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THE JAK-STAT SIGNALING PATHWAY IN CHRONIC INFLAMMATORY SKIN DISEASES

JITLADA MEEPHANSAN, MD, PHD

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FOREWORD 01

Akimichi Morita, MD, PhD

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Biologics, which target cytokines, have become increasingly popular for the treatment of refractory skin diseases, e.g., psoriasis and atopic dermatitis. The clinical response rates have been considerably improved by biologics compared with conventional topical and oral treatments. The results of clinical trials and experiences in daily practice with these drugs have provided valuable information pointing to other potential avenues of approach, illustrating the "bedside to bench" concept. Specific cytokine-targeted therapies have informed our understanding of the immunopathogenesis of skin diseases. This deeper understanding has stimulated drug development for refractory skin diseases. Biologics, however, are very expensive and must be carefully prescribed under the appropriate conditions.

With these points in mind, small molecule kinase inhibitors that interfere with the Janus kinase enzymes (JAK) -signal transducers and activators of transcription (STAT) pathway are particularly interesting. Inhibiting JAKs is effective for treating various skin disorders. Therefore, JAK inhibitors are emerging as a novel class of medicines that can be used in dermatology, either systemically or topically. Four JAKs have been identified: JAK1, JAK2, JAK3, and Tyk2. JAKs interact with STAT family members to modulate gene transcription of various cytokines through their specific receptors. JAK inhibitors have differential selectivity for the 4 JAK isoforms.

In this book, details of the dermatologic applications for new treatments targeting the JAK-STAT pathway and JAK inhibitors are described for alopecia, psoriasis, atopic dermatitis, and other inflammatory skin diseases such as vitiligo, dermatomyositis, chronic

graft-versus-host disease, cutaneous lupus erythematosus, hidradenitis suppurativa, lichen planus, and chronic hand eczema.

The information contained herein is groundbreaking and will contribute to a better understanding of the underlying mechanisms of JAK inhibitors. This volume provides many tables showing clinical trial data as well as informative illustrations and figures.

I greatly appreciate the huge efforts put forth by all the contributors, particularly Prof. Jitlada Meephansan. I am very happy to have this opportunity to provide a preface for this timely and important book.

ตัวอย่าง

FOREWORD

02

Nopadon Noppakun, MD

Associate Professor of Division of Dermatology, Faculty of Medicine
Chulalongkorn University

Nowadays we have more understanding about the pathogenesis of many skin diseases by means of knowledge at the molecular level, and we can apply that concept to develop “targeted therapy” treatment technology that focuses on directly resolving the causes of diseases with high efficacy and few complications or side effects.

A study of the JAK/STAT signaling pathway and JAK inhibitors is an excellent example that indicates scientists can study research this pathway and discover that it is a significant cause of many kinds of immune-mediated inflammatory skin diseases, such as psoriasis, atopic dermatitis and alopecia areata. Most importantly, they will be able to develop treatments that are more effective than those currently available.

This book describes this substance in a way the reader can become familiar with, understand, and practically apply in the treatment of patients, as well as to use as a basis for further research. The author systematically narrates to the reader in an easily understandable and engaging manner.

I am very pleased and proud of the author, Associate Professor Jitlada Meephansan, M.D., Ph.D. and co-authors who have taken difficult, complex knowledge coupled with experience and distilled it into this excellent book

I sincerely hope that readers will take the knowledge from this book and be able to apply it in developing patient treatments and the body of knowledge through additional research.

PREFACE

Jitlada Meephansan, MD, PhD

Associate Professor of Division of Dermatology,
Chulabhorn International College of Medicine
Thammasat University

Our knowledge of the mechanism that generates the various forms of chronic skin inflammation has grown extensively and parallels the development of drugs that are being applied to the care of these skin conditions. Currently, drugs that are grouped as targeted inhibitors and as signal-transduction inhibitors have been devised and are being applied to the care of a number of different diseases, including diseases of the skin. The development and creation of these drug groups are now proceeding with greater efficiency, with a reduction in the various side effects that tend to occur from the more conventional therapies.

In this book, I have compiled a variety of information of considerable depth pertaining to JAK inhibitors, which applied to the treatment of such chronic skin inflammations as psoriasis, atopic dermatitis, and other inflammatory skin diseases such as vitiligo, dermatomyositis, chronic graft-versus-host disease, cutaneous lupus erythematosus, hidradenitis suppurativa, lichen planus, chronic hand eczema and even certain forms of hair loss, alopecia, areata and androgenetic alopecia. I have arranged their content from a basic knowledge of the JAK and STAT pathway, JAK inhibitors and use of the aforementioned drugs in treating each of the specifically listed skin diseases. In my discussion of the diseases, I refer to the clinical manifestation, pathogenesis and role of the JAK-STAT pathway applicable to each disease. This study tested the use of the above-mentioned drug groups in experimental animals and in humans. I compiled and summarized the results of using the JAK-STAT inhibitors in a table for ease of understanding and prepared some beautiful and easily readable illustrations in combination with it. I reviewed the related medical and research literature, especially as derived from my own experience and research on JAK-STAT inhibitors in the stimulation of hair growth in mice. In this book, I include the

results of a study pertaining to the mechanism of chronic skin inflammation, especially forms of psoriasis and atopic dermatitis that have both a direct and indirect link to the JAK-STAT pathway.

This book is intended to impart knowledge and understanding to the reader. It combines a perspective of basis molecular knowledge as applicable to clinical knowledge, from which the reader can obtain a conceptual grasp of the subject. The reader can then apply the concept to drugs that belong to other targeted and signaling inhibitor groups for future treatment and research. This book is intended for the learning and instruction of resident physicians, masters-level and doctorate-level physicians specializing in the skin, dermatologists, medical personnel and any interested scientists and researchers.

In closing, I wish to offer my gratitude and thanks to all who participated with me in this writing. My thanks go to the professors for their recommendations and all who participated. I ardently hope that this writing will be of benefit and value for the readers so that they will be able to apply it to their own practice or to enhance their own researches. May it serve as a valuable source that will be cited in the days ahead.

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- I would like to present this book as a personal gift to my parents. It is they who gave me birth, trained and taught me, and guided me in acquiring knowledge and experiencing success in my life, in my family and in my duties of work as I do today.
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- Professor Akimichi Morita, my beloved instructor who lavished upon me academic opportunities and advancement on an international level
- Professor Yoshiki Tokura, Professor Yusuo Kitajima, Professor Shinji Shimada and Professor Hiroshi Shimizu, who, for me, were role models and an inspiration as people who were knowledgeable, proficient, giving and reputable on an international level.
- Professor Mamitaro Ohtsuki and Professor Mayumi Komine, supervisor and advisor who provided me with opportunities, who taught me, who urged me on, who supported me and who were an important source of inspiration for me in conducting my research

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- Associate Professor Jongkonnee Wongpiyabovorn, my beloved instructor who was always with me, helping and supporting me in every matter that ever came up
- Every author who devoted time to compose this valuable book
- Onnalin Techapuwapat, my younger sister, who drew the illustrations for this book and designed the book cover
- Every teacher whom I have ever known in my life
- The professors and personnel in the Chulabhorn International College of Medicine at Thammasat University
- All of my students
- All who had a part in supporting the creation of this book, whom I could not acknowledge at this point in time

Dedicated to all of my Dermatological Patients.

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JAKS AND STATS

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Introduction

The JAK/STAT signaling pathway is a universally expressed intracellular signal transduction pathway and involved in many crucial biological processes, including cell proliferation, differentiation, apoptosis, and immune regulation. In addition, increasing evidence indicates that the persistent activation of JAK/STAT signaling pathway is closely related to many immune and inflammatory diseases, yet the specific mechanism remains unclear. It has been implicated in the pathogenesis of immune-mediated inflammatory skin diseases such as psoriasis, atopic dermatitis, alopecia areata, as well as vitiligo. Although the mechanism of JAK/STAT signaling pathway is relatively simple, its biological consequences are complex due to its crosstalk with other signaling pathways. Therefore, it is necessary to study the detailed mechanisms of JAK/STAT signaling pathway in disease formation to provide critical reference for clinical treatments of diseases. In this review, we focus on the structure of JAKs and STATs, the JAK/STAT signaling pathway, and its negative regulators.

JAK-STAT Signaling Pathway

Cytokines and interferons (IFN) are cell-to-cell messengers inducing many important biological responses in target cells. In recent years, a new signaling pathway has been clarified. This extraordinary pathway involves Janus kinase (JAK) and single transducer and activator of transcription (STAT) protein families [1]. The JAK-STAT pathway has been constitutive to both type I (IFNα/β) and type II (IFNγ) interferons and also cytokines for type I cytokine receptor superfamily members including interleukin (IL)-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-13, IL-15, granulocyte macrophage colony-stimulating factor (GM-CSF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), growth hormone (GH), prolactin, erythropoietin (EPO), and thrombopoietin. The JAK-STAT pathway is a signaling system, which promotes rapid transfer from cell membrane to nucleus and could be induced by different cytokines to elicit signals [2].

Characteristics of JAKs

The JAK family consists of four members including JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). Two transcripts of JAK2 have been identified, while multiple spliced forms of JAK3 have been identified, including a variation lacking a part of the catalytic domain [3]. The functional significance of these variant transcripts are not well understood, but it is fascinating to theorize that a normally occurring dominant negative form of JAK3 may have regulatory functions [2]. JAKs are present in the cytoplasm and associate with the cytoplasmic region cytokine receptors in the cell membrane.

Structure of JAKs

JAKs are comparatively large kinases (approximately 1150 amino acids) with approximately 120-130 kDa molecular weight. The JAK family of protein kinases is structurally composed of tandem kinase and pseudokinase domains. The catalytic domain is known as C-terminal kinase; however, the definite function of the pseudokinase domain has not yet been clearly determined. JAK homology (JH) domains define regions of homology shared by JAKs, while C-terminal–to–N-terminal domains are named as Src homology (SH) domains [4]. JH1 and JH2 are the kinase and pseudokinase domains, respectively. These two domains characterize the unique feature of the protein as they have extensive homology to tyrosine kinase domains. The JH1 domain is a functional tyrosine kinase domain with an essential YY motif in its activation loop; hence, JH1 plays a critical role in catalytic activity [5]. The JH2 domain, a kinase-like or pseudokinase domain plays an important role in regulating JAK family protein activation and cytokine-induced signaling. A previous theoretical model strongly suggested that the JH2 domain has a negative effect on the JH1 domain kinase activity [6]. The JH5 to JH7 (as well as a segment of JH4) domains consist of the four-point-one, ezrin, radixin, moesin (FERM) domain regulating the catalytic activity and associated with mediation of receptors and other proteins. Activation of JAK1 mutants requires an intact FERM domain in order to support type I IFN signaling [7]. Moreover, in the JAK2 FERM domain, tyrosine 913 mutation has also been shown to result in kinase activation, though the cytokine stimulation is absent [8]. In the case of JAK3, FERM domain mutations could influence its function, wherein these proteins were shown to lack

kinase activity and failed to associate with receptors [9]. The binding of JAKs and box 1/proline-rich region of cytokine receptors has been mediated by residues located in the JH7 region [10], and this interaction eventually regulates localization and turnover of the receptor [11]. The N-terminal of JAKs is associated with cytokine receptor subunits. (Figure 1)

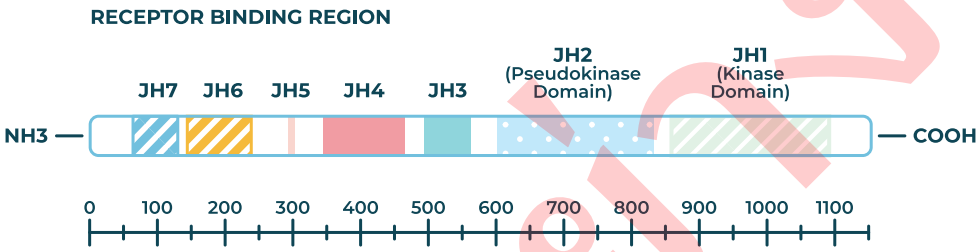

Figure 1. Structure of JAKs, scale bar indicates number of amino acid residues.

JAK Activation in JAK-STAT Signaling

Primarily, receptor-ligand binding results in dimerization/ oligomerization, which leads to juxtaposition of JAKs through homodimeric or heterodimeric interactions. The recruitment results in phosphorylation of JAKs via autophosphorylation and/or transphosphorylation by either tyrosine kinase families or other JAKs. As a result, JAK kinase activity increases the activation and phosphorylation of receptors via tyrosine residues, which leads to these targets acting as docking sites that allow other SH2 domain–containing signaling molecules to bind, including STATs, protein phosphatases, Src kinases, Shc, Grb2, and PI-3 kinase [12]. (Figure 2)

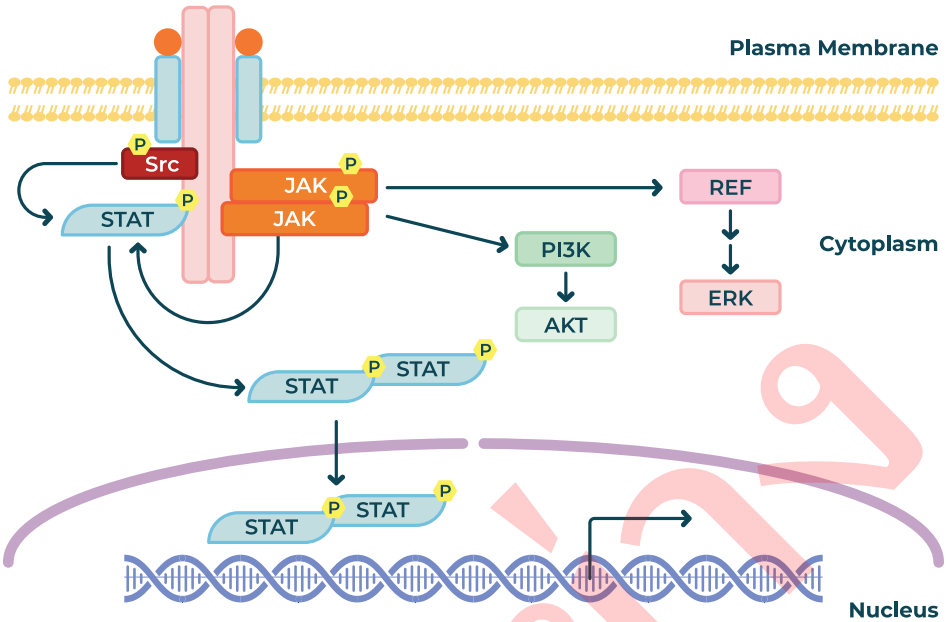

Figure 2. JAK-STAT signaling pathway.

JAK Family Members

JAK1

Previous studies show that JAK1 is complex in signaling and involves members of the IL-2 (IL-2R, IL-7R, IL-9R, and IL-15R), IL-4 (IL-4R and IL-13R) and gp130 receptor families (IL-6R, IL-11R, LIF-R, OSM-R, CT-1R, CNTF-R, NNT-1R/BSF-3R, and Leptin-R), and class II cytokine receptors (type I IFN-R, type II IFN-R, IL-10R) [13]. These receptors are pleiotropic, and Rodig et al. reported that JAK1 knockout mice display an early postnatal lethal phenotype [14], resulting in a suckling defect from a neurological lesion caused by the loss of leukemia inhibitory factor (LIF) function [15]. The LIF and IL-6 response was considerably decreased in JAK1$^{-/-}$ tissues. Also, JAK1$^{-/-}$ mice exerted defects in production of thymocyte and B cell that were

associated with defects in responses to IL-7, which is critical in early lymphocyte development [16]. Moreover, JAK1 deficiency leads to serious abnormalities in type I and type II IFN biological responses. Defects in response to IL-10 also occur in JAK1$^{-/-}$ mice. In conclusion, JAK1 exhibits an important role in biological responses to mediation by several cytokine receptor families [17].

JAK2

JAK2 is expressed extensively and its signaling is elaborate including the common β chain and certain class II receptor cytokine family members. Defects in the murine JAK2 gene cause erythropoiesis failure, leading to embryonic lethality at day 12.5 [18]. Cells harvested from JAK2$^{-/-}$ mice showed that JAK2 is necessary for IL-3, GM-CSF, IL-5, thrombopoietin, and IFN-γ, with an exception of IL-6 and IFNα/β signaling. However, JAK2 is not crucial for development of T cells, as shown by the irradiated JAK3$^{-/-}$ mice with normal thymic subsets after transfer of JAK2$^{-/-}$ fetal liver cells [19].

TYK2

At first, TYK2 was identified as a crucial component in the screening of mutants in IFN-α signaling [20]. Remarkably, profound defects in IFN-α/β signaling are found in TYK2$^{-/-}$ mice [21]. Cells harvested from these mice are insensitive to type I IFNs in low doses, but antiviral responses are rather normal. In addition, IL-10 signaling is found to be normal, and IL-12 responses were defective, but not totally absent. In response to IL-6, there was no defect observed. Unexpectedly, response to lipopolysaccharides (LPS) is defective in macrophages with ineffective TYK2, although the

mechanism of this defect has not been clarified [22]. Therefore, TYK2 appears to be the most important for mediating IL-12 and LPS biological responses [17, 19].

JAK3

Previous biochemical studies indicated that JAK3 signals through receptors that belong to the common γc receptor family including IL-2R, IL-4R, IL-7R, IL-9R, IL-15R, and IL-21R [2]. JAK3$^{-/-}$ mice exhibit severe lymphopoiesis defects, similar to those observed in γc-deficient mice [23]. Due to a critical role in IL-2 signaling of JAK3, T cells with ineffective JAK3 have problems in negative selection and maintenance of functional peripheral T cells [24]. In contrast to murine, humans develop severe combined immunodeficiency (SCID), characterized by defective T cells, but normal B cells [2]. SCID is a primary disastrous immunodeficiency that results in an illness with severe recurrent infections such as diarrhea and atopic dermatitis along with failure to thrive in children. Common γc mutations were found to regulate X-linked SCID [25]. In case of lack of this receptor subunit, lymphocytes are incapable to respond to IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, leading to defective T cell development and NK cell and B cell function. As JAK3 is selective to γc, JAK3 mutations would bring out similar sequelae [26]. However, IL-7, which is necessary for mice pre-B cell growth and is influenced by JAK3 mutations, is not affected in humans. Therefore, JAK3 plays a crucial role in lymphoid development. JAK3$^{-/-}$ mice have defects in IL-2, IL-4, and IL-7 response, leading to SCID phenotype [17].

Cytokine Receptor Signaling via JAKs

Signals of many cytokines and growth factors are mediated by JAKs. Precisely, JAK1 and TYK2 are required for IFNα/β signaling, while IFNγ requires JAK1 and JAK2 [27]. Moreover, EPO and GH have been shown to activate JAK2 [28, 29], while IL-6 activates JAK1, JAK2, and TYK2 [30]. JAK2 also associates with βc, which is a common subunit for IL-3, IL-5, and GM-CSF receptors [31]. JAK3 can only be activated by cytokines receptors in the γ chain (γc) family including IL-2, IL-4, IL-7, IL-9, and IL-15 as well as cytokines receptors that signal via JAK1 (the particular receptor subunits of cytokines in γc family (e.g., IL-2Rβ) associate with JAK1) [32]. Subsequently, all type I cytokines activate JAKs (Table 1). In case of the IFNα/β receptor, the α subunit (IFNAR-1) is associated with TYK2, whereas the β subunit (IFNAR-2) with JAK1 [33]. Furthermore, the IFNγRα subunit (IFNGR-1) associates with JAK1 and IFNγRβ (IFNGR-2) with JAK2. The β1 subunit of IL-12R associates with TYK2, while the β2 subunit with JAK2 [34]. In conclusion, JAKs are integrally associated with cytokine receptors and could be amplified by ligands in multiple receptor systems.

Table 1. Cytokines that activate JAKs and STATs. [2]

Type I Cytokines	JAKs	STATs
Cytokines whose receptors share γc		
IL-2, IL-7, IL-9, IL-15	Jak1, Jak3	Stat5a, Stat5b, Stat3
IL-4	Jak1, Jak3	Stat6
IL-13*	Jak1, Jak2, Tyk2	Stat6
Cytokines whose receptors share βc		
IL-3, IL-5, GM-CSF	Jak2	Stat5a, Stat5b
Cytokines whose receptors share gp130		
IL-6, IL-11, OSM, CNTF, LIF, CT-1	Jak1, Jak2, Tyk2	Stat3
IL-12[+]	Jak2, Tyk2	Stat4
Leptin[+]		Stat3
Cytokines with homodimeric receptors		
Growth hormone	Jak2	Stat5a, Stat5b, Stat3
Prolactin	Jak2	Stat5a, Stat5b
Erythropoietin	Jak2	Stat5a, Stat5b
Thrombopoietin	Jak2	Stat5a, Stat5b
Type II Cytokines	**JAKs**	**STATs**
Interferons		
IFN-α, IFN-β	Jak1, Tyk2	Stat1, Stat2
IFN-γ	Jak1, Jak2	Stat1
IL-10[#]	Jak1, Tyk2	Stat3

*IL-13 does not share γc but uses IL-4Rα.

[+]IL-12 and leptin do not share gp130, but their receptors are related to gp130.

[#]IL-10 is not an interferon, but its receptor is a type II cytokine receptor.

Characteristics of STATs

STATs are transcription factors that are triggered by multiple cytokines and growth factors and play important roles in signal transduction pathways [35]. The seven mammalian STAT proteins have been identified as STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. Additional forms of STATs 1 and 3 result from splicing alternation or posttranslational proteolytic cleavage [36]. Furthermore, STAT-4 has two forms denoted as STAT-4α and STAT-4β, and STAT-5 has two isoforms, STAT-5a and STAT-5b that are encoded by isolated tandem-linked genes [37]. Most STATs are 750 to 800 amino acids long, while STAT2 and STAT6 contain approximately 850 amino acids.

Structure of STATs

STATs display a modular structure and harbor seven well-defined domains consisting of an N-terminal, a coiled-coil, a DNA binding site, a linker region, an SH2, a tyrosine activation domain, and a C-terminal transactivation domain. The amino-terminal region is important for STAT functioning; if there are any deletions in this region STAT phosphorylation would be disabled. Moreover, in an inactive state, it also regulates STAT dimerization [38]. The coiled-coil domain, an alpha-helical configuration, associates with regulatory proteins, and has receptor-binding functions. The DNA binding domain is a β-barrel with an immunoglobulin fold, which lies beside the carboxy-terminal of the coiled-coil domain. The cooperation of the DNA binding domain at least, is probably important for effective transcriptional activity [17]. The linker domain is a spacer that maintains proper construction between the DNA binding domains

during dimerization. The SH2 domain is the most highly preserved domain among STATs and functions in STAT signaling such that it is important for recruiting STATs in order to activate receptor complexes and collaborating with Src and JAK kinases. Moreover, STAT homodimerization and heterodimerization also requires the SH2 domain, which is involved in nuclear localization and DNA binding activities. The transactivation domain varies among the STAT family members, and it regulates the transcriptional activation of target genes. C-terminally abbreviated STAT 3, 4, and 5 isoforms behave as dominant-negative proteins [13]. (Figure 3)

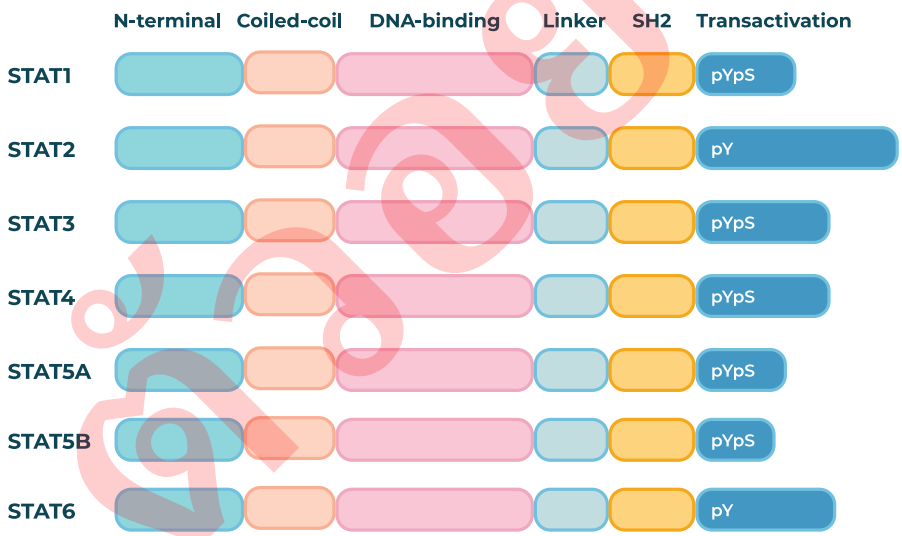

Figure 3. Structure of STAT Family Proteins.

STAT Activation in JAK-STAT Signaling

STATs are inactive within cells under unstimulated condition; the cytosolic proteins exhibit an unphosphorylated state. During cytokine stimulation, phosphorylated tyrosine residues on the receptor are induced and bind to STAT docking sites via their SH2 domains; thus, STAT family members become tyrosine phosphorylated. Such phosphorylated tyrosine residues seem to be attained by growth factor receptors as well as Src and JAK kinases, and are dependent on the cell type and nature of ligand/receptor interactions. Herein, the phosphorylation stimulates STAT protein reorientation and leads to homo/heterodimerization via interaction between the SH2 domain of one STAT molecule and the phosphotyrosine residue of the other. After phosphorylation, the dimerized STATs translocate to the nucleus (Figure 2)[39]. In the nucleus, normally, the STAT homo/heterodimers can directly bind to the DNA; however, it is not the case for activation by type I IFNs (IFNα and IFNβ). The STAT1-STAT2 heterodimer, which is activated by type I IFNs, requires p48, a DNA binding protein, to bind to the DNA. The STAT1-STAT2-p48 complex recognizes a comparatively nonpalindromic AGTTTNCNTTTCC [40] interferon-stimulated response element (ISRE) motif, while other STAT complexes recognize semipalindromic motifs, TTCNNNGAA or TTCNNNNGAA. Nevertheless, it is obviously known that such sequences can also be recognized by several other STATs.

Cytokine and Growth Factor Receptors Involved in STAT Activation

Studies on multiple hematopoietin receptors of the cytokine family reveal that the active form of the dimerized receptors is generated by ligand binding. The activation is considered to generate closely resembling cytoplasmic receptor tails and enables the transphosphorylation of the receptor-associated JAKs. Thereafter, activated JAKs phosphorylate specific tyrosine motifs, in turn mediating recruited STATs to their appropriate receptors, which require the STAT SH2 domain's ability to perceive a phosphotyrosine residue and 4-5 carboxy-proximal amino acids. The hematopoietin receptors are divided into multiple relevant families based on the nature of recruited STATs and the similarities in structure, such as the IFN/IL-10 receptor family, IFN-γ receptor, IFN-α receptor, IL-10 and IL-10 related receptors, gp130 receptor family, IL-2 receptor family, IL-3 receptor family, single chain receptor family, and non-cytokine receptors (receptor tyrosine kinases and G-protein-coupled receptors) [17].

Table 2. The recruitment of specific STATS is mediated by the implicated cytokine receptor tyrosine motifs. [17]

STAT	Receptor	STAT-binding tyrosine motif[a]
Stat1	IFN-γ	YDKPH
Stat2	IFN-α	YVFFP
Stat3	IL-6, LIF, IL-10	YXXQ
Stat1, Stat3	IL-6	YXPQ
Stat4	IL-12	YLPSNID
Stat5	IL-2	YLSLQ
		YCTFP
		YFFFH
	IL-7	YVTMS
	IL-9	YLPQE
	EPO	YLVLD
		YTILD
	Prolactin	YLDPT
		YVEIH
	GH	YVSTD
		YFCEA
		YITTE
		YTSIH
	GM-CSF	YLSLP
		YLCLP
		YVSSA
		YVELP
		YCFLP
Stat 6	IL-4	YKAFS
		YKPFQ

[a]The tyrosine is not conserved in the murine system

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