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Classical and Novel GH Receptor Signaling Pathways

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SUMMARY

In this review, I summarize historical and recent features of the classical pathways activated by growth hormone (GH) through the cell surface GH receptor (GHR). GHR is a cytokine receptor superfamily member that signals by activating the non-receptor tyrosine kinase, JAK2, and members of the Src family kinases. Activation of the GHR engages STATs, PI3K, and ERK pathways, among others, and details of these now-classical pathways are presented. Modulating elements, including the SOCS proteins, phosphatases, and regulated GHR metalloproteolysis, are discussed. In addition, a novel physical and functional interaction of GHR with IGF-1R is summarized and discussed in terms of its mechanisms, consequences, and physiological and therapeutic implications.

Keywords

growth hormone receptor; signaling; IGF-1 receptor

1. Molecules involved in initial GH signal generation

Nearly a century ago, Evans and Long published their fundamental observation that rats injected intraperitoneally with extracts of cow anterior (but not posterior) pituitary glands "…grew invariably much heavier than their litter mate sisters… Increase in weight results to a great extent from a storage of fat, but is not solely due to this, the skeleton being invariably somewhat larger and heavier, and, as would be expected, the heart, lung, alimentary canal and kidney are heavier" (Evans and Long 1922). This suggested the existence of pituitary-

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derived growth hormone (GH). Using a five step extraction and purification procedure, Li and Evans two decades later first isolated GH from ox pituitaries (Li and Evans 1944).

It was another 35 years later that molecular cloning and recombinant technology allowed discovery of the gene encoding GH (Martial, Hallewell et al. 1979) and eventually the high level production of human GH for therapeutic use. The GH gene in humans and most other vertebrates is found on chromosome 17; in humans, GH is one of five similar genes in a 48 kilobase cluster (Chen, Liao et al. 1989). The GH gene encodes a 22 kDa circulating protein hormone that emanates from the pituitary in many species, signaling the profound anabolic and metabolic actions noted by Evans and Long and others (Isaksson, Eden et al. 1985, Waters, Hoang et al. 2006, Moller and Jorgensen 2009). Elucidation of the three-dimensional structures of both porcine and human proteins in the late 1980s-early 1990s (Abdel-Meguid, Shieh et al. 1987, de Vos, Ultsch et al. 1992) revealed GH to be composed of four antiparallel α-helices connected by loops of varying length; its overall structure was similar to what at the time was an emerging group of cytokines, hormones, interleukins, and interferons.

Binding sites for GH were shown to be present in multiple tissues, being notably enriched in liver; indeed, the first isolation of cDNAs for the rabbit and human GH receptors (GHRs) in 1987 employed liver tissue as the starting material (Leung, Spencer et al. 1987). In short order, GHR cDNAs encoding mouse, rat, cow, sheep, pig, and chicken were cloned between 1989-1991 (Baumbach, Horner et al. 1989, Smith, Kuniyoshi et al. 1989, Adams, Baker et al. 1990, Cioffi, Wang et al. 1990, Hauser, McGrath et al. 1990, Burnside, Liou et al. 1991). As anticipated, the GHR proteins encoded in these species, while varying in amino acid sequence, shared similar overall topology. All predicted single membrane-spanning type 1 proteins (620 residues in length in human) with a ligand-binding extracellular domain (246 residues in human) that is N-glycosylated and a substantial (350 residues in human) intracellular domain that can be ubiquitinated (Leung, Spencer et al. 1987). As discussed in greater detail by Brooks, et al elsewhere in this volume, deVos and colleagues (de Vos, Ultsch et al. 1992), in a *tour de force* co-crystallization study in 1992, determined the three dimensional structure of human GH bound to the human GHR extracellular domain; they found a novel 1:2 GH:GHR stoichiometry that supports the notion that the signaling unit of GHR is a dimer, whether it is either constitutively or inducibly formed (Cunningham, Ultsch et al. 1991, Frank 2002, Gent, van Kerkhof et al. 2002, Liu, Berry et al. 2014, Wilmes, Hafer et al. 2020). Unlike what we now know is likely an intrinsically disordered structure in the intracellular domain (Haxholm, Nikolajsen et al. 2015), the GHR extracellular domain was found to be comprised of a set of modular elements. Each GHR monomer's extracellular domain has two subdomains (1 and 2 with 1 N-terminal to 2), each comprised of seven β-strands arranged into two antiparallel β-sheets; subdomain 1 harbors most of the GH contact points and subdomain 2 facilitates dimerization of the monomers (Leung, Spencer et al. 1987). The fact that each GH molecule in the GH/GHR assemblage has two asymmetric binding sites (one for each GHR monomer in the assemblage) was a noteworthy finding that laid the groundwork for development of therapeutically useful GH antagonists (discussed in detail elsewhere (Fuh, Cunningham et al. 1992, Kopchick, Parkinson et al. 2002)).

Validation that the cloned GHR was indeed a physiological receptor for GH came in 1997 with the generation by the Kopchick group of the GHR knockout mouse (Zhou, Xu et al. 1997) (discussed in greater detail elsewhere in this volume). Thirty years prior (Laron, Pertzelan et al. 1966), Laron had described the first cases of human GH resistance (Laron syndrome). These patients had a phenotype similar to those with GH deficiency, except that circulating GH was present and often elevated. We now know that this syndrome is explained by a variety of defects in GHR that alter receptor expression, structure, or cell surface targeting and function. (Human GHR defects leading to Laron syndrome are discussed in this volume by Guevara-Aguirre.) The GHR knockout mouse (the "Laron mouse") phenocopied human Laron syndrome in displaying substantial growth retardation and proportionate dwarfism with raised levels of GH in the serum.

By virtue of structural similarities, it was rapidly appreciated that GHR fell within the large family of so-called cytokine (or hematopoietin) receptors that included receptors for various interleukins, interferons, cytokines, and hormones (Bazan 1990, Argetsinger and Carter-Su 1996, Bole-Feysot, Goffin et al. 1998, Frank and O'Shea 1999), including the related prolactin receptor PRLR. Indeed, human GH can bind and activate human PRLR (but not vice-versa (Hughes and Friesen 1985, Cunningham, Bass et al. 1990, Fu, Arkins et al. 1992, Somers, Ultsch et al. 1994)); although beyond the scope of this review, such GH-induced PRLR signaling may prove quite physiologically and pathophysiologically relevant. Further (also beyond the scope of this review), recent studies suggest important physical and functional interactions between GHR and PRLR by which each may impact the trafficking and signaling capacities of the other (Xu, Zhang et al. 2011, Xu, Sun et al. 2013, Liu, Zhang et al. 2016, Liu, Jiang et al. 2017).

2. GH-induced JAK2 kinase activation.

Unlike other cell surface receptor proteins whose primary sequences encoded enzymatic activities (e.g., tyrosine or serine/threonine kinases), the GHR's intracellular domain sequence did not reveal activity to suggest a signaling mechanism. Yet, Carter-Su and colleagues made the seminal observations in 1988-89 that GH treatment of mouse preadipocytes acutely and robustly caused tyrosine phosphorylation of cellular proteins, including GHR itself (Foster, Shafer et al. 1988, Carter-Su, Stubbart et al. 1989), suggesting the existence of a tightly GHR-associated GH-regulated tyrosine kinase. Indeed, that tyrosine kinase was identified in 1993 by the Carter-Su group (Argetsinger, Campbell et al. 1993) as the non-receptor cytoplasmic tyrosine kinase, JAK2, one of four members of the Janus kinase family (JAKs 1-3 and TYK2) (Firmbach-Kraft, Byers et al. 1990, Wilks, Harpur et al. 1991, Harpur, Andres et al. 1992, Silvennoinen, Witthuhn et al. 1993, Witthuhn, Quelle et al. 1993, Johnston, Kawamura et al. 1994) that each possess a C-terminal kinase domain, a kinase-like domain, and an N-terminal (FERM) domain that interacts with particular hematopoeitin receptor family members. Subsequent studies in the 1990s and early 2000s by several labs identified the regions within GHR (a proline-rich proximal cytoplasmic domain element) and JAK2 (the N-terminus) that mediate physical and functional interaction between the two proteins (Frank, Gilliland et al. 1994, Sotiropoulos, Perrot-Applanat et al. 1994, Vanderkuur, Wang et al. 1994, Frank, Yi et al. 1995, Tanner, Chen et al. 1995, He, Wang et al. 2003). The mechanism(s) by which GH

binding to the dimerized GHR causes activation of the GHR-associated JAK2 have recently been intensely investigated (Jiang, Wang et al. 2004, Brown, Adams et al. 2005, Rowlinson, Yoshizato et al. 2008, Jiang, Wan et al. 2011, Brooks, Dai et al. 2014, Liu, Berry et al. 2014, Sedek, van der Velden et al. 2014, Liu, Jiang et al. 2017) and are reviewed by Brooks and colleagues in this volume. Despite these advances, many aspects of this activation process remain enigmatic and are worthy of continued research. The reader is directed to Figure 1 for a diagram of the pathways activated by the GH-engaged GHR, which are discussed below.

These studies clearly linked JAK2 structurally and biochemically to GH signaling. In terms of function among the JAK family members, JAK3 and TYK2 are largely involved in immune signaling pathways (Velazquez, Fellous et al. 1992, Johnston, Kawamura et al. 1994, Stahl, Boulton et al. 1994, Lin, Migone et al. 1995, Nosaka, van Deursen et al. 1995), while JAK2 and JAK1 mediate important signals both within and outside of the immune system (Witthuhn, Quelle et al. 1993, Lebrun, Ali et al. 1994, Smit, Meyer et al. 1996, Tian, Tapley et al. 1996, Drachman and Kaushansky 1997, Neubauer, Cumano et al. 1998, Rodig, Meraz et al. 1998). Notably, developmental knockout of JAK2 manifests not in deficient GH action, but rather as embryonic lethality resulting from ineffective hematopoiesis associated with lack of erythropoietin action (Neubauer, Cumano et al. 1998). This finding was consistent with the notion that JAK2 couples to a variety of cytokine receptors. Confirmatory *in vivo* evidence that JAK2 couples to GHR action has emerged from the elegant studies of Weiss and colleagues (Sos, Harris et al. 2011, Corbit, Camporez et al. 2017, Corbit, Wilson et al. 2019). In those studies, hepatocyte-specific deletion of JAK2 phenocopied aspects of previously-described mice with hepatocyte-specific deletion of either GHR (Fan, Menon et al. 2009) or the key GH effector, insulin-like growth factor-1 (IGF-1) (Yakar, Liu et al. 1999) (more below) in having raised circulating GH levels and markedly reduced circulating IGF-1.

3. GH-induced STAT5 activation.

STATs (signal transducers and activators of transcription) are a family of latent cytoplasmic transcription factors that translocate to the nucleus in response to various cytokines, growth factors, and hormones that effect target gene transcription by interacting with specific DNA enhancer sequences (Stark and Darnell 2012, O'Shea, Holland et al. 2013). The family has seven members (STATs 1,2,3,4,5A,5B, and 6), the first of which were discovered in the early 1990s; each intimately interacts functionally with specific cytokine receptor/JAK assemblages to initiate rapid gene expression signaling cascades. Studies in the 1990s revealed that only STATs 1,3, and 5 are activated by GH (Gronowski and Rotwein 1994, Meyer, Campbell et al. 1994, Campbell, Meyer et al. 1995, Gouilleux, Pallard et al. 1995, Gronowski, Zhong et al. 1995, Wood, Sliva et al. 1995, Han, Leaman et al. 1996, Ram, Park et al. 1996, Silva, Lu et al. 1996, Smit, Vanderkuur et al. 1997). STATs 1 and 3 were first shown to be critical in interferon signaling and antiviral immunity (STAT1) and interleukin-6-family cytokine signaling and the acute phase response (STAT3) (Darnell Jr, Kerr et al. 1994). Indeed, GH treatment in cell culture model systems causes formation of tyrosine phosphorylation-mediated dimers (homo- and hetero-) comprised of STAT1 and STAT3 on the promoter of the c-fos gene that corresponds to expression of reporter genes

relating to GH's known regulation of c-fos gene expression (Doglio, Dani et al. 1989, Gurland, Ashcom et al. 1990, Gronowski and Rotwein 1994, Meyer, Campbell et al. 1994, Campbell, Meyer et al. 1995, Frank, Yi et al. 1995). However, disruption of neither the STAT1 nor STAT3 genes in mice results in a phenotype clearly indicative of impaired GH action (Durbin, Hackenmiller et al. 1996, Meraz, White et al. 1996, Takeda, Noguchi et al. 1997); it remains unknown the degree to which either of these two STATs contributes to the physiological actions of GH.

In contrast, STAT5 has emerged as a key GH signal transducer with clearly-understood impact on GH action. As the topic is extensively reviewed in this volume by Rotwein, it will only briefly be discussed here. STAT5 was originally not distinguished as either the A or B isoform (highly homologous, but not identical gene products (Ambrosio, Fimiani et al. 2002, Hwa 2016)) and was first found as a prolactin-responsive transcription factor in sheep (Wakao, Gouilleux et al. 1994). We now know that various cytokines and growth factors activate STAT5 and that it has pro-proliferative and immunoregulatory roles in coupling to the receptors for these factors. With regards to GH action, studies in the mid-1990s implicated STAT5 in governing GH-dependent expression of genes encoding serine protease inhibitor 2.1 and a cytochrome P450 activity (Bergad, Shih et al. 1995, Subramanian, Teixeira et al. 1995). Landmark studies by Waxman and colleagues in rats and mice have shown that STAT5B, in particular, is critical in mediating sexually-dimorphic effects of GH on liver gene expression that rely on the pulsatility of GH in the circulation (Waxman and O'Connor 2006). Further, STAT5B is a key mediator of GH-induced expression in liver and other tissues of IGF-1 (Woelfle, Chia et al. 2003, Woelfle and Rotwein 2004). Indeed, targeted deletion of STAT5B in mice results in loss of sexually-dimorphic growth and hepatic gene expression, reduced serum IGF-1 levels, and elevated GH levels (Udy, Towers et al. 1997, Teglund, McKay et al. 1998), in several ways phenocopying the GHR knockout mouse and strongly implicating STAT5B in GH action. Even further evidence of this is found in humans with an autosomal recessive pattern of mutation of STAT5B (reviewed in (Hwa 2016)), who manifest short stature, low IGF-1, non-suppressed GH levels, and relative GH resistance. These human STAT5B mutations and their relationship to Laron syndrome are discussed in this volume by Hwa.

Mechanistically, STAT5B also differs from other GH-induced STATs in that its activation requires phosphorylation of at least one of several tyrosine residues of the GHR cytoplasmic tail, as well as activation of JAK2 (Hansen, Wang et al. 1996, Moriggl, Gouilleux-Gruart et al. 1996, Smit, Meyer et al. 1996, Wang, Darus et al. 1996, Yi, Kim et al. 1996, Smit, Vanderkuur et al. 1997, Rowland, Kerr et al. 2005, Rowland, Lichanska et al. 2005), consistent with the notion that transient recruitment of STAT5B to the GHR via the STAT SH2 domain allows processive tyrosine phosphorylation of STAT5B by GH-activated JAK2, followed by SH2-phosphotyrosine-mediated STAT5B dimerization and translocation to the nucleus. Indeed, genetic knock-in of GHR truncation and tyrosine mutants in the setting of the GHR knockout mouse suggest an important correlation between the GHR tail's ability to support STAT5B activation with IGF-1 expression and linear growth (Rowland, Lichanska et al. 2005).

Notably, very recent studies using this GHR knock-in system highlight the metabolic effects of uncoupling GHR activation from STAT5B signaling in that inability of GH to activate STAT5B results in both enhanced insulin sensitivity in multiple tissues and diminished hepatic gluconeogenesis (Chhabra, Nelson et al. 2019). Interestingly, liver GHR knockout in adult mice results in an augmentation of *de novo* lipogenesis, also suggesting important metabolic regulatory roles for GH in that model system (Cordoba-Chacon, Majumdar et al. 2015). Very likely, further comprehensive approaches using multi-omics (akin to recent studies of GHR-deficient pigs (Riedel, Hinrichs et al. 2020)) will better elucidate GH-dependent metabolic effects that are or are not dependent on GH's ability to couple to STAT5B activation.

4. GH-induced activation of other pathways.

4.1 Src family kinases

Like JAKs, the Src family kinases are cytoplasmic non-receptor tyrosine kinases that can couple to cytokine and growth factor receptors (Roskoski 2015, Espada and Martin-Perez 2017); in addition to Src, the family includes eight other members (Yes, Fyn, Lyn, Fgr, Hck, Lck, Yrk, and Blk), each roughly half the size of and structurally quite dissimilar from JAKs, except in the kinase domain. Src, Yes, Fyn, and Yrk are widely expressed. The others are more restricted in their tissue distribution. Collectively, they are involved in multiple cellular functions, including migration, proliferation, survival, and differentiation. Early evidence that GH acutely activated Src and Fyn came from the Lobie group, working in GHR-reconstituted CHO tissue culture cells (Zhu, Goh et al. 1998). Further work from the same group implicated a role for Src in promoting GH-dependent, JAK2-independent ERK pathway activation (more below) via small GTPases and phospholipase D activation (Zhu, Ling et al. 2002, Ling, Zhu et al. 2003). Waters and colleagues, in cell culture models, implicated Lyn and phospholipase Cγ in mediating GH-dependent ERK activation (Rowlinson, Yoshizato et al. 2008) and, in knock-in mice with GHR mutations incapable of coupling to JAK2, identified a GH-induced Src-mediated ERK activation pathway (Barclay, Kerr et al. 2010). However, GH-induced Src family kinase activation has not been universally detected (Jin, Lanning et al. 2008). Also, it is of note that knock-in mice with a GHR incapable of coupling to JAK2 do not differ from GHR knockout mice with regard to growth (Barclay, Kerr et al. 2010), suggesting the primacy of JAK2 for coupling to this aspect of GH action. Whether there are other facets of GH's effects that are specifically mediated by Src family kinases is yet unknown.

4.2 ERKs and other interrelated pathways

ERK1 and ERK2 (extracellular signal regulated kinases -1 and -2) are cytosolic serine-threonine kinases that are part of the Ras-Raf-MEK-ERK signaling cascade (Roskoski 2012). ERKs are enzymatically activated by tyrosine and threonine phosphorylation downstream of many growth factor and other receptors. ERKs themselves catalyze proline-directed serine-threonine phosphorylation of important substrates to effect cellular processes including proliferation, cell cycle progression, migration, survival, and metabolism. ERK1/2 were among the earliest identified substrates for GH-induced tyrosine phosphorylation (Anderson 1992, Campbell, Pang et al. 1992, Moller, Hansson et al. 1992, Winston and

Bertics 1992). Because other important serine-threonine kinases activated by GH (e.g., p70rsk, p90rsk, and S6 kinase) (Anderson 1993) were known to be ERK substrates, the ERK pathway was early on seen as a link between multiple GH-activated signals. As above, there are varying conclusions as to whether JAK2 activation (versus Src-family kinase activation) is necessary for ERK activation; indeed, this may vary depending on cellular context. Early mapping studies indicated that the proximal GHR intracellular domain required for JAK2 activation was sufficient for GH-induced ERK activation (Moller, Hansson et al. 1992, Sotiropoulos, Perrot-Applanat et al. 1994) and that a GHR incapable of associating with or activating JAK2 was unable to allow GH-induced ERK activation (Vanderkuur, Wang et al. 1994). Likewise, JAK2 mutants rendered either catalytically inactive or unable to couple to GHR failed to foster GH-induced ERK tyrosine phosphorylation (Frank, Yi et al. 1995). However, in these early studies, the activation state of Src-family kinases was not specifically assessed.

Independent of whether JAK2 is the only kinase required for ERK activation, several pathway components are known to be upstream of ERK activation by GH (for a more detailed discussion, the reader is directed to (Carter-Su, Schwartz et al. 2016, Bergan-Roller and Sheridan 2018, Dehkhoda, Lee et al. 2018)). Coupling of each of these pathways (and, indeed, GH-induced ERK activation itself) may be cell type- and context-specific (Love, Whatmore et al. 1998, Yang, Huang et al. 2004), much like the primacy of JAK2 vs. Src-family kinases. Substantial evidence exists for involvement of the classical SHC-Grb2-SOS-Ras-Raf-MEK1-ERK cascade in mediating GH-induced ERK activity via direct interaction of SHC with tyrosine phosphorylated JAK2 (VanderKuur, Allevato et al. 1995, Vanderkuur, Butch et al. 1997), although SHC has also been shown to bind the tyrosine phosphorylated GHR tail in an *in vitro* assay (Moutoussamy, Renaudie et al. 1998).

However, other molecules have been found to at least partially contribute to GH-induced ERK activation. GH causes activation of phosphoinositide-3 kinase (PI3K) (Kilgour, Gout et al. 1996, Hodge, Liao et al. 1998, MacKenzie, Yarwood et al. 1998, Costoya, Finidori et al. 1999, Liang, Zhou et al. 1999, Liang, Jiang et al. 2000, Jeay, Sonenshein et al. 2001) and pretreatment with chemical inhibitors of PI3K can block GH's ability to activate ERKs (Kilgour, Gout et al. 1996, Liang, Zhou et al. 1999, Liang, Jiang et al. 2000), placing PI3K upstream of ERKs in these cellular systems. Consistent with its ability to activate PI3K, GH has been amply demonstrated to cause tyrosine phosphorylation of the large adaptor protein, insulin receptor substrate-1 (IRS-1), which often associates with PI3K activity (Ridderstrale and Tornqvist 1994, Souza, Frick et al. 1994, Argetsinger, Hsu et al. 1995, Kilgour, Gout et al. 1996), and IRS-1 has been shown in mutagenesis and coimmunoprecipitation experiments to interact with JAK2 (Argetsinger, Hsu et al. 1995, Liang, Jiang et al. 2000). Further, both cellular reconstitution of IRS-1-deficient (murine promonocytic) cells with IRS-1 (Liang, Jiang et al. 2000) and shRNA-mediated knockdown of endogenous IRS-1 (in murine preadipocytes) (Wang, Yang et al. 2009) revealed that IRS-1 selectively augments GH-induced PI3K and ERK pathway signaling without affecting GHR, JAK2, or STAT5 abundance or activatability. Interestingly, GH-induced SHC phosphorylation was also lessened with IRS-1 silencing, suggesting that SHC may in part reside downstream of IRS-1 in this pathway (Wang, Yang et al. 2009). Work from our own laboratory also indicates that another large docking protein in the IRS family, Gab1 (Kim, Loesch et al. 2002), and the

protein tyrosine phosphatase, SHP-2 (Kim, Jiang et al. 1998), participate in the GH-induced selective activation of ERKs, although the exact nature of inclusion of each in the GHR's signaling complex remains uncertain. Intriguingly, for SHP-2, activating mutations associated with Noonan Syndrome (which includes short stature) cause the expected ERK hyperactivation, but also lead to reduced GH-induced IGF-1 generation in cell systems; detailed mechanisms of this uncoupling remain to be elucidated (De Rocca Serra-Nedelec, Edouard et al. 2012).

In addition to docking molecules and enzymes, another receptor has been implicated both as a link to the GH-induced ERK activation pathway and as being affected by this pathway. Epidermal growth factor receptor (EGFR; ErbB1) is a tyrosine kinase growth factor receptor involved in multiple cellular processes in health and disease. Yamauchi et al (Yamauchi, Ueki et al. 1997) demonstrated in cell culture systems that GH caused JAK2-dependent tyrosine phosphorylation of EGFR's cytoplasmic domain independent of EGFR kinase activity and that this allowed Grb2 to bind EGFR and activate the ERK cascade. Thus, EGFR can function as a docking protein for the GH-induced ERK activation pathway. The physiological significance of this is as yet unknown, but it is also interesting that GH induces ERK to phosphorylate EGFR at a cytoplasmic domain threonine residue, the net effect of which is to dampen subsequent EGF-induced EGFR downregulation and allow GH to cooperatively sustain EGF signaling (Huang, Kim et al. 2003, Li, Huang et al. 2008). One implication of these findings is that that GH-induced ERK activation may exert indirect effects by virtue of the propensity of GHR to interact physically or functionally with other receptor signaling systems (more below).

As mentioned above, GH's ability to activate ERKs may be uncoupled from its triggering of STAT5 signaling (Love, Whatmore et al. 1998). Mechanisms for this pathway selectivity are incompletely known, but there are indications that subcellular localization based on local plasma membrane architecture may play a role. In subcellular fractionation experiments in which plasma membranes were separated to isolate cholesterol-rich lipid rafts (LR) vs. non-LR fractions, GHR was highly LR-enriched in both murine preadipocytes (in which GH promotes both STAT5 and ERK activation) as well as in human IM-9 lymphoblasts (in which GH promotes STAT5, but not ERK activation); ERKs and Grb-2 were also LR-enriched in preadipocytes, but although amply expressed, ERKs and Grb-2 were not associated with LR in IM-9 cells and, in preadipocytes, GH caused further LR accumulation of ERK pathway components (Yang, Huang et al. 2004). STAT5 (activated in both cells by GH) was similarly non-membranous in both cells. Further, in preadipocytes, GH-induced ERK activation was highly LR-enriched, but markedly less so in LR when IRS-1 was silenced (Wang, Yang et al. 2009). These data raise the intriguing possibility that there is spatial compartmentalization of pathway utilization downstream of GHR.

5. Modulation of GH signaling.

What follows is a brief discussion of examples of mechanisms by which the strength of GH signaling may be modulated either by external factors or as a result of GHR activation itself.

5.1 Modulation of cell surface GHR abundance and GH sensitivity by constitutive and inducible GHR metalloproteolysis

One important determinant of cellular GH sensitivity is cell surface GHR abundance, which, not surprisingly, is regulated by a number of mechanisms (Baumann and Frank 2002, Deng, He et al. 2007, Frank and Fuchs 2008). A series of studies beginning in the late 1990s have demonstrated that the GHR in multiple species is a target for constitutive and inducible proteolysis in its extracellular domain membrane-proximal stem region (Alele, Jiang et al. 1998, Wang, He et al. 2002, Wang, He et al. 2003). This proteolysis results in loss of the full-length GHR with concomitant generation of a cell-associated cytoplasmic domain-containing GHR remnant and shedding of a soluble GHR extracellular domain (also known as GH binding protein or GHBP) (Alele, Jiang et al. 1998, Wang, He et al. 2002, Wang, He et al. 2003). The transmembrane enzyme that primarily cleaves GHR is TACE (tumor necrosis factor-α converting enzyme; also known as ADAM17 (Black, Rauch et al. 1997, Moss, Jin et al. 1997)) (Zhang, Jiang et al. 2000), which contains a zinc-dependent protease in its extracellular domain and can be activated by growth factors and stimuli via ERK and protein kinase C (PKC) pathways. Indeed, treatment of cells with serum, PDGF, or PKC activators rapidly induces GHR proteolysis and GHBP shedding (Zhang, Jiang et al. 2000, Guan, Zhang et al. 2001). The net effect is to rapidly downregulate cell surface GHR and desensitize the cell to subsequent acute treatment with GH. Of note, acute inflammatory states, as modeled by administration in rodents of lipopolysaccharide (LPS), have been shown to be associated with diminished hepatic GH sensitivity by various putative mechanisms (Defalque, Brandt et al. 1999, Mao, Ling et al. 1999, Bergad, Schwarzenberg et al. 2000, Wang, Li et al. 2002, Denson, Held et al. 2003, Hong-Brown, Brown et al. 2003, Chen, Sun et al. 2007). Interestingly, in mice, LPS treatment rapidly caused loss of hepatic GHR protein without altering GHR mRNA levels and this GHR loss was associated with diminished subsequent acute GH-induced hepatic STAT5 signaling (i.e., desensitization to GH) (Wang, Jiang et al. 2008). In this model, LPS also caused rapid proteolytic shedding of the extracellular domain (the GHBP) of the hepatically-expressed GHR. Thus, LPS-induced modulation of GHR abundance by proteolytic cleavage corresponds to desensitization to GH in the liver. Recent studies also revealed that TIMP3 (tissue inhibitor of metalloprotease3), an extracellular matrix binding protein (Blenis and Hawkes 1984, Staskus, Masiarz et al. 1991, Yu, Yu et al. 2000) and a natural inhibitor of TACE (Amour, Slocombe et al. 1998, Mohammed, Smookler et al. 2004), reversed the desensitizing effects of TACE on GHR abundance and cellular GH action (Zhang, Wang et al. 2016). These findings support the notion that modulation of GHR availability by regulation of the balance of TACE/TIMP3 activity by factors (such as inflammation) in the cell's environment may meaningfully modulate aspects of GH sensitivity at a posttranscriptional level. Given GH's influence on metabolism and energy economy, this is a topic worthy of further investigation.

5.2 Involvement of SOCS proteins

The SOCS (suppressor of cytokine signaling) proteins are a family of molecules generally rapidly translated upon activation of a number of cytokine receptors that function as a negative feedback loop to dampen cytokine signaling (Linossi, Babon et al. 2013, Dehkhoda, Lee et al. 2018). There are eight family members (SOCS1-7 and CIS), all of which are cytosolic modular proteins that each contain a central phosphotyrosine-binding SH2 domain

and a conserved C-terminal 40-residue motif called the SOCS box. This motif mediates interaction with several proteins that collectively form an active E3 ubiquitin ligase complex that facilitates proteasomal degradation of molecules targeted by the particular SOCS protein. In addition to this degradative function, SOCS proteins can variably interfere with formation of cytokine receptor-JAK-STAT complexes and diminish JAK kinase activity, all of which accomplish negative regulation of cytokine action. In terms of GH signaling, four SOCS proteins (SOCS1-3 and CIS) have been implicated to varying degrees (Adams, Hansen et al. 1998, Hansen, Lindberg et al. 1999, Ram and Waxman 1999, Tollet-Egnell, Flores-Morales et al. 1999, Paul, Seiliez et al. 2000). The most compelling *in vivo* evidence suggests particular physiological regulation of GH action is contributed by SOCS2. SOCS2 knockout mice exhibit postnatal gigantism akin to acromegaly, but unaccompanied by excess pituitary GH secretion (Metcalf, Greenhalgh et al. 2000, Greenhalgh, Bertolino et al. 2002); these studies implicated prolonged GH-induced STAT5 activation as mechanistically important in the setting of SOCS2 deficiency. Recent studies of a GHR mutant incapable of interacting with SOCS2 in the setting of lung cancer suggest that SOCS2 principally regulates GH sensitivity via degradation of GHR (Chhabra, Wong et al. 2018).

5.3 Other modulators

Although a detailed treatment is beyond the scope of this review, there have emerged other molecules, often with multiple other functions, that modulate GH signaling. The reader is referred to recent excellent reviews for more complete discussion of some of these (Carter-Su, Schwartz et al. 2016, Dehkhoda, Lee et al. 2018).

Protein tyrosine phosphatases (PTPs) catalyze removal of phosphate from tyrosine residues in their substrates and are thus often thought of as negative regulators of tyrosine kinase-induced signaling. Several PTPs (including SHP1, SHP2, PTP-H1, and PTP-1B) have been implicated as modulators of GH-induced STAT5 activity (Hackett, Wang et al. 1997, Ram and Waxman 1997, Hodge, Liao et al. 1998, Kim, Jiang et al. 1998, Stofega, Herrington et al. 2000, Gu, Dube et al. 2003, Pasquali, Curchod et al. 2003, Choi, Kim et al. 2006, Pilecka, Patrignani et al. 2007, De Rocca Serra-Nedelec, Edouard et al. 2012, Gan, Zhang et al. 2013). In most cases, PTP activity likely negatively regulates GH signaling by dephosphorylating proximal GHR signaling elements; however, as mentioned above (Kim, Jiang et al. 1998), some findings suggest a positive regulatory effect of SHP2 on GH-induced ERK activation.

The examples of modulation discussed above (inducible GHR metalloproteolysis, GH-induced SOCS expression, and GH-induced PTP involvement) generally act as brakes or negative regulators of GH signaling (either heterologous in the case of GHR metalloproteolysis or homologous in the cases of SOCS proteins and most PTPs). One type of positive modulator of GH signaling was first identified by the Carter-Su laboratory in 1997. The SH2B family of adaptor proteins (reviewed in (Maures, Kurzer et al. 2007)) were first found to be important in immune cell activation. In an attempt to define JAK2-interacting proteins, Rui, et al (Rui, Mathews et al. 1997) demonstrated that GH induced an SH2B isoform called SH2Bβ to associate with tyrosine phosphorylated JAK2 (at Tyr-813) and itself become tyrosine phosphorylated by JAK2. This group later demonstrated that

SH2Bβ is a strong activator of JAK2 in response to GH (Rui and Carter-Su 1999); this may be based on SH2Bβ's ability to enhance JAK2 dimerization to encourage activation and/or its ability to preserve JAK2's activation status. Functionally, subsequent studies have identified important roles for SH2Bβ in enhancing GH-induced cell motility by interacting with the actin cytoskeleton, as well as other non-GH signaling effects on energy homeostasis and obesity (Maures, Kurzer et al. 2007).

6. GHR and IGF-1R – a novel signaling relationship.

In this section, we discuss a new set of findings derived from cellular signaling studies that suggest a heretofore unappreciated relationship between GHR and IGF-1R and that broaden our conception of how the two receptors may collaborate. We first briefly review the essence of the somatomedin hypothesis of GH action and then review findings on the physical and functional consequences of GHR-IGF-1R interaction for GH signaling.

6.1 Somatomedin hypothesis of GH action

Although Evans and Long implicated pituitary GH in longitudinal growth and enhancement of muscle mass in the 1920s, as described above, understanding of the physiological role(s) of GH in these somatogenic actions was greatly advanced by critical experimental observations in the 1950s. Their groundbreaking work led Salmon and Daughaday to propose the "somatomedin hypothesis" of GH action in 1957 (Salmon and Daughaday 1957, Daughaday 2000) (Figure 2A). As originally suggested, this hypothesis held that circulating GH induced the liver to secrete a circulating factor (mediator of growth) known as somatomedin-C (later defined as the ~6-kD peptide, IGF-1), which then acted as an endocrine hormone to promote growth of bone, muscle, and some other tissues. IGF-1 was found to exert its effects by binding to the type 1 IGF-1 receptor (IGF-1R), which is a disulfide-linked heterotetramer comprised of two extracellular α-chains and two transmembrane β-chains, the latter of which encode intrinsic tyrosine kinase activity in their intracellular domains (Ullrich, Gray et al. 1986, LeRoith 2000, Nakae, Kido et al. 2001). Notably, liver normally has little to no IGF-1R expression (see below) (Pivonello, De Martino et al. 2014).

The somatomedin hypothesis elegantly addressed major issues in endocrinology and the physiology of GH and IGF-1 actions. Indeed, global genetic knockouts of IGF-1 and IGF-1R in mice were characterized by intrauterine growth retardation and, if viable, postnatal growth defects (Liu, Baker et al. 1993, Powell-Braxton, Hollingshead et al. 1993, Liu and LeRoith 1999, Wang, Zhou et al. 1999); the latter effect was consistent with the notion that IGF-1 functions "downstream" of GH. Notably, liver-specific deletion of IGF-1 (Sjogren, Liu et al. 1999, Yakar, Liu et al. 1999) resulted in ~75% reduction in circulating IGF-1 and substantial rise in GH, but did not diminish growth; however a further 15% reduction of IGF-1, accomplished by combined deletion of the liver acid-labile subunit of the IGF binding complex (Yakar, Rosen et al. 2002), did result in postnatal growth retardation. These and other findings suggest that either non-hepatically-derived IGF-1 and/or a minimum circulating threshold of liver-derived IGF-1 are important to facilitate GH action (at least as it pertains to growth). Yet another dual gene deletion mouse, a combined

GHR and IGF-1 global knockout (Lupu, Terwilliger et al. 2001), presented yet another wrinkle. This mouse exhibited postnatal growth retardation greater than either the GHR knockout or the IGF-1 knockout, calling into some question the primacy of the "linear" GH ► GHR ► IGF-1 ► IGF-1R pathway predicted by the somatomedin hypothesis and perhaps allowing for collaboration of GH and IGF-1 (as in (Ashcom, Gurland et al. 1992, Edmondson, Russo et al. 1999, Huang, Kim et al. 2004)) or that each contributes in independent, but overlapping, fashion.

6.2 GHR-IGF-1R physical and functional interaction

In a series of studies using several cell culture model systems, we in our own laboratory have pursued a potential novel variation on the theme outlined above for the signaling relationships between GHR and IGF-1R. As summarized below, these findings suggest that, in addition to delivering the signaling payload of the GH ► GHR ► IGF-1 ► IGF-1R pathway, IGF-1R may serve as a component of the GH signaling pathway, modulating GHR's signaling strength and allowing for more local heterogeneity of GH/IGF-1 actions.

GH-induced association of GHR with IGF-1R—GHR/IGF-1R signaling interactions were originally explored in mouse preadipocytes – 3T3-F442A and 3T3-L1 cells – that endogenously express GHR, IGF-1R, and JAK2 and respond to both GH and IGF-1 (Huang, Kim et al. 2004). Interestingly, acute GH stimulation of these cells allowed specific coimmunoprecipitation of GHR with IGF-1R. Acute formation of this novel GHR-IGF-1R complex (also including JAK2) in response to physiologic GH concentrations did not depend on IGF-1R or JAK2 kinase activity or phosphorylation of any partner, as it proceeded even with pretreatment with a chemical kinase inhibitor, and did not depend on IGF-1 treatment. GHR-IGF-1R complex formation was also observed in several GH-responsive rodent β-cell lines (Ma, Wei et al. 2011), as well as in human prostate cancer (LNCaP) cells (Gan, Buckels et al. 2014). Notably, complex formation was inhibited by pretreatment with a GHR extracellular domain antagonistic monoclonal antibody known to prevent GH-induced GHR conformational changes, but not to block GH binding (Jiang, Wan et al. 2011, Gan, Buckels et al. 2014), suggesting that GH-induced changes in GHR conformation may allow IGF-1R to associate with GHR.

IGF-1R participates in acute GH signaling—New model systems were developed to probe the question of whether the physical association of IGF-1R with GHR might have functional impact on GH signaling. The first of these systems was mouse primary calvarial osteoblasts, which acutely respond to both GH and IGF-1 (DiGirolamo, Mukherjee et al. 2007). Osteoblasts from newborns bearing lox-P-flanked IGF-1R alleles (Zhang, Xuan et al. 2002, DiGirolamo, Mukherjee et al. 2007) were infected *in vitro* with Ad-Cre (adenovirus driving Cre recombinase) or a control adenovirus and Ad-Cre treatment specifically silenced IGF-1R protein, but did not affect GHR expression or abundance (Gan, Zhang et al. 2010). Yet, notably, IGF-1R deletion resulted in marked reduction of acute GH-induced STAT5 phosphorylation and GH-dependent endogenous IGF-1 mRNA, suggesting signaling impact downstream of STAT5 (Figure 2B,C). Two other model cell line systems (mouse MIN6 β-cells (Ma, Wei et al. 2011) and human LNCaP cells (Gan, Zhang et al. 2013, Gan, Buckels et al. 2014)) were developed in which stable shRNA transfection knocked down IGF-1R

substantially without affecting GHR, JAK2, or STAT5 levels. In both systems, GH-induced STAT5 phosphorylation was markedly reduced in cells with low IGF-1R. Further, careful time course analyses in the LNCaP system revealed that lowering IGF-1R similarly led to reduced GH-induced JAK2 and GHR tyrosine phosphorylation. Because acute GH signaling was affected, these findings are not explained by altered GH-induced IGF-1 expression (somatomedin hypothesis); rather, they suggest that IGF-1R can serve as a proximal component of acute GH signaling and that full GH-induced activation is realized when IGF-1R is present.

IGF-1R determinants for its participation in acute GH signaling—If IGF-1R, by GH-regulated interaction with GHR, is a relevant and potentially modulatable participant in GH action in cells expressing both receptors, what are the IGF-1R determinants that allow this physical and functional interaction? This was explored in the osteoblast system, in which re-expression of wild-type IGF-1R in Ad-Cre-mediated endogenous IGF-1R-deleted cells rescued GH-induced STAT5 activation and IGF-1 gene expression (Gan, Zhang et al. 2010). Similarly, an IGF-1R mutant truncated just below the transmembrane domain to lack the beta chain's intracellular domain (including its kinase) also rescued GH signaling, These findings suggested that IGF-IR's presence, but not its kinase activity, augments GH signaling and that extracellular domain and/or transmembrane domain elements mediate its effect.

Examination of extracellular domain elements involved was furthered by the finding that reconstitution with the structurally-related insulin receptor (IR), unlike the IGF-1R, was unable to rescue GH signaling in osteoblasts with silenced endogenous IGF-1R (Gan, Paterson et al. 2014). In addition to emphasizing the specificity of GHR-IGF-1R collaboration, this finding allowed a platform to assess IGF-1R extracellular domain determinants involved by exploiting the interchangeability of extracellular domain modules in IGF-1R/IR chimeric constructs. Utilizing this "domain swapping" approach in rescue experiments, it was determined that an N-terminal IGF-1R α-chain extracellular domain region(s), likely within the CR and/or L2 subdomains, is critical to allow the IGF-1R to specifically augment acute GH signaling (Gan, Paterson et al. 2014). Mechanistically, it is hypothesized that GH promotes IGF-1R's interaction via its extracellular domain with another (likely transmembrane) protein, the intracellular domain of which effectively augments GH action. This protein, cartooned as "X" (see (Gan, Zhang et al. 2013)) in Figure 3, is envisioned as either a single protein or a group of proteins that enhance GH-induced JAK2 activation, delay GH-induced downregulation of activated GHR, or prevent negative regulators of GHR/JAK2 (e.g., PTP1B) from acting on targets (Gan, Zhang et al. 2013, Gan, Buckels et al. 2014).

The ability of a soluble IGF-1R-α N-terminal L1-CR-L2 fragment, when expressed alone, to affect GH signaling produced interesting and important results (Huang, Kim et al. 2004, Gan, Zhang et al. 2010, Gan, Paterson et al. 2014). This fragment (termed soluble IGF-1R or sol IGF-1R) and its analogous insulin receptor fragment (sol IR; used as a control) fold normally and do not bind ligands (Garrett, McKern et al. 1998, Menting, Whittaker et al. 2013) and sol IGF-1R, when expressed in IGF-1R-deleted cells, did not rescue diminished GH signaling (Gan, Paterson et al. 2014). However, conditioned medium of cells

programmed to express sol IGF-1R, but not sol IR, strongly inhibited acute GH-induced GHR/STAT5 signaling and downstream IGF-1 gene expression of cells bearing the normal IGF-1R and GHR (Gan, Buckels et al. 2014), indicating that sol IGF-1R affects (inhibits) very proximal GH signaling. In principle, sol IGF-1R could inhibit GH signaling by interaction with GH, IGF-1R, or GHR. Only the latter (sol IGF-1R/GHR) interaction has been detected and it is enhanced by GH treatment (Gan, Buckels et al. 2014). The sol IGF-1R/GHR functional interaction was shown to be specific for GHR and not PRLR in that only GH-induced signaling mediated by GHR, and not PRLR, is inhibited by sol IGF-1R (Zhang, Gc et al. 2019). Thus, it is hypothesized that sol IGF-1R, by a dominant-negative effect, specifically inhibits GH signaling in cells expressing IGF-1R by competing with IGF-1R for GHR association and that IGF-1R augments GH signaling, while sol IGF-1R is inhibitory (Figure 4).

Implications of these findings—These findings suggest a non-canonical role for IGF-1R as a contributor to GH action. While the classical somatomedin hypothesis clearly identifies IGF-1 as a GH effector, it is now clear that: GH can have direct effects; IGF-1 itself has endocrine, paracrine, and autocrine effects; and GH and IGF-1 can have overlapping, counteracting, and/or collaborative effects (Ashcom, Gurland et al. 1992, Edmondson, Russo et al. 1999, Le Roith, Bondy et al. 2001, Lupu, Terwilliger et al. 2001, Huang, Kim et al. 2004, Kaplan and Cohen 2007, Wu, Sun et al. 2013). Similarly, it is proposed that the novel physical and functional interaction between IGF-1R and GHR allows IGF-1R, in addition to mediating its own ligand's effects, to contribute proximally to efficient GH signaling. Why would a role for IGF-1R in proximal GH signaling evolve? One possibility is that IGF-1 action in GH-responsive tissues could be locally enhanced/modulated by virtue of IGF-1R sensitizing cells to GH, allowing enhanced local IGF-1 production and therefore local IGF-1 action, without necessarily affecting circulating IGF-1 and thus GH levels. Thus, the dynamic range of GH target tissue response could be even further enhanced by regulation of IGF-1R expression levels – via both proximal GH sensitivity and IGF-1 signaling (Figure 5). As liver normally has little to no IGF-1R expression, this could be most relevant in extra-hepatic tissues and/or in cancers, including hepatocellular carcinomas, in which aberrant IGF-1R expression is likely etiologically important (Wu and Zhu 2011, Pivonello, De Martino et al. 2014). Further, manipulation of IGF-1R's availability or its capacity for GHR interaction is a therapeutically-exploitable implication of these findings, as is further development of sol IGF-1R as a GHR antagonist. Thus, they present a more enriched paradigm for interplay between GH/GHR and IGF-1/IGF-1R that may complement and synergize with the somatomedin hypothesis.

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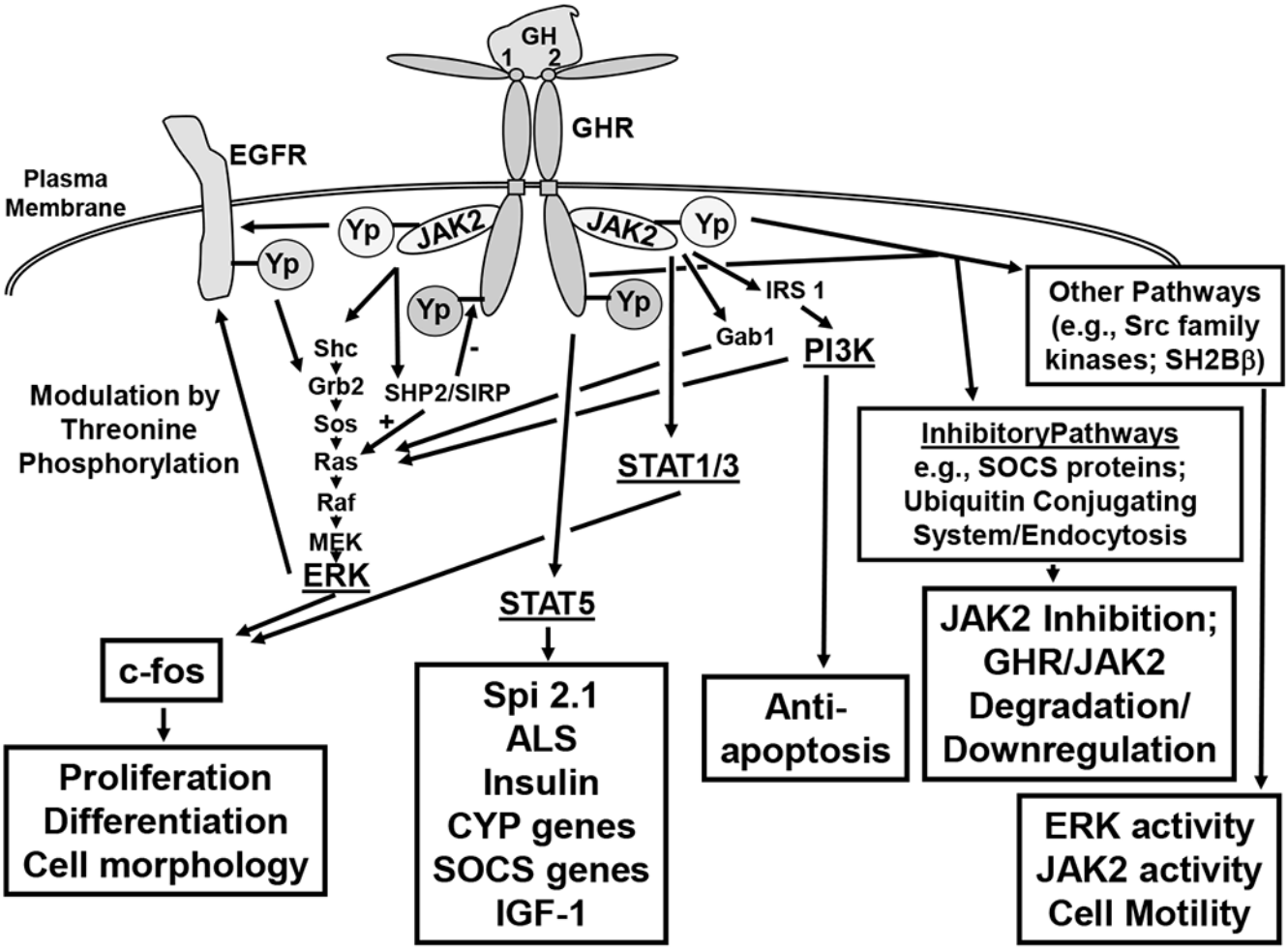

Figure 1. GHR signaling pathways.

This figure summarizes the GHR signaling pathways discussed in the text. Major signaling systems engaged downstream of the GH-engaged GHR-JAK2 complex are shown. These include the STATs, ERKs, and PI3K pathways. Intermediate molecules on these pathways are shown, as are loci of crosstalk with EGFR. Yp indicates tyrosine phosphorylation. Other pathways referred to in the text are indicated in boxes, as are cell biological and biochemical outcomes of activated pathways.

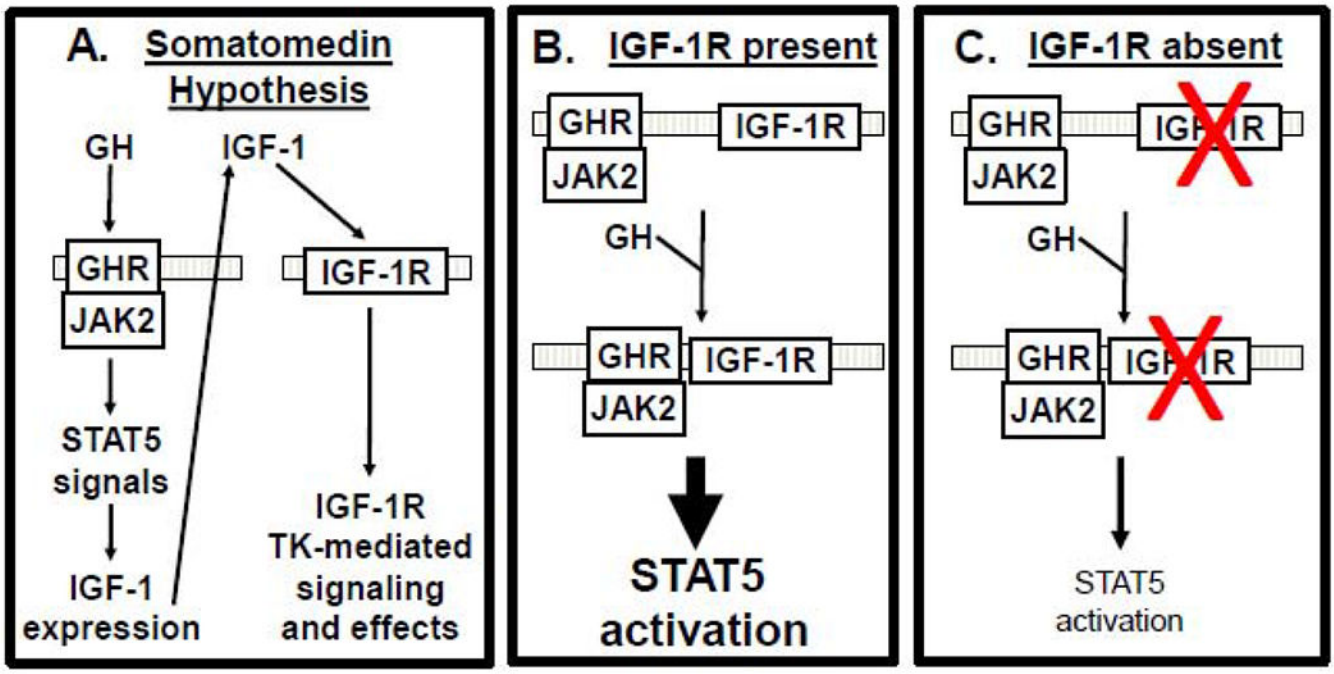

Figure 2. Role of IGF-1R-GHR interaction in augmenting GH signaling in the context of the somatomedin hypothesis.

A) Somatomedin hypothesis. GH binds GHR, activating JAK2/STAT5 and IGF-1 production. IGF-1 then acts in an endocrine fashion, stimulating IGF-1R signaling. B,C) GH promotes GHR-IGF-1R association. IGF-1R acts as a component of GH signaling (B). In IGF-1R's absence (or reduction) (red X)(C), GH action is reduced. See the text for discussion.

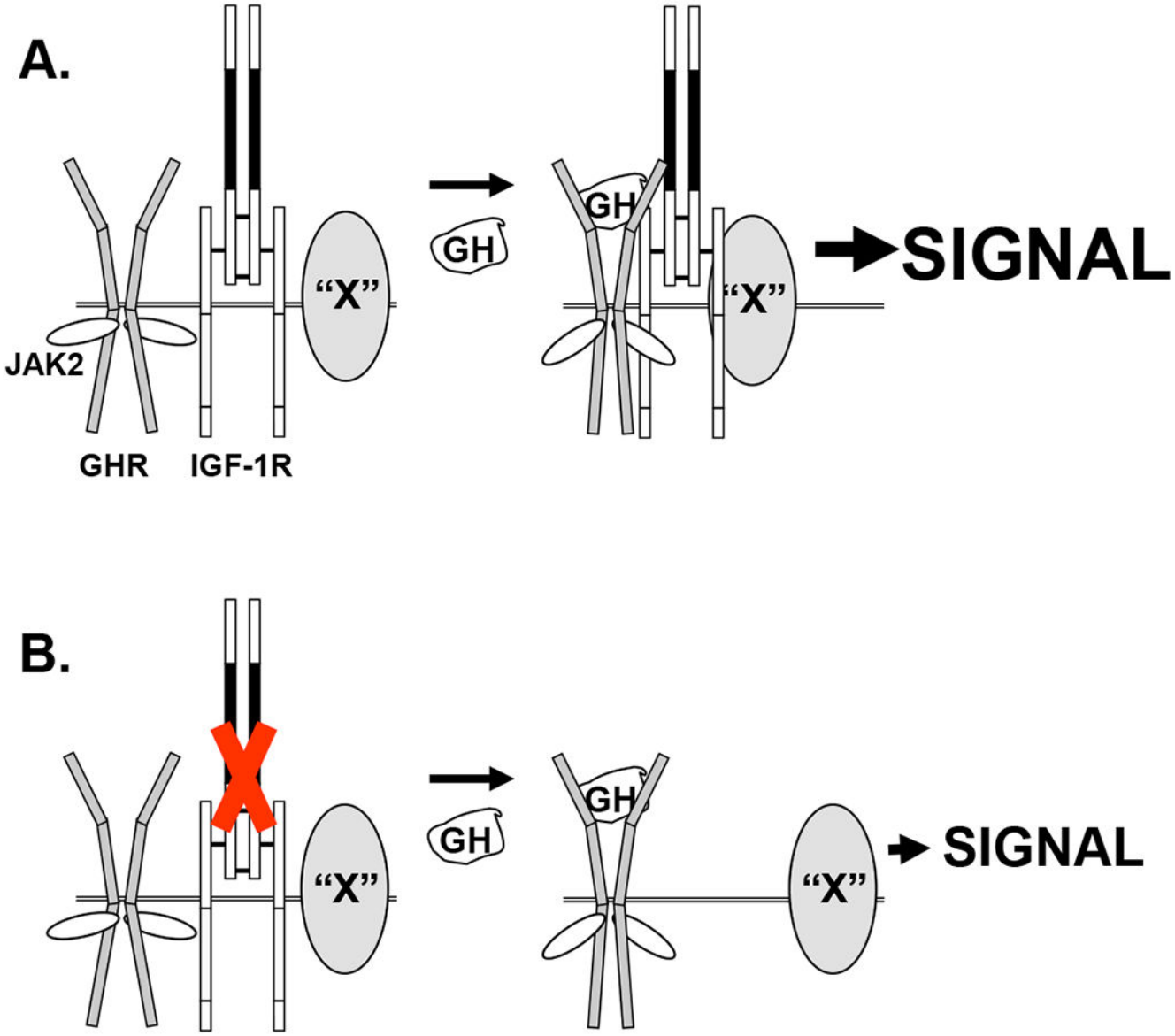

Figure 3. Putative IGF-1R-associated accessory protein(s) augment GH signaling.

A) GH enhances association of GHR/JAK2 with IGF-1R and an IGF-1R-associated protein(s), "X", augmenting GH signaling. "X" is cartooned as a transmembrane protein to suggest likely association with IGF-1R ECD and actions exerted intracellularly, but "X" could be a protein complex that either augments signaling or lessens down-regulation of signaling. B) In IGF-1R's absence, GH does not induce "X" to join the GHR/JAK2 signaling complex and signaling is relatively diminished. CR-L2 region of IGF-1R ECD is shown in solid black and is envisioned as the region of IGF-1R that interacts with GHR. See the text for discussion.

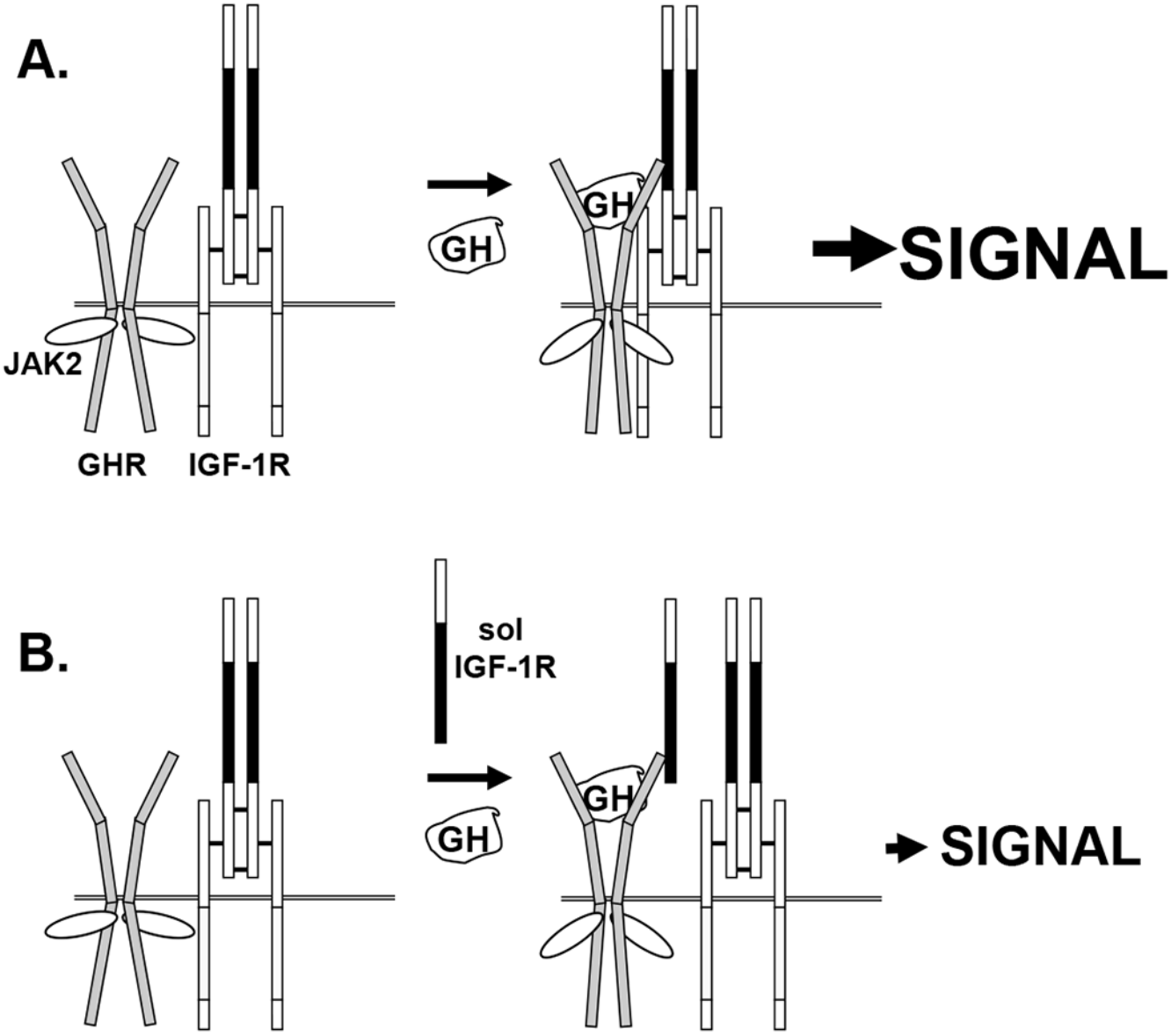

Figure 4. Putative effects of sol IGF-1R on GH signaling.

A) GH enhances association of GHR/JAK2 with IGF-1R, augmenting GH signaling, as in Figure 3A. Strong GH-induced signaling is indicated by "SIGNAL". B) GH induces GHR/sol IGF-1R association and dampened signaling ensues. Sol IGF-1R contains the L1-CR-L2 region (CR-L2 region in black). Sol IGF-1R allows GH-induced GHR and JAK2 conformational changes and signaling, but competes with IGF-1 R for GHR association. GH signaling is similar in strength as with IGF-1R silencing seen in Figure 3B. See the text for discussion.

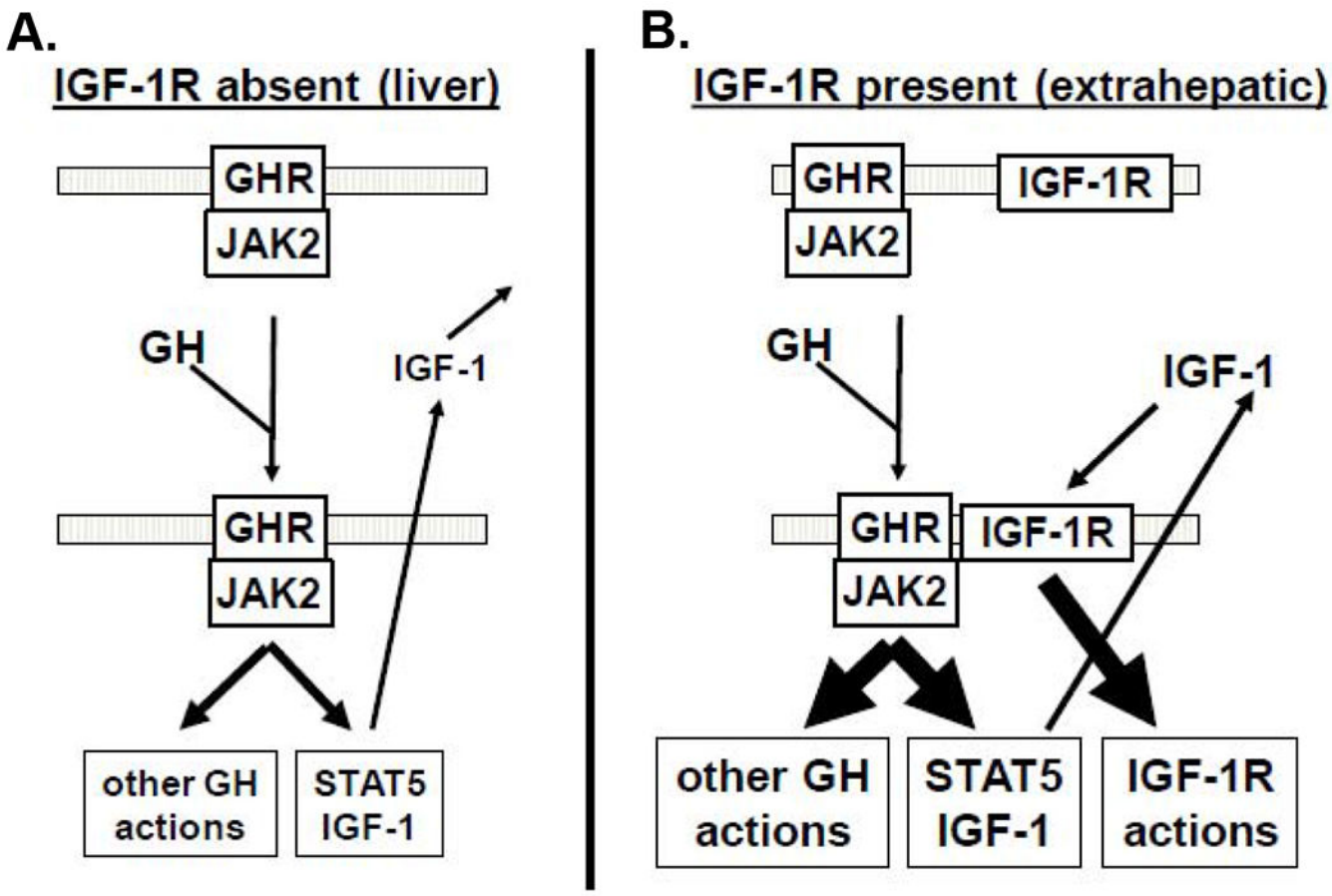

Figure 5. Potential selective modulation of local GH action in IGF-1R-expression GH target tissues.

A) In IGF-1R-negative tissues (such as liver), GH induces STAT5 signaling and other GH actions, culminating with IGF-1 secretion and endocrine actions, but not local IGF-1 effects. B) In IGF-1R-positive tissues (designated as extrahepatic) the presence of IGF-1R augments GH signaling (as above) and local IGF-1 production, which exerts further local effects via the IGF-1R, thereby augmenting the dynamic range of GH/IGF-1 action without necessarily changing the circulating GH or IGF-1 levels. See the text for discussion.