

JAK-STAT Signaling: From Interferons to Cytokines*

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50 years ago Isaacs and Lindenmann (1) first described interferons (IFNs)² as founding members of the cytokine family. Over the next 25 years, these and several other four-helix bundle cytokines were characterized. The subsequent 25 years witnessed an exponential growth in number of four-helix bundle cytokines and their corresponding receptors.

The early availability of recombinant IFNs afforded an opportunity to investigate how cytokines induce gene expression, culminating in the identification of the JAK-STAT signaling paradigm (see Fig. 1). Subsequent studies identified 7 STATs and 4 JAKs, providing important insight into how the ~50 members of the four-helix bundle cytokine family transduce their potent biological responses. This review will briefly summarize this signaling paradigm (reviewed in Refs. 2–5) and then focus on STAT-dependent transcription.

The JAKs

Members of the JAK family, Jak1, Jak2, Jak3, and Tyk2, were initially identified as orphan tyrosine kinases (2, 3, 5–7). All exhibited broad patterns of expression, except Jak3, in which expression was restricted to leukocytes. Genetic studies linking Tyk2 to the biological response to type I IFNs (IFN-I; also IFN- α/β) inspired studies associating these kinases with cytokine signaling (2, 5, 8). Specifically, these studies determined that ligand binding stimulated the rapid activation of receptor-associated JAKs, initiating JAK-STAT signaling (see Fig. 1).

JAKs range in size from 120 to 140 kDa and feature seven conserved JAK homology (JH) domains. The two carboxyl-terminal JH regions represent the kinase (JH1/Ki) and pseudo kinase (JH2/ Ψ Ki) domains (see Fig. 2). As with other tyrosine kinases, activation is driven by phosphorylation of critical tyrosines in the “inactivation loop.” The four amino-terminal JH domains (JH7–5 and half of JH4) constitute a FERM (four point one, ezrin, radixin, moesin) domain that mediates association with receptors. Specifically,

JAKs associate with the proline-rich, membrane-proximal box1/box2 domain on cytokine receptors. An SH2-related domain (SH2; JH3 and half of JH4), of unknown function, lies between the pseudokinase and FERM domains.

Tyk2—Tyk2 associates with receptors for IFN-I, IL-6, IL-10 and IL-12/23 cytokine families (2, 9). In Tyk2-deficient humans, the combined defects in the response to IFN-I, IL-6, IL-10, IL-12, and IL-23 are associated with enhanced allergic and impaired antimicrobial responses (9). By comparison, Tyk2 knock-out mice exhibit a less severe defect, indicating that murine Tyk2 is more of a response amplifier and not absolutely required (9). Like humans, however, Tyk2-deficient mice exhibit a proclivity toward type 2 immune response (9). In addition, Tyk2 contributes to the lethal effects of endotoxin through an ill defined and largely Stat1-independent pathway (10).

Jak1—Initially identified in a screen for novel kinases (7), biochemical and genetic studies have revealed a functional and physical association with the type I (IFN- α/β), type II (IFN- γ), IL-2, and IL-6 receptors (2, 3, 5). Evidence that the two IFN- α receptor chains, IFNAR1 and IFNAR2, associated with Tyk2 and Jak1, respectively, led to the notion that JAKs activate each other through transphosphorylation. Importantly, Jak1 knock-out mice die perinatally, reflecting a defect in LIF (an IL-6 family member) receptor signaling (2, 5). Characterization of Jak1 knock-out tissues, however, confirmed a critical role for this kinase in the response to IFN, IL-10, IL-2/IL-4 and IL-6 cytokine families.

Jak2—Initial biochemical studies implicated Jak2 in the response to receptors from the single-chain (*i.e.* Epo-R, GH-R, Prl-R) and IL-3 (IL-3R, IL-5R, and GM-CSFR) cytokine families, as well as the IFN- γ receptor (2, 3, 5). Consistent with a critical role in definitive erythropoiesis, Jak2 knock-out mice died of anemia at E12.5 (5). Analysis of Jak2^{-/-} tissues confirmed an important role in directing the responses to members of the single-chain, IL-3, and IFN- γ receptor families. Intriguingly, humans with Jak2 mutations exhibit myeloproliferative disorders (11). Finally, elegant biochemical studies with chimeric erythropoietin receptors provide compelling evidence that ligand binding drives two receptor associated Jak2s into close proximity, enabling them to activate each other by transphosphorylation (12).

Jak3—Leukocyte-specific Jak3 exclusively associates with the IL-2 receptor γ -chain (γ_c). This chain also serves as a component for the receptors of several lymphotropic cytokines, including IL-4, IL-7, IL-9, IL-15, and IL-21. Underscoring the critical roles that γ_c and Jak3 play in lymphoid activity, mutations in either molecule are associated with severe combined immunodeficiency disease (5). Intriguingly, Jak3 knock-out mice develop a similar, but less severe, immunodeficiency syndrome (2, 3, 5). Because of the unique role Jak3 plays in regulating lymphocytes, it has become an important pharmaceutical target.

The STATs

The seven members of the mammalian STAT family (STATs 1, 2, 3, 4, 5a, 5b, and 6) range in size from 750 to 900 amino acids

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² The abbreviations used are: IFN, interferon; JAK, Janus kinase; STAT, signal transducers and activators of transcription; JH, JAK homology; γ_c , γ -chain; SH2, Src homology 2; IL, interleukin; IFNAR, IFN- α receptor chain; ISGF, IFN-stimulated gene factor; ISRE, IFN-stimulated response element; TAD, transcriptional activation domain; GAS, γ -IFN-activated site; aa, amino acid(s); GM-CSF, granulocyte/macrophage-colony-stimulating factor; SOCS, suppressors of cytokine signaling; CBP, CREB-binding factor; pol II, polymerase II; HDAC, histone deacetylase; LIF, leukemia inhibitory factor.

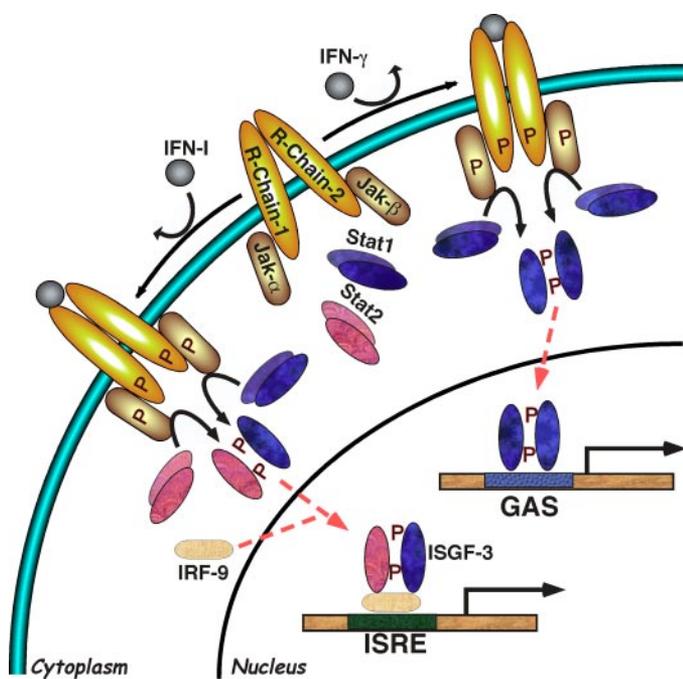


FIGURE 1. Model of IFN-I and IFN- γ dependent JAK-STAT signaling. See text for details.

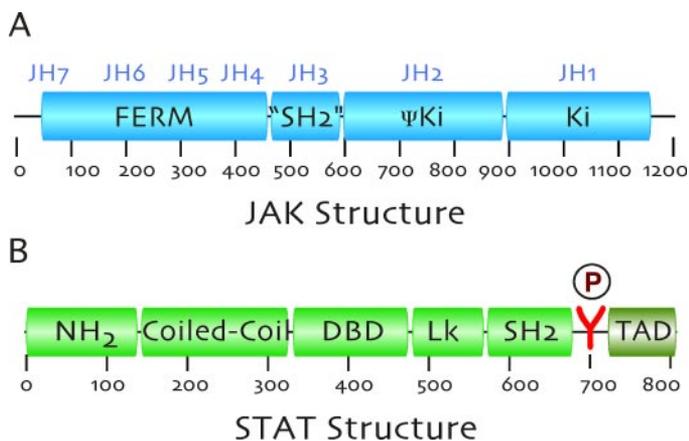


FIGURE 2. Structure of JAK (A) and STAT (B) families. See text for details.

and feature several conserved domains, notably including an SH2 domain (see Fig. 2). In resting cells, STATs reside largely in the cytoplasm as inactive homodimers (13). However, upon ligand binding, receptor-associated JAKs become activated (see above), leading to the phosphorylation of specific receptor tyrosine residues (see Fig. 1). These receptor phosphotyrosyl residues direct the SH2-dependent recruitment of specific STATs, which in turn become JAK substrates. Activated STATs are released from the receptor as they reorient into an antiparallel dimer, where the SH2 domain of one STAT binds the phosphotyrosine of the other STAT. Activated STAT dimers translocate to the nucleus and bind to specific enhancer elements. STAT homodimers bind to members of the GAS family of enhancers (a palindrome, TTTCCNGGAAA; Fig. 1). In contrast, IFN-Is promote the formation of Stat1-Stat2 heterodimers, which associate with IRF-9 (IFN regulatory factor) to form ISGF-3 and bind to the ISRE enhancer family (a direct repeat, AGTTT₃TTTCC; Fig. 1).

STAT Structure—Biochemical, genetic, and structural studies have identified seven conserved STAT domains, including the amino-terminal (NH₂), coiled-coil, DNA-binding (DBD), linker (Lk), SH2, tyrosine activation (Y), and transcriptional activation domains (TAD) (Fig. 2; Ref. 14, 15). The NH₂ domain (~125 residues) is a structurally independent moiety and appears to direct homotypic dimerization of inactive STATs (13). This domain has also been implicated in cooperative DNA binding to tandem GAS elements, as well as in nuclear import and export (16, 17). The adjacent coiled-coil domain (residues ~135–315) consists of a four- α -helix bundle that protrudes about 80 Å laterally from the core structure. This domain provides a large hydrophilic surface and binds regulators. The DNA-binding domain (residues ~320–480) consists of a β -barrel immunoglobulin fold that directs binding to the GAS family of enhancers with nanomolar avidity. The corresponding structure of the Stat1-Stat2 heterodimer has unfortunately not yet been solved. The adjacent linker domain (residues ~480–580) assures an appropriate conformation between the DNA-binding and dimerization domains. Reflecting its important role in receptor recruitment and dimerization, the SH2 domain (residues ~575–680) is the most highly conserved domain. The tyrosine activation domain (residue ~700) is positioned directly adjacent to the SH2 domain, precluding self (*i.e.* intramolecular)-association. The remaining carboxyl-terminal residues, which vary considerably among STAT family members, constitute the TAD. This divergence affords an opportunity to associate with distinct transcriptional regulators (see below).

Stat1—This founding STAT was initially identified as a component of ISGF-3, the IFN- α -stimulated, ISRE-binding factor (Fig. 1; Ref. 18). Subsequent studies determined that GAF, the IFN- γ -stimulated GAS-binding transcription factor, consists of Stat1 homodimers (19). Gene targeting studies confirmed the pivotal role that Stat1 plays in the biological response to both type I and type II IFNs (20, 21). Consistent with this, humans expressing Stat1 mutants exhibit increased susceptibility to viral and bacterial infections (22). Intriguingly, Stat1 target genes appear to promote inflammation and antagonize proliferation. This contrasts the pro-proliferative and anti-inflammatory activities associated with Stat3 (see below). Thus, the ability of several cytokines to activate both Stat1 and Stat3 (*e.g.* members of the IFN-I and IL-6 families) may reflect an effort to achieve a more balanced response.

Stat2—Stat2 was also initially identified as a component of ISGF-3. Biochemical and genetic studies have revealed that Stat2 plays a pivotal role in the biological response to type I IFNs, underscoring a critical role for Stat2 in regulating the IFN-I autocrine loop (4, 23). Stat2 remains the most enigmatic member of this family. In addition to being the largest STAT (850 aa in man, 925 aa in mouse), with a large TAD, there is little evidence that active Stat2 homodimers form or directly bind DNA. Rather, Stat2 heterodimerizes with Stat1. Finally, the mechanism by which Stat2 is recruited to IFNAR remains controversial.

Stat 3—Stat3 was initially identified as an IL-6-dependent transcription factor that promotes acute phase gene expression (24). It is now known to transduce signals for the entire IL-6

(IL-6, IL-11, IL-31, LIF, CNTF, CLC/CLF, NP, CT1, OSM) and IL-10 (IL-10, IL-19, IL-20, IL-22, IL-24, IL-26) families, as well as granulocyte (G)-CSF, leptin, IL-21, and IL-27 (2, 3). Additional studies in cultured cells have indicated that Stat3 is activated by several growth factors and oncogenes. Germ-line gene targeting has underscored a vital developmental role for Stat3 (*i.e.* Stat3^{-/-} embryos die at E6.5–7.5; (2, 3)). In contrast, tissue specific knock-outs have highlighted an important anti-inflammatory role for Stat3 (2, 3). Another important property of Stat3 is its association with cancer. “Constitutively activated” Stat3 has been identified in many cancers (*e.g.* head and neck, mammary, multiple myelomas, and other hematological malignancies). Consistent with this, Stat3 directs the expression of anti-apoptotic and pro-survival genes (2, 3). Moreover, expression of a hypermorphic Stat3 allele promotes transformation (25). Additionally, dominant-negative inhibitors, antisense oligonucleotides, decoy oligonucleotides, RNA interference, and genetic ablation have implicated Stat3 in tumorigenesis (2, 3). However, the potent anti-inflammatory activity of Stat3 is likely to contribute to these responses. Finally, several studies suggest that Stat3 promotes tumor growth through noncanonical mechanisms, *i.e.* in the absence of tyrosine phosphorylation and/or DNA binding (26).

Stat4—The gene for Stat4, identified through its homology to Stat1, was also found to lie adjacent to the Stat1 gene. Biochemical and genetic studies have underscored the important role Stat4 plays in directing the biological response to IL-12 and IL-23, which share receptor components (2, 27). Notably, IL-12 directs the Stat4-dependent polarization of naive CD4⁺ lymphocytes into potent Th1 effector cells (2, 3, 5). Stat4 plays an analogous role in IL-12-dependent NK cell activation. Additional studies have implicated both Stat4 tyrosine and serine phosphorylation in these vital immune activities (see below). More recently, Stat4 has been shown to be important in the IL-23-dependent expansion of Th17 cells and an associated autoimmunity (27).

Stat5—Two recently duplicated, tandem genes encode Stat5a and Stat5b. Along with their chromosomal neighbor, Stat3, these STATs exhibit the highest degree of homology to invertebrate STATs (28). Consistent with this ancient pedigree, they are functionally quite pleiotropic. Biochemical and genetic studies have underscored the important role that Stat5a and Stat5b play in directing a biological response to the IL-3 (IL-3, IL-5, and GM-CSF), single-chain (*e.g.* GH, Prl, Tpo, and Epo), and γ_C (*i.e.* the IL-2, IL-7, IL-9, IL-15, and possibly IL-21) receptor families. Although extensive sequence similarity between Stat5a and Stat5b (~96% aa identity) explains their functional redundancy, the responses to Prl and GH favor Stat5a and Stat5b, respectively. Finally, recent Stat5a-Stat5b gene targeting studies have revealed an important role for Stat5(s) in erythropoiesis and lymphopoiesis (29).

Stat6—Stat6 transduces signals for both IL-4 and IL-13, which share receptor components (2, 3, 5). Like Stat2, its chromosomal neighbor, Stat6 is one of the more divergent STATs. It also features a relatively large TAD (~150 aa), which interacts with numerous transcriptional regulators (see below and Ref. 30). Intriguingly, Stat6 homodimers recognize a GAS element that features an additional central nucleotide. Gene targeting

studies have confirmed a critical role for Stat6 in the IL-4/IL-13-dependent polarization of naive CD4 lymphocytes into Th2 effectors, as well as in mast cell activation. These studies have also highlighted an important role for Stat6 in promoting B-cell function, including proliferation, maturation, and MHC-II and IgE expression.

Regulation of STAT Activity

A characteristic feature of JAK-STAT signaling is its rapid onset and subsequent decay. As outlined above, activated STATs rapidly accumulate in the nucleus. Within a period of hours, however, the signal decays and the STATs are re-exported back to the cytoplasm for the next round of signaling. This decay entails down-regulation of both receptors and JAKs, as well as STAT transcriptional activity. Three well characterized mechanisms of STAT signal decay include: dephosphorylation, nuclear export, and SOCS (suppressors of cytokine signaling) feedback inhibition. However, a number of additional negative regulators have been reported, including PIAS, Nmi, and SLIM (31, 32).

Phosphatases—Phosphatases play an important role in regulating kinase-based signaling cascades. Genetic and biochemical approaches have implicated several phosphatases in the decay of cytokine receptors and JAKs, including SHP-1, SHP-2, and potentially CD45 (2, 33). Similar approaches have underscored a role for SHP-2, PTP1B, TC-PTP, and PTP-BL in STAT dephosphorylation (2, 33, 34). However, only two of these phosphatases, SHP-2 and TC-PTP, have been implicated in nuclear STAT dephosphorylation, which appears to be critical for STAT nuclear export (16, 17, 33).

Nuclear Import-Export—Despite a dramatic ligand-dependent accumulation of STATs in the nucleus, the process of nuclear import and export is complex (16, 17, 35). The predominantly cytosolic localization for inactive STATs has been shown to reflect a steady state, where continuous basal nuclear import is balanced by continuous basal nuclear export. This appears to be regulated by multiple nuclear export sequence (NES) and nuclear localization sequence (NLS) elements. During activation, the balance is shifted toward nuclear accumulation and during signal decay toward nuclear export.

The SOCS Family—The SOCS proteins were identified as STAT target genes that directly antagonize STAT activation, resulting in a classic “feedback loop” (reviewed in Ref. 36). Gene targeting studies have underscored the important role that SOCS-1, SOCS-2, and SOCS-3 play in antagonizing responses to IFN- γ -Stat1, IL-12-Stat4, IL-4-Stat6, GH-Stat5, and IL-6-Stat3.

STAT Modifications

STATs undergo several well characterized covalent modifications in addition to canonical tyrosine phosphorylation, including serine phosphorylation, acetylation, and *O*-glycosylation. Potential roles for *R*-methylation (Stat1) and SUMOylation (Stat1) remain more controversial (37, 38).

Serine Phosphorylation—All STATs except Stat2 are phosphorylated on at least one serine residue in their TAD (reviewed in Ref. 39, 40). Conserved phosphorylation sites included a PMS*P motif (specifically, Ser⁷²⁷ in Stats 1 and 3 and Ser⁷²¹ in

Stat4), a PS*P motif (Ser⁷²⁵ in Stat5a; Ser⁷³⁰ in Stat5b), and a SS*PD motif (Ser⁷⁵⁶ in Stat6) (41). Stat1 and Stat5 possess at least one additional serine phosphorylation site in their TAD, Ser⁷⁰⁸ and Ser⁷⁷⁹, respectively. STAT serine kinases have been identified through the use of inhibitors, dominant-negative alleles, and *in vitro* kinase assays. They include MAPK (p38MAPK: STATs 1, 3, 4; ERK: Stat3, 5; JNK: Stat3), PKC δ (Stat1, Stat3), mTOR (Stat3), NLK (Stat3 (42)), and CaMKII and IKK ϵ (Stat1 (39, 40, 43)). A role for these kinases has however only been confirmed by gene knock-out or knockdown in a limited number of cases. Subcellular localization may add an additional level of specificity, as serine phosphorylation of IFN- γ -activated Stat1 dimers appears to occur exclusively in the nucleus.

STAT serine phosphorylation regulates transcriptional activity (see below). Consistent with this, mice expressing a Stat1S727A mutant exhibit defective IFN- γ -mediated innate immunity (44). Stat3S727A homozygous (SA/SA) mice exhibit a ~50% reduction in target gene expression but without an overt phenotype (45). By contrast, expression of Stat3S727A in Stat3^{-/-} background yields perinatal lethality (75%), growth retardation, and biological defects not evident in Stat3^{+/-} controls (45). Likewise, IL-12-induced production of IFN- γ is impaired in Stat4S721A expressing T-cells (46).

Following TLR (Toll-like receptor), IL-1R, or TNFR (tumor necrosis factor- α receptor) stimulation, Stat1 becomes phosphorylated on Ser⁷²⁷ in the absence of tyrosine phosphorylation, raising the intriguing question of whether serine-only-phosphorylated STATs direct biological activity (39). Consistent with this, transcriptional activity has been reported for Stat1 and Stat3 mutants defective in tyrosine phosphorylation (26, 47). However, these mutants appear to regulate transcription by squelching other transcription factors like NF κ B. Additional studies suggest that some Stat1-dependent apoptotic responses require phosphorylation of Ser⁷²⁷ but not tyrosine (40).

Acetylation—Reversible lysine acetylation has been reported for Stat1, Stat3, and Stat6. Interestingly, Stat1 and Stat3 acetylation impinges on NF κ B signaling, yielding a pro-apoptotic effect in the case of Stat1 and an anti-apoptotic effect in the case of Stat3 (49, 50). Stat3 acetylation also appears to regulate transcriptional activity and homodimer stability (51, 52).

O-Glycosylation—O-Glycosylation of Stat5 Thr⁹² is associated with an increased affinity for the coactivator CBP (53). Intriguingly, this O-glycosylation site is conserved in Stat1, Stat3, and Stat6.

STAT Transcriptional Activation

The STAT TAD was initially identified by analysis of natural Stat1 splice variants Stat1 α and Stat1 β . Stat1 β , which lacks 39 carboxyl-terminal amino acids, forms transcriptionally inactive homodimers. Likewise, STAT carboxyl-terminal domains impart transcriptional activity when fused to a Gal4 DNA-binding domain (3). Many of these TADs contain conserved serine phosphorylation sites that direct the recruitment of coactivators, *e.g.* CBP or MCM (mini-chromosome maintenance) complex (40, 54). Another regulatory role for the STAT TADs appears to be protein stability, as several STATs, including Stats

4–6, can be targeted for ubiquitin-dependent destruction, whereas Stats 1–3 are considerably more stable (32, 41).

Alternatively spliced STAT proteins lacking a TAD may still direct transcription through an interaction with partners possessing a TAD. For instance, Stat3 β can stimulate gene expression through its ability to recruit c-Jun as a cooperating transcription factor (55, 56). Interaction between Stat3 and c-Jun appears to induce gene expression in liver but has been associated with transcriptional inhibition on the Fas promoter, highlighting an intriguing area for future study (57, 58).

STATs also recruit chromatin-modifying enzymes through their TADs. All STATs likely bind to p300 and CBP (3). Stat2 also binds two histone acetyltransferases (HATs), PCAF and GCN5 (59). Additional HAT enzymes have been implicated in STAT transcriptional activity, in particular NcoA-1, which interacts with the TADs of Stat3 and Stat5, and an LXXLL motif in Stat6 (60, 61).

Nucleosome remodeling also contributes to STAT-dependent transcription. Cells defective in the SWI/SNF-like BAF chromatin remodeling complex are impaired in the transcription of Stat4 target genes (62), IFN- γ -induced genes (63), and a subset of IFN-I-stimulated genes (64, 65). The gene-specific effect of BAF in the IFN-I response is surprising, as a BAF subunit interacts with Stat2 and is required for most IFN-I-inducible genes (23). Differential regulation of STAT target genes has been observed in other contexts as well. The PIAS1 negative regulator appears to target mainly promoters that possess relatively weak affinity STAT binding sites (66). Additionally, ISGF-3 binding site affinity may also be regulated by IKK ϵ -dependent serine phosphorylation (43).

Several individual components of mammalian mediator interact with the Stat2 TAD and are recruited to active promoters along with pol II. Some of these interactions directly enhance the frequency of transcriptional initiation, suggesting that consecrating Stat2-mediator-pol II interactions may be necessary and possibly rate-limiting for IFN-stimulated transcription (67). Another bridging molecule connecting STAT TAD with pol II is p100, a staphylococcal nuclease-like Tudor domain-containing protein (68). This suggests that p100 may serve to integrate Stat6 DNA binding and transcriptional initiation.

Finally, an interesting feature of Stat1-, Stat2-, and Stat5-mediated transcription is the requirement for HDAC as a coactivator. Although HDAC activity is typically associated with transcriptional repression, pharmacologic and gene-targeting studies have revealed that several STATs require HDAC as a transcriptional activator (69).

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