INTERVIEW about

HSP60 and SOCS3

with

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What do we know about HSP60 as an innate immune signal?

A. Zanin-Zhorov & Irun R. Cohen: The relationship between the immune system and HSP60 is complex (1,2). The HSP60 molecule, as it performs its chaperone function inside stressed cells, also functions as an innate molecular signal for the immune system: HSP60 is expressed by cells exposed to stress or immune activation, is present in the blood during inflammation, and has been found to be a target of autoantibodies and autoimmune T cells in healthy individuals and, to a greater extent, in those suffering from autoimmune diseases. Thus, HSP60 has been considered to be a pro-inflammatory danger signal. Nevertheless, HSP60 treatment has been demonstrated to arrest inflammatory damage *in vivo*. The administration of HSP60 was found to arrest joint inflammation in models of autoimmune arthritis. Moreover, despite being targeted by diabetogenic T cells in the NOD mouse, vaccination with HSP60 or certain of its peptides can induce the arrest of beta-cell destruction in both the spontaneous diabetes of NOD mice and the autoimmune diabetes induced by streptozotocine or cyclophosphamide. These beneficial effects of HSP60 were marked by a shift in the autoimmune response from a damaging Th1 phenotype to a healing Th2 phenotype (3,4).

What is the role of SOCS3 in the immune system?

A. Zanin-Zhorov & Irun R. Cohen: The suppressors of cytokine signaling (SOCS) family of proteins have been identified as cytokine-induced feedback negative-regulators of JAK/STAT activation, through their binding to JAK kinases or cytokine receptors (5,6). SOCS3 is involved in T-cell differentiation: SOCS3 is selectively expressed in murine Th2 cells. Furthermore, SOCS3 expression in peripheral T cells from patients with Th2 type diseases, such atopic asthma and dermatitis closely correlates with the severity of the disease. In contrast, however, under pathological conditions, such as IBD and colitis, SOCS3 can suppress inflammatory reactions, in which IL-6 and related cytokines have an important function. SOCS3 also regulates T cell function by negatively regulating IL-2 signaling and inhibiting TCR and CD28 signaling pathways. The regulatory role of SOCS molecules is not limited to the cytokine receptor superfamily: by binding to chemokine receptor CXCR4, SOCS3 blocks JAK/STAT complex activation and association to CXCR4, inhibiting SDF-1α-mediated responses both *in vivo* and *in vitro* (7).

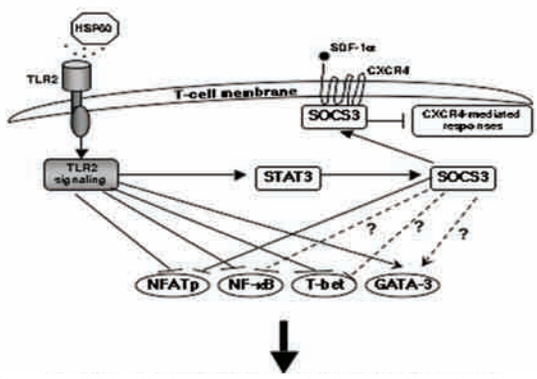
The interplay between HSP60, SOCS3 and the immune system?

A. Zanin-Zhorov & Irun R. Cohen: Recent work from our group indicates that the anti-inflammatory effects of HSP60 could be explained by its direct innate effect on T-cell functions: HSP60 inhibits T-cell chemotaxis (8,9), and shifts the cytokine secretion profile towards Th2 (10). We have found that activation of SOCS3 is a key factor in the modulation by HSP60 of T-cell responses to SDF-1α. SOCS3 activation, which follows HSP60-induced TLR2-signaling, appears to down-regulate CXCR4-mediated T-cell functioning. Our findings show that HSP60, at defined concentrations and time intervals, is capable via SOCS3 of exerting an anti-inflammatory effect on T cells. In fact, a brief exposure of murine T cells to a concentration of HSP60 that inhibited human and murine T-cell chemotaxis towards SDF-1α and up-regulates SOCS3 expression, also abrogated the ability of antigen-reactive T cells to adoptively transfer a DTH response in mice.

The innate effects of HSP60 on the T-cell cytokine profile were explained by the regulation of transcription factors: HSP60 down-regulates T-bet, NF-κB, and NFATp, and up-regulates GATA-3. Moreover, we found that treatment of mice with HSP60 induced significant suppression of the cytological and pathological signs of ConA-induced hepatitis in mice. Interestingly, HSP60-induced suppression was accompanied by increased levels of SOCS3 and GATA-3 and decreased levels of expression of T-bet in the mouse T cells. Thus, our results implicate a SOCS3-mediated molecular signaling mechanism for the innate anti-inflammatory effects of HSP60 on T cells.

The possible role of SOCS3 in regulation of transcription factors in T cells.

A. Zanin-Zhorov & Irun R. Cohen: The findings that HSP60 can regulate the activation of transcription factors in T cells and up-regulate the expression of SOCS3, raises the question whether SOCS3 is involved in this regulation, similar to its involvement in the inhibitory effects of HSP60 on T-cell chemotaxis (Figure 1). Evidence for the ability of SOCS3 to regulate the activation of transcription factors in T cells was provided by Banerjee et al. (11). This work demonstrated that SOCS3 inhibits calcineurin-dependent dephosphorylation and activation of the IL-2 promoter-binding transcription factor, NFATp. Based on our findings, we think that it is quite possible that SOCS3 is involved in the regulation of other transcription factors, such as NF-kB, T-bet, and GATA-3, which are crucial for T-cell function.



The role of HSP60 and SOCS3 in T-cell mediated inflammation. HSP60 inhibits T-cell chemotaxis via up-regulation of SOCS3 expression through TLR2 signaling and STAT3 activation. In addition, HSP60 shifts the cytokine secretion profile towards Th2, by inhibition of NFATp, NF-κB, and T-bet and up-regulation of GATA-3. The role of SOCS3 in the regulation of transcription factors by HSP60 still remains to be clarified. As a result of the above, HSP60 down-regulates T-cell chemotaxis and Th1-mediated inflammation *in vivo*.

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