The ability to mutate individual genes in the mouse has permitted detailed studies on their roles in development, physiology, and disease. In particular, gene knockout mice have provided in-depth insight into the molecular structure and dynamics of signal transduction networks. However, in many cases the physiological consequences observed in mutant mice, or lack thereof, were unexpected and irreconcilable with the proposed functions of the protein under investigation. Genomewide gene expression profiling from gene knockout mice should provide an inroad into better understanding of the roles of cytokine-STAT5A/B networks in hepatocytes. We also explore whether this wealth of information on gene activity can be used to further understand the roles of cytokines in liver disease.

signal transducers and activators of transcription; knockout; metabolism

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variety of functions in diverse cell systems ranging from hematopoietic stem cells to hepatocytes and lactation.

Four distinct mouse models have been generated to explore the role of STAT5A/B in development, physiology, and disease: mice lacking either a functional Stat5a (57) or Stat5b (82) gene, mice carrying mutant Stat5a/b genes that encode STAT5A/B lacking the NH2-terminal tetramerization domain (Stat5ΔN mice) (81), and mice in which the entire Stat5a/b locus can be deleted in specific cell types with Cre-mediated recombination (Stat5Δ−/− mice) (16). Defects observed in mice carrying deletions of either the Stat5a or Stat5b gene largely reflect the distribution pattern of the respective protein. STAT5A-deficient mice mature normally, but mammary development during pregnancy is impaired and females fail to lactate after parturition (57). In STAT5B-deficient male mice, body growth is decreased to levels observed in wild-type males (81, 82). STAT5ΔN mice have a reduced body size due to disrupted GH signaling, and females are infertile because of defects in the corpora lutea (81). In contrast to STAT5A and STAT5B functions, the deletion of the Stat5a/b locus was found to disrupt GH signaling in females (82). The expression of some gene sets was elevated in females the expression of some gene sets was elevated in males (13). However, the expression of some gene sets was elevated in males (13). However, these mice developed hepatosteatosis, glucose intolerance, insulin resistance, late-onset obesity, and impaired liver regeneration on partial hepatectomy (PHx). Deletion of the Stat5a/b locus with a Cre transgene under control of the albumin gene promoter and the α-fetoprotein enhancer provided overall similar results but also revealed distinct features (24). Mainly, these mice displayed impaired postnatal growth, indicating a different expression pattern of the Cre gene and loss of STAT5A/B at early stages. Importantly, this study demonstrated a physical and functional interaction between STAT5A/B and the glucocorticoid receptor. This interaction was shown to be critical for the regulation of specific subsets of metabolic genes (24).

**STAT5A/B Target Genes**

STAT5A/B target genes in liver tissue have been identified in several systems. Waxman and colleagues have performed microarray analyses on liver tissue from mice lacking STAT5A (13) or STAT5B (12) globally and from liver-specific Stat5a/b KO mice (32). Engblom and colleagues (24) have identified target genes from mice in which the Stat5a/b locus was deleted with the AFP-Cre transgene. Our laboratory (15) has profiled gene expression in liver tissue on deletion of the Stat5a/b locus with the Alb-Cre transgene. Rowland and colleagues (69) analyzed gene expression profiles in liver tissue from mice that carry truncated GHRs that impair STAT5A/B signaling, and Vidal et al. (84) analyzed gene expression in mice on GH stimulation. On the basis of these experiments, a large set of genes was identified whose expression was altered on the deletion of STAT5A/B. The use of different microarray platforms and possibly different mouse strains makes it challenging to fully compare different data sets. Regardless of these caveats, a coherent theme emerged.

In mice, pulsatile secretion of GH in males is distinct from that in females and sexual dimorphic expression patterns of genes in liver tissue have been observed (89). In liver, STAT5B is 20-fold more abundant than STAT5A, suggesting that the vast majority of GH signaling is conveyed through STAT5B. Studies on global Stat5a- and Stat5b-null mice confirmed STAT5B as the transcription factor conveying sexual dimorphism, but a distinct role for STAT5A has been established as well. STAT5B-deficient male mice are characterized by reduced body growth and a loss of sex-specific expression of genes encoding cytochrome P-450 (Cyp) enzymes (82) as well as other genes. In liver tissue of Stat5b-null mice 90% of male-predominant genes were suppressed and 60% of female-predominant genes were induced (12). Microarray studies published in this journal (13) identified several gene sets displaying sexual dimorphic expression. Notably, the expression of 15% of female-predominant genes was dependent on the presence of STAT5A. These studies highlight sex-specific roles of the two STAT5 isoforms, with STAT5A preferentially regulating gene expression in the female liver while STAT5B plays the predominant role in the male. It can be speculated that STAT5B binding sites (GAS sites) in regulatory sequences of 15%
of female-predominant genes are recognized exclusively by STAT5A. Whole genome analyses, such as ChIP-seq using massive parallel sequencing, will be needed to elucidate the specificity of GAS sites for the two STAT5 isoforms. On the basis of their comparison of sexual dimorphic genes dependent on either STAT5 isoforms the authors defined STAT5A as a “feminizing” factor in female mouse liver and STAT5B as a “masculinizing” factor in male liver (13).

A comparison of gene expression data from mice in which the entire Stat5a/b locus was deleted from liver tissue with two independent Cre transgenes (15, 24) yielded several genes with an altered expression pattern that could, at least in part, explain the altered metabolism and pathology in these mice (Table 1). As expected, IGF-I mRNA levels were reduced in the absence of STAT5A/B. GH activates hepatic Igf-1 gene expression through STAT5B (5, 27), and systemic IGF-I promotes growth of target tissues, such as muscle and bone. Surprisingly, however, mice with an Alb-Cre-mediated liver-specific STAT5A/B deletion grew normally without effect on body size (15). In these mice the targeted Igf-1 deletion resulted in an ~75% decrease in circulating IGF-I and elevated levels of plasma GH (74, 95). These results indicate that hepatic IGF-I is not essential for normal postnatal growth. Furthermore, skeletal muscle-specific STAT5A/B-null mice displayed a >60% reduction in muscle IGF-I mRNA content but only a 15% reduction of circulating IGF-I and showed significantly reduced postnatal growth and skeletal size (41). These data support the concept that autocrine/paracrine-derived IGF-I is essential for normal postnatal growth. In contrast to the liver-specific Stat5a/b-Alb-Cre mice generated in our laboratory, mice in which the Stat5a/b locus has been deleted with the α-feto-protein Cre transgene displayed a reduced body growth similar to that seen in complete STAT5B-null mice (82). The reason for this discrepancy is not known. At 4 wk of age IGF-I levels in both strains were reduced. It is possible that the temporal expression pattern of the two Cre transgenes or slight differences in their cell specificity are the underlying causes, because the Afp gene is expressed in fetal tissues, such as liver, kidney, and yolk sac (28). Stat5a/b-Alb-Cre mice develop obesity and display glucose intolerance, which could to some extent compensate for the reduced body weight caused by growth retardation. Alternatively, strain differences might have an effect as well. For example, while Stat5-null mice in a C57BL/6 background die perinatally, fetal death at embryonic day 14.5 is observed in a BALB/c background (G. W. Robinson and L. Hennighausen, unpublished observations). To fully understand the differences observed between these two studies, it would be necessary to perform them in the same strain background and monitor both the temporal and cell-specific deletion of the Stat5a/b locus imposed by the two Cre strains.

On the basis of current evidence it is clear that STAT5A/B are essential for Igf-1 gene expression in hepatocytes, but it is still an open question as to what extent the hepatic STAT5A/B-IGF-I axis is responsible for body growth. Severely reduced expression of other bona fide STAT5A/B target genes, such as those encoding glutathione S-transferase and IGF binding protein 3, were found in the different mouse models (Table 1).

### Table 1. Genes induced in hepatocytes lacking STAT5

<table>
<thead>
<tr>
<th>Gene</th>
<th>STAT5 /fl/</th>
<th>STAT5 /fl/</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAT5 target genes involved in liver metabolism and body growth</td>
<td>Alb-Cre</td>
<td>Alb/AFP-Cre (KO/Con)*</td>
</tr>
<tr>
<td>IGF-1</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Glutathione S-transferase (mu 6)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Serine protease inhibitor (clade A, member 3K)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Prolactin receptor</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>IGF binding protein 3</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>STAT5 target genes involved in negative regulation of JAK-STAT pathway</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOCS2</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>SOCS3</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CIS</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>IFN-STAT1 target genes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN-α-inducible protein</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>IFN-γ-inducible protein</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>IFN regulatory factor-1</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Guanylate-binding protein</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Complement protein C3</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Stat1</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>STAT3 target genes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>↓</td>
<td>N/A</td>
</tr>
<tr>
<td>Complement C3</td>
<td>↑</td>
<td>N/A</td>
</tr>
<tr>
<td>Fibrinogen α</td>
<td>↑</td>
<td>N/A</td>
</tr>
<tr>
<td>Fibrinogen β</td>
<td>↑</td>
<td>N/A</td>
</tr>
<tr>
<td>Fibrinogen γ</td>
<td>↑</td>
<td>N/A</td>
</tr>
<tr>
<td>CEBP β</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>p21</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cyclin D1</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Mcl-1</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Data were compiled from liver-specific Stat5a/b-null mice (15, 24). Arrows indicate changes in gene expression levels (up, down, or unchanged). N/A, nonapplicable. *Expression of a selected set of genes in STAT5A/B mutant (KO) and control (Con) mice.

As negative regulators of the JAK/STAT pathway, suppressors of cytokine signaling (SOCS) and cytokine-inducible SH2-containing proteins (CIS) are intimately connected to STAT5A/B. The strength and duration of STAT signals are regulated by SOCS and CIS proteins, which attenuate or terminate cytokine/growth factor signals (30). Excessive or constitutive activation of STAT pathways can induce oncogenic transformation, tumor cell invasion, and metastasis (18, 29). Defects in negative-feedback regulation of STAT pathways have been identified in diverse tumors (62, 77, 80). As a negative feedback, SOCS/CIS proteins inhibit cytokine-stimulated STAT5A/B signaling through several mechanisms (65). Several reports have provided evidence that cytokines such as GH, IL-6, and interferon (IFN) induce Socs/Cis gene expression, and that these inhibitory molecules suppress STAT signal by means of negative feedback (reviewed in Refs. 61, 98). Adams and colleagues (2) first reported that GH activates the genes encoding Socs1, Socs2, Socs3, and CIS through STAT5A/B, which is abrogated in liver-specific STAT5A/B-null mice (Table 1). Gene profiling experiments have shown that the levels of SOCS2 (15), SOCS3, and CIS mRNA are greatly reduced in liver tissue from liver-specific STAT5A/B-null mice (Table 1).
An important concept emerges from the observation that loss of STAT5 results in the disruption of negative feedback loops that rely on SOCS2, SOCS3, and CIS; namely, abrogation of SOCS-mediated inhibition could permit an enhanced activation of other STATs (Fig. 1). Denson’s work demonstrates that IL-6 inhibits hepatic GH signaling through an increase of CIS and SOCS3, and thus causes acquired GH resistance in patients with inflammatory diseases or sepsis (10, 21).

Balancing STAT Signaling

Evidence has been accumulating that loss of a given STAT member can result in the activation of “illegitimate” STATs (61, 83). Although this concept appears to be universal, cell-specific differences at the levels of individual STAT members would need to be taken into account. In mouse liver, GH activates STAT5B preferentially (Fig. 1) and little or no activation of STAT1 or STAT3 can be detected. In contrast, extensive hepatic nuclear STAT1 and STAT3 can be observed in Stat5fl/fl;Alb-Cre mice (Fig. 1). Because each STAT member targets its own set of genes, which possibly includes some common ones, the aberrant activation of STAT1 and STAT3 is likely not to result in compensation but rather in a gain of function (Fig. 2). Evidence for this comes from gene profiling of liver tissue in the presence and absence of STAT5. Notably, induction of STAT1 and STAT3 target genes was detected (17).

STAT1 Target Genes

IFNs regulate cellular antiviral, antiproliferative, and immunologic responses. In liver, STAT1 is activated by both IFN-α/β and IFN-γ (19). Although STAT1 is also activated by other cytokines and growth factors, including IL-2, EGF, and GH, STAT1-deficient mice exhibit selective signaling defects only in their response to IFNs (23, 68). It is not clear whether the activation of STAT1 by cytokines other than IFNs is an evolutionary footprint merely pointing to the fact that the SH2 domains of all STAT members exhibit some promiscuity or whether there is an underlying biological significance. Such relevance could be masked by the fact that EGF mainly activates STAT3 and GH and IL-2 preferentially activate STAT5. STAT1 target genes shown in Table 1 are induced in Stat5fl/fl;Alb-Cre mice, further supporting the notion that STAT1 can efficiently dock to the GHR and transduce its signal in the absence of STAT5. Surprisingly, STAT1 mRNA levels were also elevated in the absence of STAT5, suggesting the presence of a positive feedback loop.

STAT1 is a key regulator of the gene encoding IFN regulatory factor-1 (IFR-1), which was originally identified as a nuclear factor binding to the upstream regulatory region of the human IFN-β gene (52, 59). In liver, STAT1 and IFR-1 are essential in liver injury induced by lipopolysaccharide LPS/d-galactosamine through inducible nitric oxide synthase (iNOS) and nitric oxide (NO) production, as well as elevated reactive
oxygen species (ROS) production (39, 48). STAT1 activation not only contributes to liver injury but blocks liver repair through inhibition of hepatocyte proliferation in the PHx model (79). Stat5fl/fl;Alb-Cre mice have impaired proliferation of hepatocytes on PHx, suggesting upon first view a role of STAT5 in liver regeneration. However, this defect is ameliorated on the concomitant deletion of STAT1, suggesting that defective liver regeneration in the absence of STAT5 was the result of an aberrant activation of STAT1. STAT1 hyperactivation in the absence of STAT5 is probably mainly due to GH and IL-2 stimulation. Inhibition of SOCS/CIS expression, described above, could exacerbate STAT1 and STAT3 activation. Taken together, loss of STAT5A/B causes not only impaired GH signaling in liver but inhibition of SOCS expression followed by the activation of other STATs, which results in impaired proliferation of hepatocytes on PHx (Fig. 3).

STAT3 Target Genes

The presence of STAT3 is critical for acute-phase response (66, 91), protection against liver injury, promotion of liver regeneration (6, 92), glucose homeostasis, and hepatic lipid metabolism (34). STAT3 is mainly activated by IL-6 family members, such as IL-6, IL-11, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor, and cardiotrophin-1, which utilize combinations of a common signal-transducing subunit, gp-130, and various ligand-binding subunits (40). Among these cytokines, IL-6 has been extensively investigated, and is thought to play the most important role in the liver. IL-6 stimulates hepatocytes to produce a variety of target genes, which include acute-phase proteins, such as C-reactive protein, complement C3, fibrinogen, and haptoglobin, and cell cycle-related and apoptosis-related genes, such as cyclin D1, C/EBPβ, p21[^WAF1/CIP1], Bcl-2, and Bcl-xL. Expression of most of these genes was elevated in liver tissue from Stat5fl/fl;Alb-Cre mice, some of which are listed in Table 1, further supporting the notion that loss of STAT5A/B leads to an aberrant activation of STAT3 signaling (Figs. 1 and 2). While STAT3 functions as an important factor contributing to the hepatoprotective and hepatomitogenic effect (14, 54), it has also been linked to tumorigenesis (reviewed in Refs. 7, 29). Experimentally, constitutively activated STAT3 mutants can induce some aspects of cell transformation (9), and dominant-

![Fig. 2. JAK-STAT signaling in hepatocytes in the presence and absence of STAT5A/B. A: cytokine-induced signaling in the presence of STAT5A/B. The growth hormone receptor (GHR) specifically recruits and preferentially activates STAT5A/B, which in turn induce the expression of specific sets of genes and elicit a STAT5 response. Suppressors of cytokine signaling (SOCS2 and SOCS3, 2 negative regulators of the JAK/STAT pathway, are encoded by genes that are controlled by STAT5. Members of the interleukin (IL)-6 family of cytokines activate STAT3 and elicit a STAT3 response in the cell, while interferons (IFNs) activate STAT1. B: cytokine-induced signaling in the absence of STAT5A/B. In the absence of STAT5, both STAT1 and STAT3 can be recruited to the GHR, although with lower affinity than STAT5. Thus GH can aberrantly activate a STAT1 and a STAT3 program in hepatocytes as demonstrated by gene expression profiling. Moreover, impaired expression of negative regulators from the SOCS family will exacerbate STAT3 signaling.](http://physiolgenomics.physiology.org/)

![Fig. 3. Loss of STAT5 modifies the physiology of liver cells through direct and indirect pathways. Several distinct mechanisms are responsible for the altered physiology of hepatocytes in the absence of STAT5A/B. First, reduced expression of specific classes of STAT5A/B target genes, such as those encoding different members of the cytochrome P-450 family, results in an altered metabolism of hepatocytes. Among the physiological changes are the emergence of glucose intolerance and hepatosteatosis. Second, reduced levels of SOCS proteins result in enhanced STAT3 signaling through receptors containing the gp130 subunit, such as IL-6. Third, in the absence of STAT5, STAT1 and STAT3 can dock to the GHR and thus elicit their respective biological responses on GH stimulation. This includes the activation of genes involved in cell proliferation and survival. Finally, the development of GH resistance results in elevated GH levels, which exacerbate aberrant STAT1/3 signaling.](http://physiolgenomics.physiology.org/)
negative STAT3 blocks STAT-dependent transcription and transformation induced by activated tyrosine kinases. It has been proposed that constitutively activated STAT3 facilitates cellular transformation by inducing the expression of genes critical to the initiation and/or maintenance of transformation. STAT3 regulates the expression of genes that mediate proliferation (e.g., c-myc and cyclin D1), suppress apoptosis [e.g., B-cell leukemia/lymphoma (Bcl)-xL and Bcl-2], or promote angiogenesis (e.g., VEGF).

Some inhibitory molecules are also regulated by STATs. Expression levels of p21WAF1/CIP1 are related to malignant tissue formation (4, 22, 63) as STAT1 activation in response to IFN-γ results in induction of p21WAF1/CIP1 and growth arrest (8, 11, 33). Therefore, in contrast to STAT3 and STAT5, STAT1 is thought to be a tumor suppressor. This is supported by studies using Stat1-mutant mice, which develop more frequent and more rapidly growing tumors when exposed to chemical carcinogens (38). In part this can be explained by impaired immune responses, because these mice do not respond to IFN-γ and have defects in natural killer cell activity. Moreover, STAT1 is also required for growth inhibition through the induction of p21WAF1/CIP1. Since STAT3 also induces p21WAF1/CIP1 through binding to the p21WAF1/CIP1 gene promoter (73), one can hypothesize that two independent signaling pathways induce the same, but possibly cell-specific, program. In Stat5B/B;Alb-Cre mice, levels of p21 and cyclin D1 are elevated. We propose that this is the result of an aberrant activation of STAT1 and STAT3. At this point it is not known whether this illegitimate activation leads to the onset of tumors.

Oncogenesis is frequently associated with a deregulated expression of pro- and antiapoptotic genes. Two principal pathways in apoptosis activate intracellular cysteine proteases, so-called caspases (1). One is the mitochondrion-dependent intrinsic (stress) cell death pathway, and another is the extrinsic (death receptor) pathway. The two pathways are largely independent; however, in hepatocytes these two pathways intersect through processing the proapoptotic protein BID into its active truncated form (tBID) (36). The antiapoptotic Bcl-2 family proteins, Bcl-2, Bcl-xL, and myeloid cell leukemia sequence 1 (Mcl-1), play important roles mainly by inhibiting intrinsic cell death pathways (26). This pathway induced by cytokine deprivation, intracellular damage, and oncogene expression is initiated by Bcl-2 homology domain (BH)3-only proteins, such as Bad, Bik, Bid, Bim, Bmf, Hrk, Noxa, and Puma, which inactivate Bcl-2 family proteins and thereby unleash Bax and Bak. Expression of the Bcl-2 family is regulated to some extent by the STAT3 pathway, and a strong correlation exists between elevated levels of these family members and human cancer (9, 25, 35, 55, 67, 70). Proliferation of cancer cell lines can be controlled by inhibiting STAT3 activity with Stat3 small interfering RNA (siRNA), decoy, or selective inhibitors (53, 71, 78, 90, 93). Additional attention needs to be paid to the fact that STAT5 also contributes to the induction of the Bcl-2 family (75, 76). In the erythroid lineage, Epo-dependent activation of STAT5 is used by Epo-responsive progenitor cells to induce the expression of bcl-xL and consequently to inhibit apoptosis (72). De Groot et al. (20) also reported that bcl-xL is induced through BCR-Abl. STAT1 is known to induce apoptosis by activating proapoptotic regulatory genes, such as Bak, Bax, caspases 3 and 8, Fas, and Fas ligand (33, 47, 50, 64, 94). Furthermore, STAT1 plays a role in the expression of Bcl-2 and Bcl-xL (43). Thus cell apoptosis or survival is determined partly by STAT activation, including STAT1, STAT3, and STAT5, through expression of pro-antiapoptotic regulatory genes. The balance of each STAT activation is also important for the determination of cell fate as in the case of cell growth.

**Contribution of STAT5 in Liver to Human Physiology and Disease**

Patients with homozygous inactivating mutations in the Stat5B gene provide some answers to the question of whether cytokine-STAT5 signaling in the liver contributes to the physiology and pathophysiology of the human body (42, 87). Poor weight gain and growth failure were noted in these patients, reminiscent of patients with classical GH insufficiency (44). Circulating GH levels were elevated, and serum concentrations of IGF-I and IGF-binding protein-3 (IGFBP-3) were markedly reduced, with poor response to daily GH injections. However, these patients lack functional STAT5B not only in liver but globally, and it is difficult to ascertain that the phenotype is due to its absence in liver. Fibroblasts of these patients displayed elevated levels of STAT1 and aberrant GH- and prolactin-induced activation of STAT1 and STAT3, reminiscent of what has been seen in liver-specific Stat5a/b-null mice. While these patients will provide insight into the global function of STAT5B in human physiology and disease, Stat5B/B;Alb-Cre mice as well as other cell-specific STAT5-KO mice will be instrumental in understanding the molecular underpinnings.

Is there a link between STAT5A/B activation and liver disease? Notably, STAT5 activation has been observed in clinical samples from patients with hepatocellular carcinoma (HCC) by some (51) but not by others (37). Even if activated STAT5 is detected in HCC, it is not clear whether the activation of STAT5 is a primary event in the development of cancer or the result of malignant transformation. Because HCC is accompanied by chronic hepatitis (CH) and liver cirrhosis (LC), it would be informative to analyze STAT5 activity in patients with CH or LC. Moreover, it will be necessary to have a more global view and compare the activation status of other STATs as well as how their balance might determine the physiology of the cell.

In contrast to a constitutive activation of STAT5 in some diseases, STAT5 activity in liver is inhibited in several syndromes, such as dwarfism and Laron syndrome (45). In dwarfism, GH secretion is suppressed as a consequence of different genetic defects, such as impaired pituitary function. In patients with GHR mutations STAT5 fails to be activated and expression of STAT5 target genes, such as IGF-I, is severely impaired. As pointed out above, recent studies on mutant mice suggest a more complicated mechanism that could involve the deregulation of feedback loops composed of IL-6 and SOCS3. Impaired STAT5 activation has also been observed in sepsis with an accompanying endotoxin release. In these patients hepatic expression of SOCS-1, SOCS-3, and CIS was transiently increased during sepsis and temporally associated with the development of hepatic GH resistance (10, 99). It is likely that increased SOCS/CIS expression is the result of elevated IL-6 levels that accompany severe inflammation.
Conclusions

Mice that carry mutations in the GHR-JAK2-STAT5A/B signaling pathway have been used extensively to explore the function of GH in the physiology and pathophysiology of mammals. Gene expression profiling of cells lacking functional STAT5A/B has provided a glimpse into the molecular mechanisms underlying the phenotypes observed in mutant mice and human patients. This review has focused on the link between molecular and physiological consequences encountered on the deletion of two highly conserved individual transcription factors (STAT5A/B), the archeological founding members of the STAT family. The seven members of the STAT family are the integral components of a communication network that is used by the majority of cytokines. Loss of STAT5A/B leads not only to the deregulated expression of its target genes but also to the aberrant activation of other members of the STAT family, which leads to a qualitative shift in the JAK-STAT communication network (Fig. 2). While the aberrant activation of STAT1 and STAT3 by GH might compensate for some molecular and physiological consequences encountered on the deletion of two highly conserved individual transcription factors, it is clear that STAT1 and STAT3 activate their own set of target genes and thus promote a different biology (Fig. 3). Emerging technologies, such as ChIP-seq, which require massive parallel sequencing, will be essential in our understanding of how cytokines use the JAK-STAT network to achieve specificity.

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