

cally flawed, the use of valacyclovir in combination with glucocorticoids could still be considered in patients with severe or complete facial palsy.

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STAT3 Signaling and the Hyper-IgE Syndrome

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The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signaling pathway has emerged over the past decade as a major relay between cell-surface receptors and cytokine responses. The human genome encodes four JAK family members — JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) — and seven STAT proteins.¹ JAKs are protein tyrosine kinases that interact with the intracellular domains of cytokine receptors (Fig. 1) and that have enhanced catalytic activity toward substrate proteins after receptor activation. The primary JAK substrates are STAT proteins — latent transcription factors that require their tyrosine residues, and sometimes serine residues, to be phosphorylated before they can induce the transcription of target genes.

The primary model of JAK-STAT signaling was established by delineation of the interferon pathway — wherein the JAK-STAT signal-transduction system was discovered.² Oligomerization of cytokine receptors in response to ligand binding leads to transphosphorylation of associated JAK enzymes, stimulating their ability to phosphorylate both the cytoplasmic domains of the

cytokine receptors and the subsequently recruited STAT proteins (Fig. 1). Once phosphorylated, the STAT proteins dimerize through interactions between the phosphotyrosine and SRC homology 2 (SH2) domains. Active dimers accumulate in the cell nucleus, bind specific DNA target sequences of gene promoters, and recruit coactivator and transcriptional regulatory proteins that drive gene expression. The requirement of signal-dependent phosphorylation of STAT tyrosine residues, coupled with the sensitivity of STAT to dephosphorylation by nuclear phosphatases, renders the protein a dynamic, sensitive on–off switch for gene expression.

Molecular genetic analysis of cells from humans and from engineered mice has revealed that STAT proteins usually have highly specific functions, dictated both by the specific receptors that serve as activators and by the intrinsic DNA binding preferences of STATs and thus their spectrum of target genes. This inherent specificity is most easily observed in the phenotypes of mice lacking individual *Stat* genes (Table 1). Mice lacking *Stat1*, a protein activated primarily by interfer-

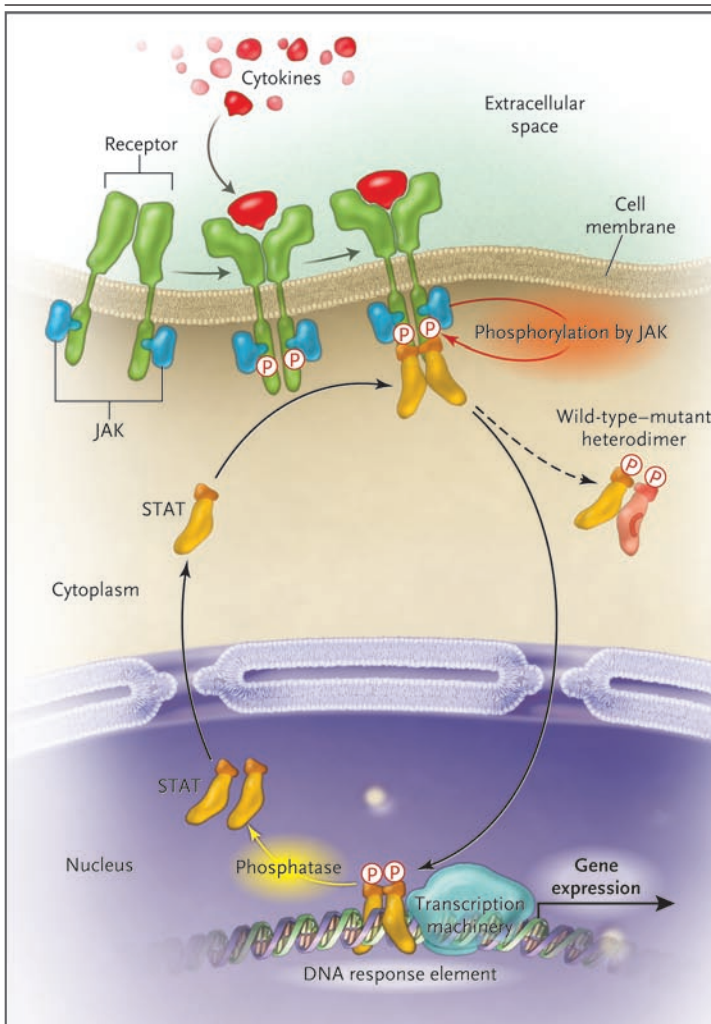


Figure 1. The JAK-STAT Pathway.

JAK phosphorylates the cytoplasmic portions of cytokine receptors, which aggregate in response to ligand binding. STAT proteins are recruited to the resulting binding sites. The STATs are subsequently phosphorylated (by JAK), creating dimers capable of accumulating in the nucleus, binding to promoters, and activating transcription through recruitment of the RNA polymerase II machinery. The signal-transduction cycle is terminated by dephosphorylation of activated STAT proteins by nuclear phosphatases. Mutant STAT proteins unable to bind DNA can nonetheless interact with wild-type STAT proteins, resulting in nonproductive dimers that have a dominant negative effect on STAT function.

on- α , interferon- β , and interferon- γ , show virtually no response to interferons and are highly susceptible to bacterial and viral infections, whereas mice lacking Stat2, which is selectively activated by interferon- α and interferon- β , cannot mount an innate immune response to viral infections. Similarly, mice lacking Stat4, Stat5a or Stat5b, or Stat6 display relatively circumscribed immune de-

fects largely consistent with the biologic functions of their primary cytokine activators. However, an absence of Stat3 results in embryonic lethality,³ and selective inactivation of Stat3 in various adult mouse tissues leads to a wide spectrum of defects.⁴ Moreover, although all STAT proteins have been implicated in either heritable or spontaneous human diseases, the role of STAT3 may prove to be the most diverse, with a variety of roles in malignant transformation, cancer, and inflammatory and immune diseases.

The possibility of a role of STAT3 in cancer emerged from studies of experimental carcinogenesis. The seminal discovery of STAT3 as a phosphotyrosine substrate of the viral Src oncogene⁵ led to numerous observations of inappropriately activated STAT3 in both experimentally induced and spontaneous cancers, making the therapeutic inactivation of STAT3 in numerous cancers — such as breast cancer, prostate carcinoma, multiple myeloma, leukemia, and lymphoma — an attractive goal.^{6,7}

A directly causative role for STAT3 has been established in many experimentally induced cancers, and the inhibition of its activation or function or the reduction of its levels by means of a battery of strategies has had dramatic therapeutic effects. For instance, the expression of dominant negative STAT3 mutants capable of inhibiting endogenous STAT3 reverses the inappropriately activated phenotype and diminishes the malignant potential of human tumor-cell lines. Similarly, reducing or eliminating Stat3 levels in tumor cells in mice abrogates the malignant phenotype of numerous cancers, and “decoy” oligonucleotides that compete for STAT3 DNA binding have shown promise in the treatment of head and neck cancers in humans.⁸ Activated STAT3 also contributes to the tumor environment: its expression in infiltrating leukocytes can impair their antitumor activity and thereby promote tumor progression.⁹ These findings, in aggregate, have stimulated an aggressive pursuit of STAT3 inhibitors with therapeutic potential.⁷

However, in addition to promoting disease through hyperactivity, STAT proteins are also protective, which again is best observed through the effects of their absence (Table 1). The first mutations in the human JAK-STAT pathway were characterized in the interferon- γ system; heritable mutations in *STAT1*, in the gene encoding the interferon- γ receptor, and in genes encoding oth-

Table 1. Janus Kinase (Jak)–Signal Transducer and Activator of Transcription (Stat) Mutant Phenotypes in Mice and Humans.

Absent Mouse Gene	Mouse Phenotype	Mouse Cytokine Response with Primary Defect	Human Phenotype
<i>Tyk2</i>	Susceptibility to infection	Interleukin-12	Autosomal recessive hyper-IgE syndrome
<i>Jak1</i>	Perinatal lethality	Interleukin-6 family	Not reported
<i>Jak2</i>	Embryonic lethality	Erythropoietin	Polycythemia vera*
<i>Jak3</i>	Severe combined immunodeficiency	Interleukin-2 family	Severe combined immunodeficiency
<i>Stat1</i>	Susceptibility to infection	Interferon- α , interferon- β , interferon- γ	Susceptibility to infection
<i>Stat2</i>	Susceptibility to viral infection	Interferon- α , interferon- β	Not reported
<i>Stat3</i>	Embryonic lethality, multiple defects in adult tissues	Interleukin-6 family, interleukin-10, leptin, granulocyte colony-stimulating factor, others	Hyper-IgE syndrome
<i>Stat4</i>	Impaired differentiation of type 1 helper T lymphocytes	Interleukin-12	Not reported
<i>Stat5a</i>	Impaired lymphopoiesis and mammary-gland development	Lymphokine and prolactin	Not reported
<i>Stat5b</i>	Impaired lymphopoiesis and postnatal growth	Lymphokine and growth hormone	Insensitivity to growth hormone
<i>Stat6</i>	Impaired differentiation of type 2 helper T lymphocytes	Interleukin-4	Asthma and atopy†

* Polycythemia vera occurs as a result of an activating mutation.

† Inheritance of sensitivity to asthma and atopy has been linked to polymorphisms in *STAT6*.

er pathway components were found in children highly susceptible to mycobacterial and some viral infections.¹⁰ As expected from the interactions of TYK2 with numerous cytokine receptors, TYK2 mutations cause multiple defects of innate and acquired immunity.¹¹ JAK3 has an essential role in signaling by T lymphocyte cytokines; not surprisingly, mutations in *JAK3* cause severe combined immunodeficiency.¹² Now, in an article in this issue of the *Journal*¹³ and another report,¹⁴ mutations in *STAT3* that cause profound, multisystem inflammatory disorders are identified. Remarkably, only heterozygous missense mutations (predicted to affect the DNA-binding or SH2 domain) were detected, suggesting either haploinsufficiency or dominant negative mechanisms. Consistent with a dominant negative mode of action, mutations within segments encoding the DNA-binding domain resulted in a protein with an impaired ability to target promoter DNA sequences and induce the expression of relevant genes.¹⁴ Mutations affecting the SH2 domain led to similar reductions in target-gene expression,¹³

although a dominant negative mechanism for these mutations is more difficult to envisage.

The clinical phenotype associated with these mutations is the hyper-IgE syndrome, a well-recognized multisystem disorder for which a molecular explanation has long been awaited. As the name suggests, the hyper-IgE syndrome is characterized by elevated serum IgE levels and is associated with early-onset eczematous rash similar to atopic dermatitis. In contrast to allergic disorders, the hyper-IgE syndrome is largely an immunodeficiency disease, and affected persons have impaired resistance to cutaneous and sinopulmonary bacterial disease, typified by abscess and cyst formation, often in the absence of signs of adverse effects, such as fever. Moreover, patients with the syndrome have a variety of skeletal, dental, and soft-tissue defects.

The realization that impaired *STAT3* function underlies this disorder provides remarkable clarity about these diverse symptoms. For instance, *STAT3* is an essential mediator of the immunosuppressive action of interleukin-10, and the loss

of responsiveness of this interleukin may underlie much of the proinflammatory nature of the hyper-IgE syndrome. Similarly, the selective loss of Stat3 function in various adult mouse tissues has been linked to impaired wound healing, defective cardiomyocytes, and altered hematopoiesis — leading to eosinophilia, osteopenia, impaired expression of β -defensin, and lethal proinflammatory reactions,⁴ results consistent with manifestations of the hyper-IgE syndrome. STAT3 is implicated in the differentiation of interleukin-17–producing CD4⁺ T lymphocytes,¹⁵ important for immunity to some bacterial infections. Loss of these functions in patients with the hyper-IgE syndrome could contribute to impairment of the immune response.

STAT3 mutations related to the hyper-IgE syndrome are consistent with the survival of those who have the mutation, despite the embryonic lethality found in mice lacking the protein. Perhaps this reflects incomplete abrogation of function; alternatively, it could imply a new, nontranscriptional role of Stat3 in mouse embryos.⁷ In any event, the discovery that mutations in STAT3 underlie many cases of the hyper-IgE syndrome should propel the development of early diagnostic tests for this disorder and spur the search for genetic causes of diseases that share some of its features. Of particular interest is the possibility that less disruptive variants of STAT3 or other pathway components could contribute to a range of disorders frequently encountered in the clinic, such as osteoporosis in the elderly or recurrent staphylococcal infections in patients with atopic dermatitis. However, the implications of these new findings for the use of STAT3 inhibitors in cancer therapy remain to be evaluated.

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