

INTERVIEW about

SOCS1 and antigen presentation

with

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What is the role of SOCS1 regarding antigen presentation by dendritic cells?

Si-Yi Chen: Suppressor of cytokine signaling (SOCS) 1 is an inducible negative feedback inhibitor of the Janus kinase (Jak)/signal transducer and activator of transcription (Stat) signal pathway utilized by various cytokines (1,2). In our recent studies, we found that SOCS1 is an essential antigen presentation attenuator and

plays a critical role in regulating the magnitude of antigen presentation and preventing dendritic cells (DC) overactivation and autoimmunity (3,4). Our studies further reveal a novel regulatory mechanism for the control of self-tolerance at the host level by DCs through the restriction of positive cytokine feedback signaling by SOCS1.

Is it possible to manipulate SOCS1 in dendritic cells?

Si-Yi Chen: SOCS1 expression in DCs can be manipulated by various means. For example, we have used small interfering RNAs (siRNA) to specifically downregulate ~90% of SOCS1 mRNA in DCs (3,4). siRNA molecules can be transfected

into DCs by using liposome, electroporation and viral vectors. Other techniques, such as anti-sense RNA, transdominant negative mutants, and intrabodies, could also be used to inhibit SOCS1 expression or functions in DCs.

Is it possible to generate dendritic cell vaccines capable of breaking self tolerance?

Si-Yi Chen: The major effort on DC-based tumor vaccines has been focused on enhancing DC maturation/costimulation and antigen presentation in order to break tolerance against self tumor-associated antigens. A puzzling paradox of DC vaccines, viewed as one of the most promising strategies for tumor vaccination, is that DC immunization can effectively break self tolerance at the cellular level, i.e. activate autoreactive cytotoxic T cells, but rarely cause autoimmune pathologies against normal tissues and tumors, suggesting that self tolerance at the host level is still maintained in a host's natural immunosuppressive environment, impeding the efficacy and usefulness of DC-based tumor vaccination. Our recent studies demonstrate the requirement of persistent antigen presentation by DCs for inducing pathological autoimmune responses against normal tissues and tumor, which can be achieved by silencing SOCS1 to unleash unbridled

positive feedback cytokine signaling loops. In contrast, the use of higher affinity self peptides, enhancement of DC maturation, and persistent stimulation with cytokines or TLR agonists fail to break self tolerance. We further demonstrate that the inhibition of SOCS1 permits DC vaccine to break self tolerance at the host level and induce effective anti-tumor cytotoxic T cell responses (3,4). In addition, immunization with SOCS1-silenced DCs loaded with antigens, which are preferentially expressed on tumor cells, but not or at low levels on normal cells (5), would induce antigen-specific immunity against tumors, in contrast to the targeting of CTLA-4 on effector CTLs, an approach that non-selectively activates autoreactive T-cells against vital normal tissues. Thus, the inhibition of antigen presentation attenuators represents an attractive and effective strategy to break self tolerance. A combined vaccination strategy of inhibiting antigen presentation

attenuators and promoting antigen presentation (6) may lead to

the development of more effective tumor vaccines.

Does inhibition of SOCS1 also enhance DNA-immunisation?

Si-Yi Chen: DNA immunization represents a simple, potentially effective vaccination approach. However, currently described DNA vaccines are not very potent, especially in humans. Recently we demonstrate that co-immunization with SOCS1 siRNA DNA significantly enhances the potency of HIV DNA vaccination, likely

due to the enhanced immunostimulatory capacity of the co-transfected antigen-presenting cells that play a critical role in inducing immune responses in the immunized mice (7). Thus, this SOCS1 inhibition strategy is applicable to *ex vivo* DC-vaccines and *in vivo* vaccination against tumors and pathogens.

What is the underlying mechanism responsible for the breaking of self-tolerance by SOCS1-silenced DCs?

Si-Yi Chen: Breaking self-tolerance at the cellular level, i.e. induction of autoreactive T cell responses, is fairly easily accomplished by various immunization approaches in mice and humans. However, most of currently described tumor vaccines fail to break self-tolerance at the host level, i.e. induction of pathological autoimmunity against tumor and normal tissues. The results of our recent study (4) indicate that SOCS1 blocks positive cytokine feedback loops, restricting overactivation of antigen presenting DCs and autoimmunity by tumor vaccines.

We further demonstrate that that unbridled IL-12 and the downstream cytokine signaling are essential in the breaking of tolerance by SOCS1-silenced DCs. Importantly, overexpression of IL-12 by wild-type DCs cannot lead to the breaking of self-tolerance, due to the restriction of IL-12 feedback signaling. Thus, the establishment of autocrine and paracrine cytokine feedback loops is primarily responsible for the overactivation of antigen-presenting SOCS1-silenced DCs to persistently stimulate autoreactive CTLs and break self-tolerance in a natural, suppressive environment.

Is inhibition of one of many inhibitory molecules in DCs sufficient to break self-tolerance?

Si-Yi Chen: Clearly, there are multiple regulatory mechanisms used to maintain peripheral self-tolerance. Three families of proteins, including SOCS, protein-tyrosine phosphatases (PTP), and the protein inhibitors of activated STATs (PIAS), have been identified to attenuate distinct aspects of cytokine signal transduction in antigen presenting cells (APCs) and other immune cells (8). SOCS proteins are induced in response to cytokine signaling and can inhibit JAK activity by direct interference with signaling and by targeting the receptor complex for ubiquitin-mediated proteasomal degradation. SHP proteins are constitutively expressed and can attenuate cytokine signal transduction by dephosphorylating signaling intermediates such as JAK and its receptor. Constitutively expressed PIAS proteins inhibit the transcriptional activity of STATs by various mechanisms such as blocking the DNA binding activity of STATs. In addition, regulatory T cells can express

IL-10 and TGF- to suppress effector T cell function. However, the function of these negative regulators is largely non-redundant. The deficiency of one of these negative regulators leads to the failure of the immune regulation, as mice with genetic KO of one of these regulators develop autoimmune diseases and macrophages or DCs from genetic KO mice are hyperactivated. Such control at multiple, non-redundant manners indicate that the negative regulators are individually necessary but insufficient to attenuate pro-inflammatory signaling pathways. Thus, breaking self-tolerance against self tumor-associated antigens can be accomplished by disabling one of these essential negative regulators such as SOCS1 in DCs.

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