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STAT5 Signaling in Sexually Dimorphic Gene Expression and Growth Patterns

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Summary

The past 10 years have seen enormous advances in our understanding of how cytokine signals are mediated intracellularly. Of particular significance was the discovery of a family of seven Signal Transducer and Activators of Transcription (STAT) proteins. Each of these has now been studied in detail, and appropriate gene-disrupted mouse models are available for all except STAT2 (Leonard and O'Shea 1998). Fetal lethality is observed in Stat3-deficient mice, and various immunodeficiencies characterize mice with disrupted *Stat1*, *Stat4*, and *Stat6* genes, which is consistent with impaired signaling from the specific cytokines that activate each of these proteins. The recent characterization of *Stat5*-deficient mice has led to several unanticipated findings that point to diverse biological functions for the two STAT5 forms, STAT5a and STAT5b. These include roles for one or both STAT5 forms in the immune system, hematopoiesis, sexually dimorphic growth, mammary development, hair growth, deposition of adipose tissue, and pregnancy. Here we review the hormone- and cytokine-activated signaling pathways in which STAT5 participates and the extensive evidence, from laboratory animals, that these factors are required for sex-specific aspects of development, including control of body size. Finally, we consider human growth disorders that may involve defects in STAT5-dependent signal transduction.

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Cytokine Signal Transduction–JAK/STAT5 Pathway

Cytokines simultaneously activate multiple intracellular-signaling pathways, including the mitogen-activated protein (MAP) kinase pathway and the Janus kinase (JAK)–STAT pathway (fig. 1). The initial step in the JAK-STAT pathway is the binding of a cytokine to its cognate cell-surface receptor, which then dimerizes and is trans-phosphorylated, on specific intracellular tyrosine residues in the receptor's cytoplasmic domain, in a reaction catalyzed by a receptor-associated JAK tyrosine kinase. Latent cytoplasmic STAT proteins are then recruited to the activated receptor-kinase complex, via the STAT's COOH-terminal SH2 (phosphotyrosine-binding) domain, and are phosphorylated on a COOH-terminal–region tyrosine residue and, secondarily, on serine or threonine residues. The activated STATs then form homo- or heterodimers via mutual and complementary SH2-domain interactions, and, within minutes, translocate to the nucleus, where they bind to specific promoter elements and transactivate their target genes (Leonard and O'Shea 1998; Matsumura et al. 1999).

The promoter elements that are regulated by STAT homo- or heterodimers contain γ-interferon-activated sequence-like motifs (GAS; $TTC(N)_3GAA$). Because both the sequences flanking the GAS-like site and the number of nucleotides in the core vary, these promoter elements interact preferentially with specific STAT dimers. In addition, some promoters contain adjacent GAS-like motifs that can recruit two STAT dimers. The NH_2-terminal regions of STAT1, STAT4, and STAT5 have been shown to mediate dimerization of juxtaposed STAT dimers to form tetramers that may enhance target-gene specificity and binding to low-affinity STAT-binding sites (Leonard and O'Shea 1998; John et al. 1999).

The *STAT* family of genes is believed to have arisen from a single ancestral *STAT* gene, via a series of gene and chromosomal duplications (Copeland et al. 1995). Because the mammalian *STAT5* genes are most similar to the single *STAT* orthologues found in insects (Barillas-Mury et al. 1999), it appears that *STAT5* is the original gene, which has retained diverse functions, and that the

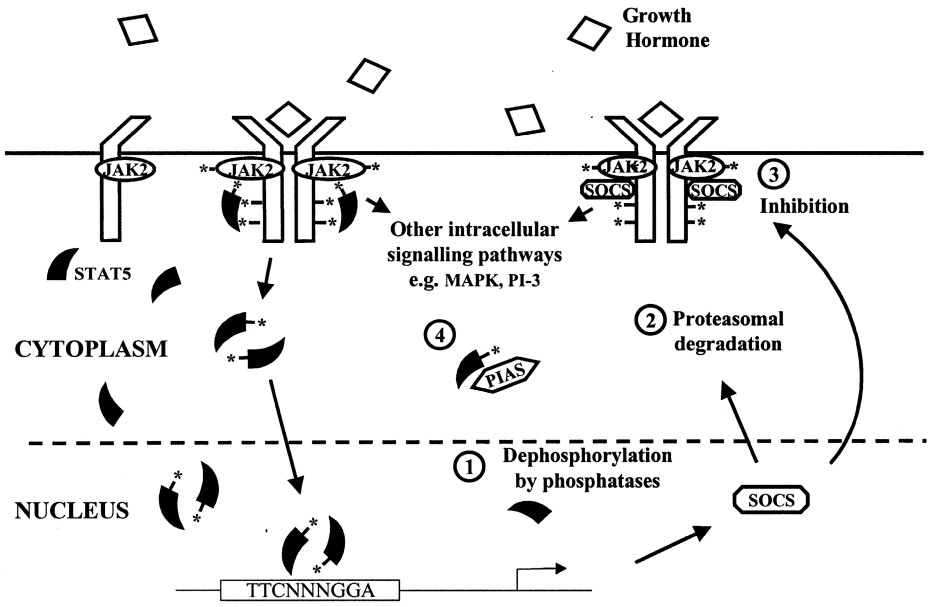

Figure 1 The GH JAK-STAT intracellular signaling pathway. GH binds to dimerized GH receptors, and the receptors and associated JAK2 phosphotyrosine kinases are phosphorylated (*). Latent cytoplasmic STAT5 proteins are recruited to the receptor-JAK2 complex and are activated by phosphorylation. Phosphorylated STAT5 proteins homo- or heterodimerize and translocate to the nucleus, where they bind to target DNA sequences. Intracellular signaling is turned off by several mechanisms. These include: (1) dephosphorylation by phosphatases; (2) degradation by proteasomes; (3) cytokine induction of SOCS proteins that either bind to receptor or JAK proteins to block subsequent signaling or mediate interactions with elongins B and C; and (4) PIAS proteins that interact directly with specific STAT proteins (note that PIAS5 has yet to be identified).

other STAT genes, once duplicated, diverged from that sequence and adopted specific biological roles. In the human genome, this history of duplication and mutation has resulted in three clusters of homologous genes: *STAT*s *1* and *4* on 2q, *STAT*s *2* and *6* on 12q, and *STAT*s *3*, *5a*, and *5b* on 17q. A relatively recent duplication of *STAT5* is believed to have given rise to the closely related *STAT5a* and *STAT5b* homologues.

The detailed structure within these gene clusters remains uncertain. Physical and genetic data from both humans and mice suggest that the *STAT5a* and *STAT5b* genes are very close together, with *STAT3* probably more remote; FISH studies on human cells have assigned the *STAT3*, *STAT5a*, and *STAT5b* genes to different chromosomal bands (17q21 and 17q 11.2, respectively), perhaps separated by a megabase or more (see GDB Genome Database), whereas, in mice, genetic mapping does not resolve these genes (Copeland et al. 1995). Teglund et al. (1998) suggest that the murine *Stat3* and *Stat5a* genes may lie within 5 kb of each other. It is interesting to speculate that the proximity and the high degree of sequence similarity between *STAT5a* and *5b* may promote the loss of one of these genes through unequal crossing-over or gene conversion (Lupski 1998). Although such recombination events are best characterized at the meiotic level, where they can persist over generations in a family or a population, they may also occur mitotically at surprisingly high frequencies, 10^{-4} or greater (Tusie-Luna and White 1995), leading to somatic mosaicism for STAT5a and/or STAT5b function.

Biological Role of STAT5

STAT5 was first identified as a mammary-gland factor (MGF) that is activated by prolactin and required for the expression of the milk protein β-casein in cultured mammary epithelial cells (Wakao et al. 1994). MGF was subsequently renamed STAT5a when a closely related gene product, designated STAT5b, was discovered. STAT5a and STAT5b proteins share ~90% amino-acid identity and are activated by a wide range of cytokines and growth factors (Leonard and O'Shea 1998).

Gene-disruption studies have helped to elucidate the physiological functions of STAT5a and STAT5b. In Stat5a-deficient mice, mammary-gland development and lactation are severely impaired (Liu et al. 1997). These mice also exhibit lymphohematopoietic defects, including defective responsiveness to granulocyte macrophage–colony-stimulating factor (GM-CSF) in bone marrow–derived macrophages and defective IL-2–in-

duced receptor α-chain expression in T cells (Leonard and O'Shea 1998; Teglund et al. 1998). By comparison, the phenotypes of Stat5b-deficient mice indicate that this factor affects a wider range of biological functions. Defects in these animals include altered hair-growth cycles and adipose-tissue deposition, reproductive failure, immunologic defects, impaired mammary-gland development and lactation, and loss of sexually dimorphic body-growth rates and liver gene expression (Udy et al. 1997; Imada et al. 1998; Teglund et al. 1998; Park et al. 1999). When the *Stat5a* and *Stat5b* genes are both disrupted, the phenotype is similar to the combined phenotypes resulting from the individual gene disruptions, with additional loss of functions associated with growth hormone or prolactin, and impaired peripheral T-cell activation by IL-2 (Teglund et al. 1998; Moriggl et al. 1999).

Thus, as summarized in table 1, STAT5a and STAT5b have nonredundant, as well as redundant, function. While some of the divergent phenotypic effects of the two mutations may result from known tissue-specific differences in the relative abundance of STAT5a- and STAT5b-protein expression (e.g., STAT5a > STAT5b in mammary gland, versus STAT5b > STAT5a in liver), the two STAT5 proteins exhibit distinct serine-phosphorylation patterns and DNA-binding-site preferences (Verdier et al. 1998; Yamashita et al. 1998). Multiple forms of STAT5a and STAT5b, resulting from degradation or alternative splicing, are also present in some tissues. The roles of these STAT5 forms are not fully understood, but COOH-terminal–truncated STAT5 variants may act in a dominant negative manner to inhibit STAT5-dependent signal transduction (Leonard and O'Shea 1998). It also seems likely that transcriptional activation of at least some STAT5 target genes may exhibit specific requirements for STAT5a homodimers, STAT5b homodimers, or STAT5a/STAT5b heterodimers (Verdier et al. 1998; Park et al. 1999).

Termination of STAT Signaling

Recent studies have revealed a number of potential mechanisms by which hormone- or cytokine-stimulated STAT signals can be turned off. First, activated STAT proteins, like many cytoplasmic or nuclear proteins, are subject to ubiquitin-dependent degradation mediated by the proteasome (Leonard and O'Shea 1998; Gebert et al. 1999*b*). Second, the SH2 domain–containing tyrosine phosphatases SHP-1 and SHP-2 may dephosphorylate and, hence, inactivate STAT proteins (Ram and Waxman 1997; You et al. 1999). Third, STAT proteins may be inactivated by interaction with several classes of proteins, including the protein inhibitor of activated STAT (PIAS) proteins and the suppressor of cytokine-signaling proteins (SOCS; also known as STAT-induced STAT inhibitors [SSI] and cytokine-inducible SH2-containing proteins [CIS]). PIAS1 and PIAS3 bind directly to STATs 1 and 3, respectively (Chung et al. 1997; Liu et al. 1998), and, although no PIAS5 has been identified as yet, PIAS proteins may well exist for each of the STAT proteins.

SOCS proteins contain a COOH-terminal–conserved SOCS box that mediates interactions with elongins B and C and that may affect the rate of proteasomal-protein degradation (Zhang et al. 1999). A subgroup of the SOCS proteins also contains SH2 domains that mediate binding to phosphotyrosine residues on receptors or on other STATs (Hilton et al. 1998). SOCS proteins form part of a classic negative-feedback loop, in that their expression is induced by cytokines and they inhibit signal transduction by binding to the cytokine receptor or JAK kinase. STAT5a or STAT5b is required for the expression of CIS in the murine ovary and medullary thymocytes (Teglund et al. 1998; Moriggl et al. 1999), and STAT5b is required for the growth hormone (GH)–induced expression of SOCS-2 and SOCS-3 mRNA in the mouse liver (H. W. Davey et al., unpublished observations). In addition to impaired JAK-STAT signaling, a defect in STAT5 may, therefore, cause cytokine hypersensitivity or, perhaps, hyperstimulation (from prolonged signaling via the MAP kinase or via alternative pathways), due to impaired or reduced induction of SOCS genes that normally feed back to turn off the initial cytokine signal.

STAT5b and Sexually Dimorphic Body-Growth Rates

In rats, mice, and certain other species, the expression of a number of liver-expressed genes is highly sexually dimorphic. This sex difference is primarily determined by plasma GH profiles, which are sexually dimorphic in many species, and is only secondarily regulated by other hormones. Although more pronounced differences can be seen in some species (e.g., rats), the consistent characteristic that defines the male plasma GH pattern is a period of negligible GH for at least 1 h between the pulses of GH. The longer GH interpulse interval that occurs in males, compared with females, is responsible for the sex differences in liver gene expression and for the sexually dimorphic whole-body growth patterns that emerge at puberty (Waxman and Chang 1995). In rats, exposure to androgens during the first three days of life is sufficient to set ("imprint") the male-specific pituitary GH secretory pattern that emerges at puberty. This androgen-imprinted adult GH pattern is, in turn, responsible for inducing the expression in liver of male-specific genes and for suppressing the expression of genes normally restricted to females. Nearly continuous GH exposure, a characteristic of adult female rats, may also induce the expression of other liver-expressed genes that are associated with females (Waxman 1988; Waxman et al. 1991).

The involvement of Stat5b in GH signaling was first

Table 1

Functions of STAT5, Identified by Analyzing Phenotypes of STAT5a-, STAT5b-, and STAT5a/b-Deficient Mice

Area of Function	STAT5a$^{-/-}$	STAT5b$^{-/-}$	Additional Effects in STAT5a/b$^{-/-}$ Mice
Sexual dimorphism of gene expression and growth	Some female-specific proteins decreased in liver	Sexually dimorphic growth and liver gene expression decreased in males; some female-specific proteins decreased in liver; serum insulin-like growth factor (IGF)-1	Growth of both males and females further depressed; expression of both male- and female-specific genes in the liver decreased; serum IGF-1 decreased
Mammary gland	Impaired lobuloalveolar development during pregnancy; whey acidic protein and α-lactalbumin decreased	Impaired mammary development; failure of lactation; expression of all the major milk proteins decreased	Not examined (infertile)
Hematopoiesis/immune functions	Responsiveness of bone marrow–derived macrophages to GM-CSF decreased; T cells associated with defective interleukin (IL)-2 signaling decreased; defective GM-CSF–induced proliferation of bone-marrow macrophages; natural killer (NK) cells decreased (normal function)	Response of splenocytes to IL-2 and IL-15 decreased, resulting in decreased NK cells; small decrease in thymocytes and splenocytes	Response to IL-3 and IL-5 in bone marrow–derived macrophages decreased; T cells decreased; numbers of pre-B and B-cells decreased; numbers of neutrophils increased; response of bone marrow–derived macrophages to IL-7 decreased; impaired peripheral T-cell activation by IL-2
Reproduction	Normal?	Failure of reproduction due to abortion; pregnancy can be maintained by exogenous progesterone in some mice	Infertility because of failure to maintain a functional corpus lutea
Hair growth	No data	Altered hair growth cycles; extended telogen before growth of the second coat of hair	No data
Fat deposition	Fat decreased	Amounts of adipose tissue in young mice decreased; obesity in some older mice	Fat decreased (epididymal fat pads approximately one-fifth that of wild type)

recognized by comparing liver nuclear-protein tyrosine-phosphorylation patterns in male and female rats. Intermittent plasma GH pulses stimulate tyrosine phosphorylation and nuclear translocation of Stat5b in intact male rats while the more continuous presence of GH in female rats down-regulates the Stat5b signaling pathway (Waxman et al. 1995; Gebert et al. 1999*a*). Experiments using a rat-liver cell line indicate that Stat5b is deactivated by tyrosine dephosphorylation and then cycles from the nucleus back to the cytoplasm, at the end of a GH pulse, to be reutilized. Activated Stat5b is significantly more abundant in liver from males than in liver from females, and it is reduced to negligible levels in hypophysectomized male rats but is restored by GH treatment (Waxman et al. 1995) under conditions that mimic the male pulsatile GH-secretion pattern. Overall, expression of Stat5b in liver is up to 10-fold greater than that of Stat5a (Park et al. 1999). However, Stat5a exhibits the same preferential activation by male plasma GH pulses that is seen in Stat5b (Choi and Waxman, in press).

Thus, the simplest explanation for the phenotype of *Stat5b* gene-disrupted male mice is that they have an impaired cellular response to the pulsatile pattern of pituitary GH release. This impaired GH-pulse responsiveness would account for the observed feminization of pubertal body-growth rates and the loss of male-specific liver P450 expression seen in Stat5b-deficient male mice. It also can explain the apparent increase, in males, of female-predominant liver gene products to near-female levels (Udy et al. 1997). To confirm that these are, in fact, effects of a defect in the cellular response to the plasma pattern of GH secretion, rather than changes in the sexually dimorphic pattern of pituitary GH secretion, we hypophysectomized young male Stat5b-deficient and wild-type mice and then treated them with pulses of GH to mimic the male plasma GH pattern. Whereas GH pulse injections restored male growth rates and a male pattern of liver gene expression in hypophysectomized wild-type mice, no such restoration was achieved in hypophysectomized *Stat5b*-knockout mice (H. W. Davey et al., unpublished experiments). These findings demonstrate that STAT5b-deficient mice do, indeed, have impaired GH intracellular signaling. Nevertheless, there is some evidence to suggest that GH secretion may be increased in STAT5b-deficient mice (Luckman et al. 1998).

STAT5 and Liver Cytochrome P450 Gene Expression

Cytochrome P450 is a large superfamily of monooxygenase enzymes that participate in a wide range of metabolic processes, including cholesterol metabolism, bile-acid synthesis and metabolism, steroid hormone hydroxylation, and the metabolism of drugs and toxic chemicals. In many instances, P450 metabolism leads to detoxification and elimination of foreign chemicals, but, in other cases, it results in the formation of toxicologically or pharmacologically active metabolites. Several liver-expressed P450 enzymes have dual specificities; they oxygenate foreign chemicals, but also display narrow stereoselectivities for hydroxylation of testosterone and other endogenous steroids (Waxman 1988; Waxman and Chang 1995).

Animal experiments, principally in rats, have revealed that expression of a number of these P450 enzymes is sex-dependent and regulated by GH secretory patterns. Particular attention has been paid to members of the *CYP2* and *CYP3* families and to their involvement in hepatic steroid hormone hydroxylation, which differs for each sex and is also subject to postnatal developmental control (Waxman and Chang 1995). Rats have exaggerated sex differences in drug metabolism, compared with mice and humans, and have, therefore, been used as a model to study mechanisms regulating this dimorphism (Shapiro et al. 1995). Nevertheless, mice exhibit marked male-female differences in the liver patterns of expression of steroid hydroxylase P450s (Shapiro et al. 1995) and of several non-P450 liver enzymes that are also dimorphic in rats. Intriguingly, the actual patterns and levels of enzymes that are sexually dimorphic vary markedly from species to species, and even from one mouse strain to another. Our analyses of CYP-expression patterns in Stat5a- and Stat5b-deficient mice have shown that Stat5b is required to maintain normal sexually dimorphic GH responses. While Stat5a is fully dispensable for the male pattern of liver gene expression, both Stat5a and Stat5b are required for the expression of certain female-specific, GH-regulated liver gene products (Udy et al. 1997; Park et al. 1999). A simple interpretation of these data is that STAT5b homodimers mediate GH pulse-regulated gene expression, whereas STAT5a-STAT5b heterodimers regulate the expression of some female-specific GH-regulated genes.

As a consequence of these sex differences in liver P450 gene expression, males and females may differ substantially in rates of drug metabolism. Although major sex-based differences in hepatic P450 profiles have not been observed in humans, such differences could be masked by much larger differences between individuals, associated with P450 polymorphisms and P450 induction caused by exposure to foreign chemicals. Nevertheless, human P450-associated drug-metabolism activities are determined in part by age, sex, and/or GH status (Cheung et al. 1996). One would predict, based on the animal data, that individual variations in the efficacy of, or actual dysfunctions in, STAT5b signaling pathways could have significant effects on the patterns of human liver-enzyme expression. Further study is required to ascertain whether this is a fundamental contributing cause

to individual variations in drug sensitivities/toxicities, along with the well-established variations arising from genetic and environmental factors (Wormhoudt et al. 1999).

STAT5 and Human Growth Defects

Based on the phenotype of the STAT5b-deficient mouse, one would predict that humans with a dysfunctional STAT5b protein, or a defect in STAT5b-dependent signaling, would have discernible pubertal growth defects. More specifically, at the molecular level, one would expect that the actual defect would be in the intracellular responses to pulsatile GH signaling and that such patients would retain both functional GH receptors and circulating serum GH-binding protein. Some patients with Laron syndrome display precisely these characteristics (MIM 245590). While the classic (type I) Laron syndrome is caused by dysfunction of the GH receptor, this nonclassic (type II) Laron-type dwarfism is attributed to postreceptor defects in signal transduction. Indeed, preliminary work by Freeth et al. (1998) suggests that STAT5 activity is dysfunctional in fibroblasts isolated from affected individuals in one such family affected by Laron syndrome. Unfortunately, genetic heterogeneity complicates the study of this extremely rare disorder (Adam et al. 1981), and, in another family with Laron syndrome type II, STAT5 appears to function normally (Clayton et al. 1999). Of less certain connection with STAT5b dysfunction, but certainly worthy of investigation, is the relatively large number of idiopathic short-stature defects, some of which have some symptoms similar to those of Laron syndrome (Attie et al. 1995).

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

GDB Genome Database, http://www.gdb.org/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for Laron syndrome)

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