

**Stony Brook University
The Graduate School**

Doctoral Defense Announcement

Abstract

Characterization of Nucleocytoplasmic Transport of the Transcription Factor STAT5a

By

Janaki K Iyer

Signal Transducers and Activators of Transcription (STATs) are a family of latent DNA binding proteins that play critical roles in cytokine signaling. As the name suggests, these proteins have the dual role of transducing signals from the cell membrane into the nucleus where they can perform their role as transcription factors. STATs are normally present in the cell in an inactive state and are activated by phosphorylation on a conserved tyrosine. Tyrosine phosphorylation confers a conformational change and the ability to bind specific target DNA. Thus STATs must have a cytoplasmic presence to transduce signals from the cell membrane and have the ability to enter the nucleus to fulfill their role as transcription factors.

STAT5a plays an important role in a number of physiological processes like hematopoiesis and mammary gland development. Accurate cellular localization of STAT5a is necessary to execute its function as a signaling molecule and transcription factor. STAT5a responds to cytokines such as growth hormone, prolactin, and interleukin-2, and undergoes tyrosine phosphorylation to form dimers with the ability to bind DNA. This study explores the nuclear trafficking of STAT5a both prior to and following tyrosine phosphorylation. STAT5a shows a constitutive nuclear presence in the absence of tyrosine phosphorylation. With the use of live cell imaging we demonstrate the continuous shuttling of STAT5a in and out of the nucleus. Evaluation of a series of mutations and deletions identifies a region within the coiled coil domain of STAT5a that is critical for nuclear import of both unphosphorylated and tyrosine phosphorylated forms. The mechanism that regulates transport of STAT5a through nuclear pore complexes into the nucleus is therefore independent of tyrosine phosphorylation. However, following tyrosine phosphorylation STAT5a accumulates in the nucleus due to its retention by DNA binding.

STAT5a is also continually exported from the nucleus. A region in the DNA binding domain shows the presence of an NES that can be recognized by Crm1. The positioning of the NES might suggest that it is accessible when STAT5a is not bound to DNA. These findings should lay a foundation for further studies that involve targeting the activity of STAT5a.

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