Deficits in Cell Mediated Immune Recovery among HIV$^+$ Individuals on Effective Antiretroviral Therapy

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Objective: To determine the in vivo role of SOCS proteins in the turnover of CD127 (IL-7Rα) in human CD8 T-cells. Understanding the mechanisms by which these proteins act will allow for more informed use of IL-7 as a therapeutic agent and may provide insight into diseases, like HIV, which are hallmarked by down-regulated CD127 levels in patients.

Hypotheses: IL-7 binding to CD127 induces receptor internalization and up- regulates SOCS expression. SOCS proteins bind to CD127 and the complex is then directed to the proteasome for degradation. Recycling of CD127 in HIV positive individuals involves a different set of SOCS proteins than in healthy (HIV negative) individuals.

Results (Abstract): The Suppressor of Cytokine Signaling Proteins (SOCS) are a family of 8 proteins (CIS and SOCS1-7) that share the common Src homology 2 (SH2) and C-terminus SOCS box domains. It is known that select SOCS proteins are inducible by cytokines and that these same SOCS proteins participate in negative feedback loops to limit the effects of cytokine signaling. SOCS proteins interact with ubiquitin ligases through their SOCS box, and when complexed with cytokine receptors target the receptor for degradation by the proteasome. Our lab has shown that stimulation of CD8$^+$ T cells with Interleukin-7 (IL-7) results in degradation of CD127, the α chain of the IL-7 receptor, and that this phenomenon is dependent on the 26S proteasome, potentially implicating the SOCS proteins in the process. We have shown that CIS, SOCS1 and SOCS2 mRNA transcripts are induced by IL-7, whereas SOCS 3-7 transcripts are not. I confirmed by Western blot analysis that SOCS1, 2, and CIS proteins are induced by IL-7, with CIS and SOCS 1 protein levels increasing 4-fold 3 hrs post IL-7 stimulation. While CIS, SOCS 1 and 2 physically interact with CD127 as demonstrated by co-immunopercipitation, CIS and SOCS2 binding increases significantly upon the addition of IL-7 to CD8$^+$ T cells. I demonstrated that SOCS 3-7 do not physically interact with CD127, and therefore are not likely to be involved in regulating the expression of the IL-7 receptor. IL-7 signaling is known to be deregulated in HIV infection, and preliminary western data suggests that the involvement of the SOCS family of proteins in regulating IL-7 receptor expression may differ between healthy individuals and those who are HIV positive.

Conclusion: Understanding how expression of the IL-7 receptor is regulated will allow for more informed therapeutic use of this cytokine and to a deeper understanding of diseases states, like HIV.

Key words: CD 127, CD8$^+$ T cells, HIV, IL-7, SOCS proteins