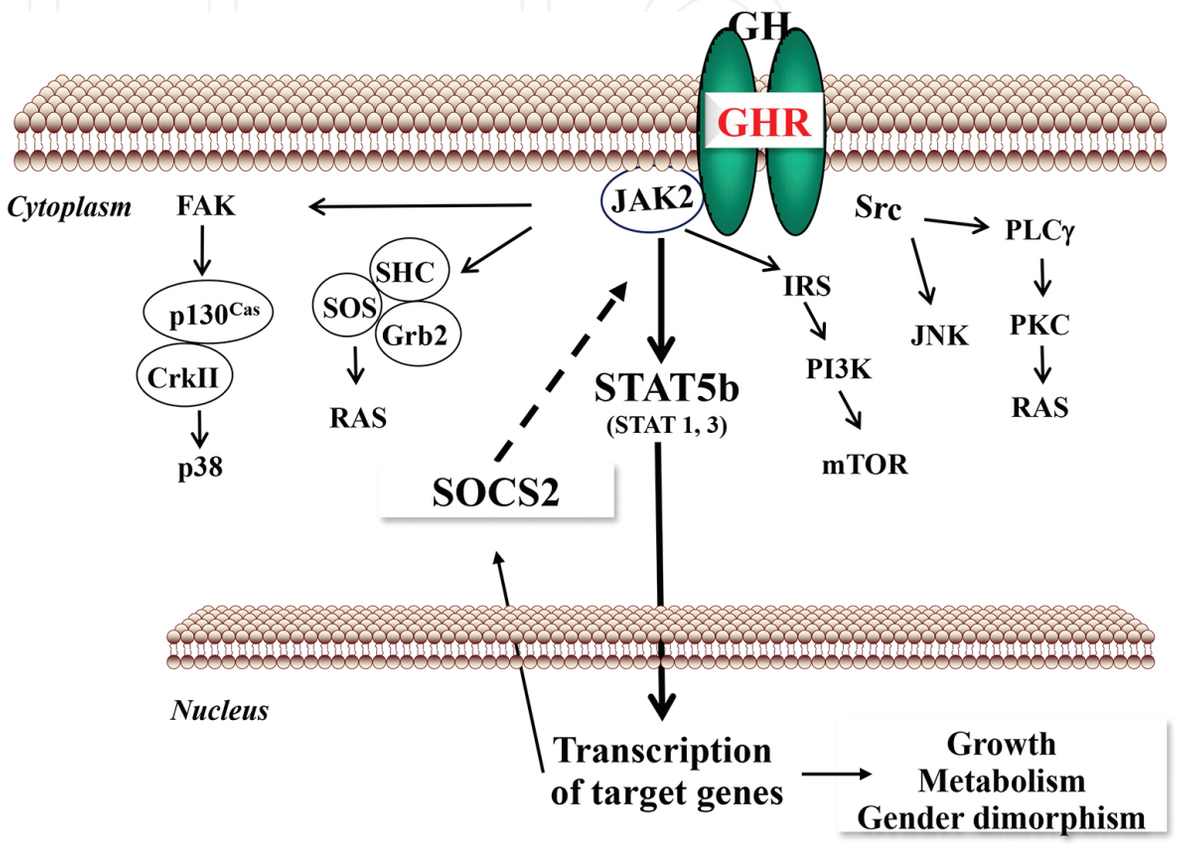

Figure 1. Negative regulation of GHR-STAT5b signaling pathway by SOCS2: The JAK2-STAT5b signal transduction pathway requires an exquisite cellular control and loss of its regulation can promote alterations in body growth. Intracellular activation of GHR-JAK2-STAT5b signaling pathway is transient and it is followed by a period of inactivation that is characterized by an inability to achieve maximal JAK2-STAT5b activation by GH. GHR-STAT5b activity induces the transcription of SOCS2 that acts as part of an E3 ubiquitin ligase complex that plays a key role in the negative regulation of GHR-JAK2-STAT5b signaling pathway.

The physiological role of SOCS2 as negative regulator of GH signaling was clearly demonstrated after the engineering of SOCS2-/- mice that are 40% larger than their wild-type (WT) mates. This phenotype of enlarged growth is not observed in mice lacking other members of the SOCS family such as SOCS1 or CIS (Cytokine-inducible SH2-containing protein), which strengthen the role of SOCS2 as key negative regulator of GH signaling. These *in vivo* studies highlight the role of SOCS2 as a key negative regulator of GH-dependent signaling and its role in the control of lipid and glucose homeostasis [26]. High SOCS2 expression levels have been found in the liver and the heart [16, 27], and, importantly, SOCS2 actions may not be confined to regulating GH signaling. There is evidence that SOCS2 can directly bind the IGF-IR, and,

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therefore, it is possible that SOCS2 also regulates IGF-I signaling, although IGF-I does not induce SOCS2 expression [28, 29]. In addition, SOCS2 has been shown to inhibit signaling by IL-6, LIF, IGF-I, and prolactin (Prl) [19].

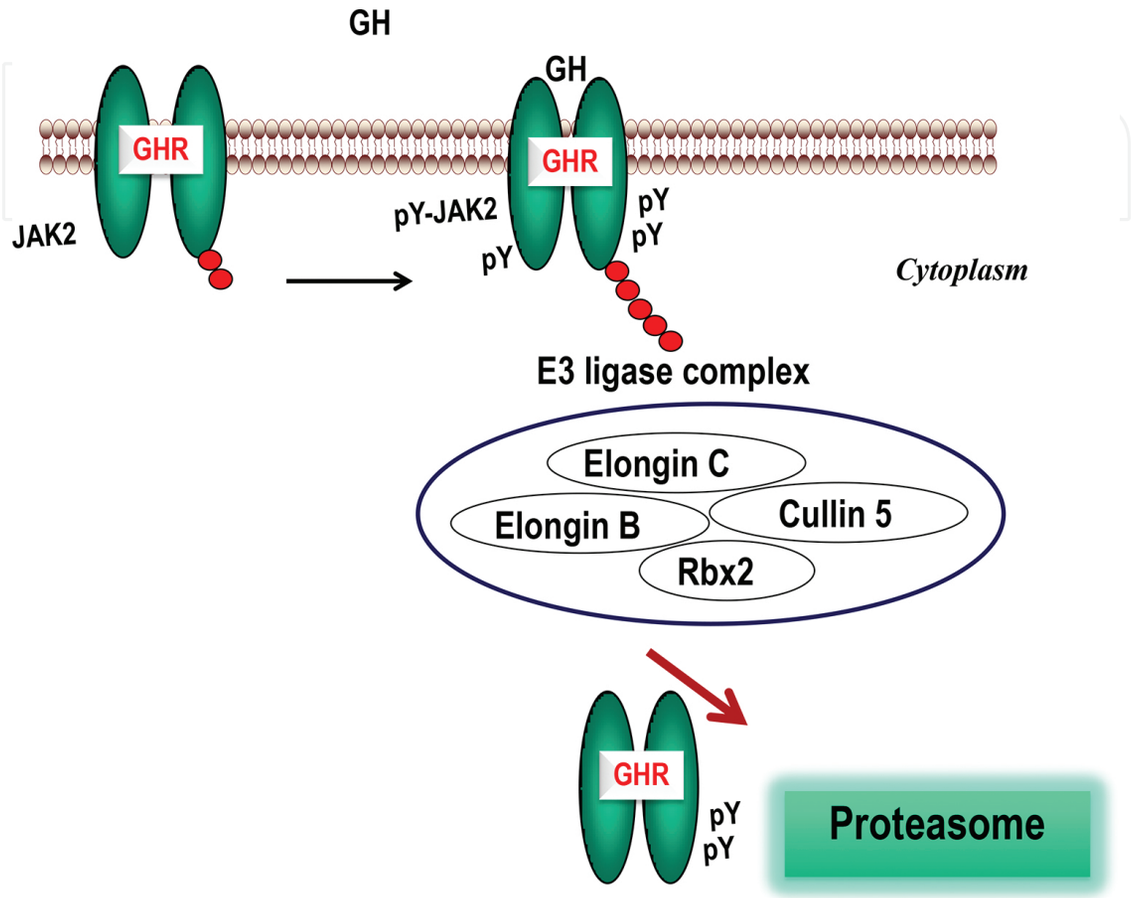

Figure 2. E3 ligase activity of SOCS2 and GHR degradation by proteasome: SOCS2 is part of an E3 ubiquitin ligase complex with a key role in the negative regulation of GHR-JAK2-STAT5b signaling pathway. SOCS2 binds to phosphorylated tyrosines (pY) at GHR cytosolic domain while recruits Elongin B and C, the scaffold protein Cullin5, and the ring finger protein Rbx2 to assemble an E3 ubiquitin ligase complex that mediates ubiquitination of target proteins (e.g., GHR) and their subsequent proteasomal degradation. The activation loop of JAK2 is also a target of SOCS2 that prevents JAK2 tyrosine phosphorylation and activation of STATs.

4. Other mechanisms of GHR signaling inhibition

In addition to SOCS2, GHR signaling induces the expression of other SOCS family members (SOCS-1, -3, and CIS) in a transient fashion. In vitro studies shown that SOCS1, SOCS3, and to a lesser extent CIS, are able to inhibit GHR signaling [30, 31]. Both SOCS1 and SOCS3 can directly bind phosphorylated JAK proteins via their SH2 domains inhibiting the kinase activity through the N-terminal kinase inhibitory region (KIR) [32]. Knockouts (-/-) of SOCS1 and SOCS3 genes are incompatible with life. SOCS1-/- mice died soon after birth due to hyperac-

tivation of INFγ signaling. Combination of SOCS1 deletion with genetic depletion of INFγ or treatment with anti-INFγ antibodies ameliorates this phenotype [33]. Under these conditions, no changes in body growth have been reported, suggesting that SOCS1 may not play a major role in GHR signaling inhibition *in vivo*. On the other hand, CIS-/- mice exhibit no obvious phenotype, although overexpression of CIS results in restricted growth [16, 34]. Despite certain degree of redundancy within the SOCS family, the results obtained from mouse models suggest that SOCS2 is a major negative regulator of GH signaling *in vivo*. In addition to SOCS, the level of cell surface GHRs can be influenced by transcriptional, translational, and posttranslational factors (e.g., nutritional status, endocrine context, developmental stage, and sex steroids), which thereby regulate cell sensitivity to GH actions [16]. GHR translocation is also directly inhibited by IGF-I, likely contributing to a local feedback loop to hamper GH sensitivity [35]. As mutations in the GHR [15] and STAT5b genes [11] result in growth deficiencies, activating mutations of the tyrosine phosphatase SHP2 (PTPN11) also generates growth retardation linked to the Noonan syndrome [36]. PTPN11 is involved in the negative regulation of GH signaling, rendering lower IGF-I production after GH stimulation through regulation of the RAS/ERK1/2 pathway. Noonan syndrome driving PTPN11 mutants hyperactivates the RAS/ERK pathway in response to GH *in vitro* and *in vivo*, suggesting that GH-induced ERK1/2 activation could contribute to GHR signaling inactivation [36]. In the future, it will be interesting to study whether hyperactivation of ERK1/2 inhibit GHR through induction of SOCS expression [37]. Other protein phosphatases such as SHP1 and PTP1b (encoded by the PTPN6 and PTN1 genes, respectively) also play a role in controlling intracellular GH signaling. Upon GH stimulation, SHP1 translocates into the nucleus, where it binds to STAT5b inhibiting its activity [38]. SHP1 also interacts with phosphorylated JAK2 after GH stimulation, inhibiting the propagation of the signal, accordingly, SHP1-/- mice show prolonged GH signaling [39]. On the other hand, PTP1b is able to dephosphorylate GH-activated GHR and JAK2 [16, 40, 41].

5. GH regulation of body growth

Currently, it is accepted that GH is predominantly linked with postnatal growth, whereas IGF-I is linked with both pre and postnatal growth [42, 43]. The original somatomedin hypothesis, which proposed that pituitary GH increases tissue growth by stimulating production of hepatic IGF-I, has developed gradually, from a simple to a more complex form, by studies showing that (1) GH and IGF-I have both dual and overlapping functions on growth plate [44, 45]. However, there are still unanswered questions about the independent and combined relationships of GH and IGF-I on the growth plate and bone growth, including whether or not GH mediates any IGF-I independent effects on bone growth [46] and (2) conditional liver-specific IGF-I null mice exhibited body weights that were indistinguishable from wild-type littermates [47, 48]. These studies showed that, although the liver is the main source of circulating IGF-I, it is local IGF-I that is important for regulating postnatal growth [47]. Indeed, stimulation of hepatic IGF-I production in IGF-I null mice demonstrated that liver derived endocrine IGF-I contributes to 30% of adult body size and sustains postnatal development [49, 50]. In addition, GH is more effective than IGF-I because GH exerts additional growth-

http://dx.doi.org/10.5772/64606

promoting actions independent of IGF-I. Previous studies have nicely demonstrated that STAT5b is important for sexual dimorphism of body growth (male-specific body growth) and liver gene expression [51]. Indeed, GH-dependent transcription of IGF-I is directly regulated by STAT5 [3], and the mode of GH administration (i.e., continuous vs. intermittent) influences GH actions on body growth rate, IGF-I expression, and STAT5b activity, which might be clinically relevant. Intermittent (male-like pattern) GH administration to rodents is a more potent stimulus of body growth rate, IGF-I expression, and STAT5b activity in liver than is continuous (female-like pattern) administration [17]. Global disruption of STAT5b in mice caused loss of sexually dimorphic growth characteristics, so that the affected males reduced their size to female size while female mice appeared unaffected. In addition, circulating IGF-I is reduced by 30–50% in affected male but not in female mice. In addition to STAT5b, other transcriptions factors are related with body growth. This is exemplified by the glucocorticoid receptor (GR), which is a critical coactivator of STAT5b in liver [52], or by interactions between estradiol (E2)/estrogen receptor alpha (ERα) signaling and STAT5 [53]. In addition to endocrine actions, paracrine involvement of STAT5a/b in the effects of GH on muscle is also evident in the loss of muscle IGF-I transcripts and mass seen with muscle-specific deletion of STAT5a/b [54].

6. SOCS2 and body growth

The importance of SOCS2 in the negative regulation of body growth through inhibition of GHR-JAK2-STAT5b signaling was further demonstrated using genetically modified mice. Thus, the SOCS2-/- overgrowth phenotype is fully dependent on GH and can be rescued by inhibiting GH expression in these mice by crossing them with $Ghrhr^{lit/lit}$ mice that have no circulating GH. Both the double-knockout mice and the $Ghrhr^{lit/lit}$ mice exhibited a similar 60% growth retardation. Furthermore, administration of GH to these knockout mice caused an increase of growth to a size indistinguishable from SOCS2-/- mice [21, 55]. Similarly, mice resulting from crossing SOCS2-/- with STAT5b-/- mice show growth rates close to wild-type mice [56]. Similar phenotypes to the SOCS2-/- mice have been observed in high-growth (hg) mice, a phenotype that occurs following spontaneous mutation in mouse chromosome 10 [57]. However, in contrast to SOCS2-/-, hg mice have higher plasma IGF-I levels [57]. Surprisingly, overexpression of SOCS2 results in a similar phenotype to SOCS2-/- mice [34, 58], which suggests that the effects of SOCS2 on GH signaling are dose-dependent, with dual effects [16, 58]. It has been proposed that at physiological levels, SOCS2 inhibits GH signaling, by promoting GHR degradation, but at higher doses, it inhibits signaling of other, more potent GH inhibiting SOCS (i.e., SOCS1 and 3) [34, 58]. This could be through association with SOCS3 binding sites on the GHR, thus blocking SOCS3 action, or by binding the other SOCS themselves and suppressing them through proteasomal degradation [22]. The validity of these mechanisms has been questioned [59] and their physiological relevance remains uncertain. A more likely explanation of the effects created by SOCS2 overexpression would be a disruption of its E3 ligase activity by sequestering components of the multimeric E3 ligase away from the GHR.

Several studies have demonstrated that polymorphisms in the GH/IGF-I/SOCS2 system can also modulate the efficacy of GH treatment in humans. In humans with GH insensitivity due to a GHR defects, growth retardation, and reduced bone density, which are the result of IGF-I deficiency, are observed [60]. More recently, abnormalities of STAT5b, the IGF-IR gene itself, and the binding proteins that influence IGF-I bioavailability at the tissue level have all been reported to be associated with a variable extent of short stature in humans [12]. The effects of GH treatment on growth can also be influenced by polymorphisms on GHR or IGFBP3 genes and by their interactions among polymorphisms [61–64]. Genetic polymorphisms in the SOCS2 gene have been associated with adult height variation in healthy individuals [13, 14, 65]. Recently, Braz et al. observed that SOCS2 polymorphism and its interaction with polymorphisms in GHR and IGFBP3 loci influenced the adult height of children with Turner syndrome and GHD (Growth Hormone Deficiency) after GH therapy [66]. Moreover, a SNP (Single Nucleotide Polymorphism) in the SOCS2 gene was reported associated to increased pubertal height in a Finnish cohort, supporting the role of SOCS2 in body growth in humans [67].

7. SOCS2 actions in bone and skeletal muscle

The overgrowth phenotype of the SOCS2 null (SOCS2-/-) mice [68] led to the confirmation that SOCS2 is a key effector of GH/IGF-I axis, in line with the anabolic role of GH on the skeleton [69, 70]. An interaction between SOCS2 and GH signaling in regulating body growth is consistent with the temporal increased expression of the GHR and the overgrowth of SOCS2-/- mice [68], with both occurring at around 3 weeks of age [68, 71]. Adult male SOCS2-/- mice are 40% heavier than their WT littermates while adult females reach the same size as the WT males [68]. Notably, the increased body weight of SOCS2-/- is not a result of any increase in fatty tissue but rather a proportional increase in size of most internal organs, muscle, and bone. SOCS2-/- mice have increased body length with longer longitudinal bones (femur, tibia, radius, and humerus) [68, 72]. No alterations to the growth plate were noted in the first description of SOCS2-/- mice [68]. Later investigations, however, found that epiphyseal chondrocytes express SOCS2 and growth plates from SOCS2-/- mice were enlarged with wider proliferative and hypertrophic zones. These findings were associated with an increased long bone length [72]. Recently, microtomography (μCT) analysis at 7 weeks of age showed that SOCS2-/- mice have increased bone mass (i.e., increased bone volume, trabecular number, and trabecular thickness), although these mice exhibit no difference in bone mineral density (BMD) compared to WT littermates [72]. In contrast, others authors have described lower trabecular and cortical bone mineral density in SOCS2-/- mice (at 4 and 15 weeks of age) as well as reduced cortical cross-sectional area and cortical thickness (at 4 weeks of age) [73]. Interestingly, these studies found elevated serum levels of osteocalcin (a marker of bone growth) [72, 73] and TRAP5 (a marker of osteoclast number) [72], which would indicate increased bone turnover in SOCS2-/- mice [68, 72]. Although circulating IGF-I levels are normal in SOCS2-/- mice [68, 72], they have elevated IGF-I mRNA in some tissues (heart, lung, and spleen but not liver, bone, fat, and muscle). Therefore, it is likely that the increased bone growth and observed structural differences within SOCS2-/- growth plates are a direct consequence of altered SOCS2-mediated

GH signaling at the growth plate [33, 72]. Recent studies of Dobie and coworkers support this hypothesis. Using *ex vivo* metatarsal cultures, they showed that GH was able to induce linear growth only in the absence of SOCS2 [74] via a mechanism that is independent of IGF-I.

In addition to increased bone length, enhanced GHR signaling by GH treatment or SOCS2 deficiency causes skeletal muscle enlargement [68]. The molecular effects of GH and SOCS2 on skeletal muscles are uncertain. GH actions on skeletal muscles are a consequence of its systemic metabolic effects but also in part mediated by hormone-induced changes in gene expression within the muscle, as demonstrated by studies that show GH-induced changes in gene expression, including SOCS2, in human [75, 76] and murine [77] skeletal muscles. SOCS2 also modulates signaling pathways in the muscle independently from GH. Using C2C12 mesenchymal precursor cells, Ouyang et al. have shown that SOCS2 interferes with myotube formation and favors the differentiation into osteoblast in a process that, although not fully understood, would require the regulation of JunB [78]. In line with these observations, SOCS2 would also suppress myotube formation by inhibiting mitochondria biogenesis by interfering with the p38/ATF2 pathway [79]. Overall, these investigations highlight the importance of SOCS2 actions on bone and muscle development and growth through the modulation of multiple pathways, not restricted to GH signaling. Moreover, SOCS2 plays a key role as mediator of the interplay between sex steroids and GH signaling in these tissues.

8. Other functions of GH in the regulation of body weight

Disruption of GHR-STAT5-SOCS2 signaling pathway is also associated with metabolic disorders [17, 26, 51, 80–84]. An inefficient GHR-JAK2-STAT5b signaling pathway results in fatty liver and adiposity in rodents and humans due to enhanced lipogenesis and reduced triglyceride secretion as well as reduced lipolysis [4, 80, 81]. This is supported by original findings showing that STAT5b null male mice become obese in later life [51] and that STAT5b deletion in a mature human was associated with obesity [85]. Therefore, GHR activated STAT5b plays a critical role in regulation of key enzymes involved in lipid and energy balance. Liver-specific GHR ablation leads to fatty liver because of reduced STAT5 activation despite normal plasma free fatty acid and minimal adiposity. Relevant to this review, agonists of liver X receptor (LXR), which cause hepatic steatosis [86], inhibit GH-STAT5b signaling [87]. This inhibition is mediated by SREBP1, a LXR target gene, through the downregulation of STAT5b gene transcription and stimulation of STAT5b protein degradation [87]. In contrast, ablation of SOCS2 in mice, which increased STAT5 signaling, protects them from high-fat diet-induced liver steatosis by increasing hepatic triglyceride secretion. As a result, these mice have increased peripheral fat accumulation both in adipose and muscle tissues. Although this is not associated with changes in systemic insulin sensitivity when mice are fed on a normal chow diet, under high-fat diet conditions, SOCS2-/- mice are glucose intolerant and insulin resistant and show increased expression of inflammatory cytokines [26]. The latter has been suggested to be a consequence of increased sensitivity of SOCS2-/- macrophages to lipopolysaccharide (LPS), leading to increased NF*k*B activation and inflammatory signaling in the liver despite reduced steatosis [26]. In contrast, SOCS2 deletion protected against streptozotocin-induced

type I diabetes in adult male mice presumably by enhancing antiapoptotic actions of STAT5b [88]. Notably, SOCS2 can regulate inflammation by modulating the actions of other inflammatory cytokines [89]. The role of SOCS2 in the regulation of the inflammatory response seems to be independent of GH signaling. Furthermore, the effects of inflammatory cytokines on SOCS2 have been poorly investigated, with evidence that some interleukins induce SOCS2 gene expression only in specific cell types [89]. Thus, it has recently reported that in a sheep model, a point mutation in the SOCS2 gene not only resulted in higher body weight and size but also elevated leukocytes count in the milk as a sign of enhanced inflammatory response [90]. In addition, altered SOCS2 expression has also been associated with malignancies [84, 91–93]. Therefore, how to target SOCS2-regulated pathways without causing negative side effects that systemic and chronic reduction in SOCS2 protein might cause is still a challenge.

9. SOCS2 mediates the cross-talk between steroids and GH

Until recently, most studies concerning the interaction among GH and steroids have been focused on the influence of sex steroids on gender-specific pituitary GH secretion that has a great impact on hepatic transcriptional regulation [17, 94]. However, a direct target of steroids may also occur because interaction with androgen receptor (AR), estrogen receptor alpha or GR, and the signaling pathways linked to these receptors are connected with lipid and glucose homeostasis [95] and tissue growth [96, 97]. The relationship between GH and sex steroids relative to body growth has been extensively studied, but it is not fully understood. Sex steroids can directly modulate pituitary GH secretion [94, 98] in a process that in men seems to require prior aromatization of testosterone into estrogen [99] but also indirectly through regulating liver IGF-1 production. Thus, hypogonadal children have reduced GH secretion [100, 101] and girls with precocious puberty show increased levels [102]. Additionally, sex steroids also exert GH-independent effects on growth [103, 104]. During puberty, children experience a growth spurt concomitant with increasing levels of gonadal steroids and GH secretions [98, 103]. This pubertal growth spurt has been attributed primarily to the actions of estrogens [105], acting directly on the growth plate cartilage inducing proliferation and finally promoting epiphyseal fusion [106]. Thus, in girls with Turner syndrome, hormone replacement therapy results in growth spurt [107]. Due to these effects on bone maturation, pharmacological doses of sex steroids have been used in prepubertal children with the nonpathological condition of constitutionally tall stature to limit their final height since 1950s [108, 109].

At the molecular level, increasing amount of evidences suggests that SOCS2 as a key mediator of the interplay between GH and steroid hormones. Both androgens and estrogens are able to induce the expression of SOCS2, which in turn limits GH signaling in cells from different tissue origins such as liver, breast, and prostate [84, 110]. Transcriptional induction of SOCS2 expression by sex steroids is mediated by the steroid receptors, AR, for androgens, and ERα, in the case of estrogens. This activation seems to be mediated by STAT5 [84] in a similar fashion to what happened with another steroid receptor, the GR, which acts as cofactor for STAT5-mediated transcription of SOCS2 after glucocorticoid stimulation [27]. Thus, direct upregulation of SOCS2 expression by steroid hormones would limit GH actions on target tissues. The

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liver, a major target tissue of GH, expresses both AR and ERα. Therefore, SOCS2 might play a central role in the modulation of GH signaling by androgens and estrogens, which defines the gender dimorphism in response to GH. In good agreement to the role of SOCS2 as mediator of sex steroids and GH signaling, SOCS2 KO mice show a less pronounced growth reduction after E2 treatment than their WT mates (unpublished observations). Recently, Bolamperti and colleagues described a novel SOCS2 regulation by estradiol in human osteoblasts [111]. Here, E2 induces GH signaling (STAT5 phosphorylation after treatment with GH) by inhibiting SOCS2 expression through a mechanism that involves proteasomal degradation of the protein but not genomic actions. The molecular characterization of this regulation, e.g., whether these effects are ER mediated, as well as the elucidation of this regulation as a general mechanism or whether it is restricted to osteoblast cells deserve further investigation. Overall, steroids in general and sex steroids in particular can modulate GH actions by controlling SOCS2 expression in several ways and in a tissue-specific manner. In the liver, SOCS2 induction by steroids would modulate central metabolism as well as influence IGF-I secretion that in turn affects GH secretion. In the bone, however, estrogens would potentiate GH actions by reducing the expression of SOCS2.

10. General conclusions

GH is the main regulator of somatic growth through pleiotropic actions on systemic metabolism and local actions on the bone growth plate. Relevant is the critical role of SOCS2 for the negative regulation of body growth. However, many aspects on the actions of SOCS2 in physiological and pathological models have yet to be understood. Particularly, more studies investigating the mechanisms by which SOCS2 regulates metabolism (e.g., lipid metabolism), insulin actions, malignancies, or GHR signaling at the growth plate are certainly needed. Notably, how to target the elements of the SOCS2-regulated pathways without causing negative side effects that systemic and chronic reduction in SOCS2 protein might cause is still a challenge. Finally, the consequences of long-term exposition to steroid compounds (particularly, sex hormones-related compounds) on normal development, as a consequence of their influence on GHR signaling, are largely unknown. Understanding this complex interaction in physiological and pathological states could contribute to prevent health damage and improve clinical management of patients with somatic growth disorders.

Acknowledgements

We thank all the authors that have made a contribution to the understanding of the negative regulation of GHR signaling. We apologize to those whose work deserves to be cited but unfortunately are not quoted because of space limitations. The research program in the author's lab was supported by grants-in-aid from the Spanish Ministry of Economy and Competitiveness (MINECO) with the funding of European Regional Development Fund, European Social Fund, and Alfredo Martin-Reyes Foundation (Arehucas)—Canary Islands

Foundation for Cancer Research (FICIC). D.I.-G. and A.F.-M. are supported by grants from the Novo Nordisk Foundation and the Danish Cancer Society.

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