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STAT dynamics

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Abstract

The ability of transcription factors to gain entrance to the nucleus is critical to their role in gene expression. Signal transducers and activators of transcription (STATs) are latent DNA binding factors activated by specific tyrosine phosphorylation. There are seven mammalian STAT genes encoding proteins that display constitutive nuclear localization and/or conditional nuclear localization. This review will focus on STAT1 and STAT2 that are activated in response to interferon and exhibit conditional nuclear localization. The dynamic redistribution of STAT1 and STAT2 between the cytoplasm and the nucleus is coordinate with their gain of ability to bind DNA.

Keywords: Nuclear import; Tyrosine phosphorylation; Transcription factor; DNA binding

1. Introduction

Signal transducers and activators of transcription (STAT) possess the ability to both sense environmental cues and to transmit those cues to regulate specific gene expression. The founding members of this family, STAT1 and STAT2, were identified as latent DNA binding factors activated in response to type I interferons (IFNs)[1,2]. Following IFN binding to cell surface receptors, the receptor-associated Janus kinases phosphorylate STATs on a specific tyrosine residue [3–8]. Tyrosine phosphorylation induces a conformational change that generates STAT dimers via reciprocal phosphotyrosine and SH2 domain interaction [9–11]. The dimer conformation confers their ability to recognize specific DNA targets in the promoters of responsive genes, and the products of these genes contribute to the biological effects of IFNs on viral resistance, proliferation, and immune cell activation [12–15].

STAT-mediated gene expression can have dramatic effects on cellular function, and for this reason it is not surprising that STAT activity is regulated by various means including receptor activated Janus kinases, cytoplasmic and nuclear tyrosine phosphatases, protein inhibitors of activated STATs (PIAS), and suppressors of cytokine signaling (SOCS) [16–18]. To affect gene transcription the STATs must gain access to the nucleus, and consequently nuclear localization is yet another mechanism of STAT regulation [19,20]. Proteins as large as the STATs are restricted from passive diffusion into the nucleus, and so transport must be facilitated. Transport is an active energy-requiring process usually mediated by association with soluble transporters. Since nuclear trafficking has a significant impact on STAT function, understanding the mechanisms that regulate STAT localization should provide information valuable to enhance or prevent their action.

2. Properties of STAT molecules

Seven mammalian STAT genes have been identified, and although the encoded proteins share many properties, they respond uniquely to specific stimuli and confer distinct biological responses. The STATs have a similar structural arrangement of functional motifs (Fig. 1) [12]. These include an amino terminus that plays a role in dimerization, a coiled coil domain that can be involved in interactions with other proteins, a central DNA binding domain (DBD), a Src

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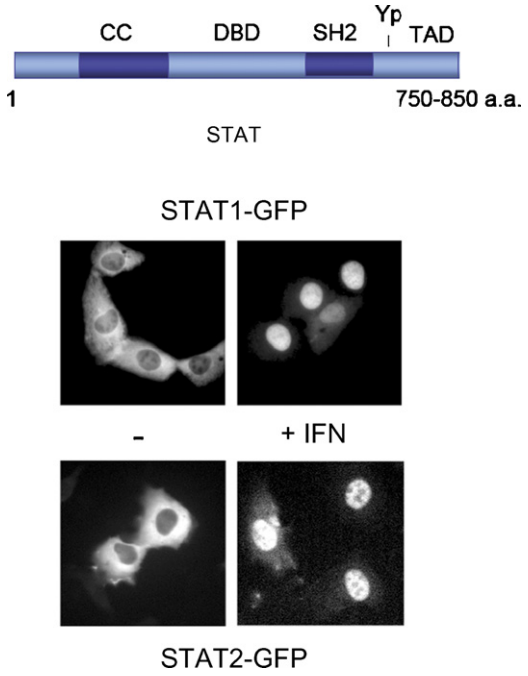

Fig. 1. STAT cellular redistribution. (Top) Schematic consensus of STAT domain arrangement with coiled coil domain (CC), DNA binding domain (DBD), Src homology domain 2 (SH2), tyrosine target of phosphorylation (Yp), and transcriptional activation domain (TAD). (Bottom) Fluorescence microscopy of cells expressing STAT1-GFP or STAT2-GFP. Cells were untreated (−) or treated with 1000 U/ml IFN-α for 1 h (+). Figure is modified from previous publications [24,45].

homology 2 (SH2) domain, a conserved tyrosine residue that is phosphorylated in response to stimuli, and a carboxyl transcriptional activation domain (TAD). Recent evidence indicates that the STAT molecules can exist as dimers in a latent state, however following tyrosine phosphorylation homodimers or heterodimers form via reciprocal SH2-phosphotyrosine interactions [9–11]. The conformational change that accompanies tyrosine phosphorylation provides the dimers with the ability to bind specific target DNA.

2.1. Interferon signaling with STAT1 and STAT2

STAT proteins can be tyrosine phosphorylated by receptor-associated Janus kinases, by growth factor receptor tyrosine kinases, or by non-receptor tyrosine kinases [19]. STAT1 and STAT2 are the founding members of the STAT family, identified as latent DNA binding factors activated in response to IFN stimulation. As signal transducers, STAT1 and STAT2 respond to extracellular cues in the cytoplasm, and then move to the nucleus to regulate gene expression. The dynamic redistribution of STAT1 and STAT2 following IFN treatment can be visualized by fluorescence microscopy with GFP tagged STAT proteins (Fig. 1). Unphosphorylated STAT1-GFP is primarily in the cytoplasm, although if overexpressed a portion of STAT1 can be found in the nucleus [21–23]. Following tyrosine phosphorylation in response to IFN, STAT1-GFP clearly accumulates in the nucleus. Similarly unphosphorylated STAT2-GFP resides primarily in the cytoplasm and accumulates in the nucleus following IFN stimulation [24].

The Janus kinases TYK2 and JAK1 are associated with type I IFN receptor subunits IFNARI and IFNARII, and are activated in response to binding type I IFN (primarily IFN-α/β)(Fig. 2). These kinases phosphorylate tyrosine residues on the receptors and on STAT1 and STAT2. STAT2 is unique among the STAT proteins because it is constitutively associated with a non-STAT protein, IFN regulatory factor 9 (IRF-9)[25–27]. IRF-9 is a member of a family of DNA binding factors that play diverse roles in the innate immune response [28]. The IRFs share a similar amino terminal DNA binding domain, but they have distinct carboxyl domains. The carboxyl domain of IRF-9 associates with the coiled coil domain of STAT2 [25]. Following IFN-α stimulation, STAT1 and STAT2 heterodimerize via phosphotyrosine and SH2 domains. Because IRF-9 is associated with STAT2, a tyrosine phosphorylated STAT1-STAT2-IRF-9 multimeric complex forms and has been designated the IFN stimulated gene factor 3 (ISGF3)[1,29]. ISGF3 binds to a specific DNA sequence in type I IFN induced genes called the IFN stimulated response element (ISRE) that contains a direct GAAA repeat spaced by two nucleotides [29–32].

The type II IFN receptor subunits IFNGR1 and IFNGR2 are associated with JAK1 and JAK2, and are activated in response to type II IFN (IFN-γ)(Fig. 2). In response to IFN-γ, STAT1 is tyrosine phosphorylated and forms dimers via phosphotyrosine and SH2 domains [7,12,32,33]. IFN-γ binding leads to tyrosine phosphorylation of STAT1, but not

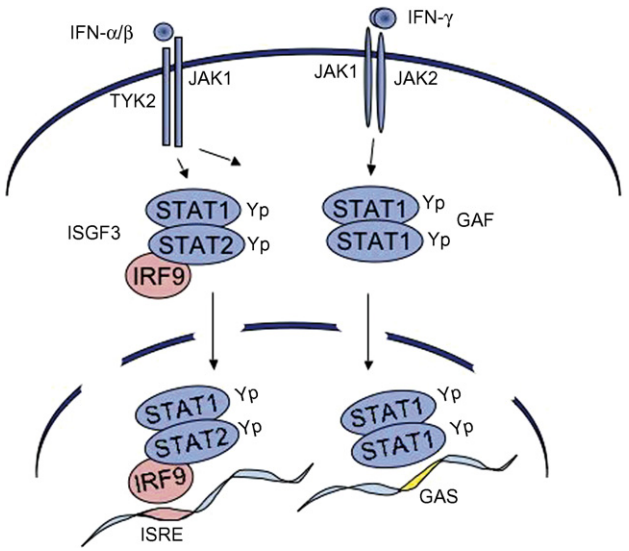

Fig. 2. Schematic of JAK/STAT signal pathways stimulated by IFNs. (Left) Type I IFNs (primarily α/β) bind to the IFNAR activating JAK1 and TYK2. The JAKs phosphorylate the receptors and recruited STAT1 and STAT2. The STATs heterodimerize and with IRF-9 form ISGF3 to bind to the ISRE in target genes. STAT1 homodimers are also formed and can bind to the GAS. (Right) Type II IFN (γ) binds to a distinct IFNGR activating JAK1 and JAK2. These JAKs phosphorylate sites on the receptor and the recruited STAT1. STAT1 factors dimerize and gain the ability to bind to the GAS in target genes.