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New sociology for better understanding severe eosinophilic asthma: introducing the SOCS family

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SOCS proteins' involvement in severe eosinophilic asthma <http://ow.ly/IG943023yxZ>

Severe asthma is a heterogeneous condition characterised by a persistent uncontrolled situation with an inadequate response to current therapy [1]. This definition points the serious unmet needs of the patients and an urgent research effort to understand better the mechanisms sustaining this clinical condition for our community. However, severe asthma is still not identified as a distinct entity and is very heterogeneous. At present, several endotypes have been described based on the presence of upregulated cytokines leading to the recruitment, activation and increased survival of inflammatory cells such as eosinophils. One major endotype is related to T2 lymphocyte (T-helper cell type 2 and innate lymphoid cell type 2) activation, which is observed in most severe asthma patients. Fortunately, several new drugs are or have been developed to interfere with this endotype, but there are still important gaps of knowledge to be filled and clearly, other targets should be identified to develop innovative treatments [2].

The SOCS (suppressors of cytokine signalling) family is composed of eight proteins, *i.e.* SOCS1–7 and SH2 cytokine-inducible protein (CIS) [3, 4], each of which has a central SH2 domain, an amino-terminal domain of varying length and sequence, and a carboxy-terminal 40-amino-acid-long module known as the SOCS box [5]. SOCS proteins act as a substrate-recruiting component of E3-ubiquitin ligase complexes and target interacting proteins for degradation. The regulation exerted by SOCS proteins is critical to the normal functioning and cessation of the primary cytokine signal, and is achieved at many levels in the intracellular biochemical cascade [6]. Aberrant regulation of SOCS proteins has been linked to a variety of inflammatory diseases [7]. The most studied family members, CIS, SOCS1, SOCS2 and SOCS3, are important regulators of the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway, and SOCS1–3 have been studied in detail, including the development of knockout mice [8–10]. SOCS1 is a member of this cytokine signalling pathway inhibitor family and is induced by a variety of cytokines, including interferons (IFNs). It inhibits signalling by suppression of JAK kinase activity [11] and by a promotion of the degradation of the activated cytokine–receptor complex [12]. T2-associated cytokines, such as interleukin (IL)4 or IL13, are major factors of the ongoing inflammation, including airway eosinophilia, found in severe asthma. Interestingly, they mediate their actions *via* the JAK-STAT pathway and are regulated by several proteins including the SOCS family.

Little information is available concerning the potential role of SOCS proteins in human asthma. A polymorphism in the SOCS1 promoter has been identified by HARADA *et al.* [13] in a Japanese population of adult asthma patients. This polymorphism correlates with asthma severity and with increased SOCS1 expression in nasal epithelial cells *in vitro*. An association between increased SOCS1 expression, allergic

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sensitisation and T2 polarisation has been subsequently reported [14]. Animal studies showed that SOCS1-deficient mice die within 3 weeks of age. This lethality is associated with the infiltration of many organs by macrophages and granulocytes, and with a profound depletion of lymphocytes [15, 16]. A cross onto either an IFN- γ - or a Stat6-null background is necessary to prolong survival, indicating that both IFN- γ -driven T1 and IL4-driven T2 responses may contribute to the rapid death [8, 17]. LEE *et al.* [18] have investigated the role of SOCS1 in regulating the asthma response using SOCS1^{-/-} IFN- γ ^{-/-} mice in an acute ovalbumin-driven model of asthma. They reported elevated IgE levels, pathological evidence of eosinophilic lung infiltration and elevated T2 cytokine levels (IL4, IL5 and IL13). These results clearly indicate that SOCS1 is an important regulator of T2-type responses and in the presence of IFN- γ , SOCS1 would be involved in regulating both T1 and T2 responses [18]. In mice, SOCS2 negatively regulates T2 immunity [9], and SOCS3 mRNA levels of T-cells are increased in asthmatic patients and correlate with IgE levels [10]. Notwithstanding that, a functional role for SOCS3 in human asthma has not been described.

Interestingly, in this issue of the *European Respiratory Journal*, DORAN *et al.* [19] investigated SOCS1–3 expression within the airways of subjects with asthma, and explored the relationship between SOCS expression and persistent eosinophilic inflammation within the airways. They reported decreased epithelial SOCS1 expression in asthmatics with persistent eosinophilia and increased T2 inflammation. These results corroborate previous findings in animal models. Moreover, they demonstrated that SOCS1 mRNA was significantly decreased in the airways of severe asthma patients when compared to mild/moderate asthma patients but that no difference was found when compared to healthy subjects. However, a recent study investigating SOCS1 and SOCS3 proteins in endobronchial biopsies showed that SOCS1, but not SOCS3, protein staining intensity was significantly increased in the bronchial epithelium of patients with asthma, as compared to healthy volunteers [20]. These observed differences could be partially explained by the fact that the data from DORAN *et al.* [19] were obtained from whole endobronchial biopsy mRNA and, therefore, integrated several cell types, not exclusively epithelial cells. The mechanistic relationship between IL13 and SOCS1 signalling shown *in vitro* in an epithelial cell line would have been better justified after proving SOCS1 expression decreased specifically in epithelial cells from healthy and asthma patients. The discrepancies between studies should be acknowledged. The severity of the population studied is different (mild/moderate *versus* severe asthma), with a potential specific regulation of SOCS family proteins in severe asthma. Additionally, GIELEN *et al.* [20] found that SOCS1, but not SOCS3, mRNA expression levels are increased in primary human bronchial epithelial cells from children with severe asthma. This last finding points to the age of patients as a confounding factor, which may be crucial to understanding the biology of the SOCS proteins. Genomic single-nucleotide polymorphisms in the human *SOCS1* gene were found to be associated with serum IgE levels [21]. Hence, an allergic status may be another important factor driving the expression of SOCS proteins irrespective of the age of the subjects or the severity of their asthma.

In their study, DORAN *et al.* [19] confirmed that SOCS1 is a potent physiological negative regulator of T2 cytokines such as IL13. Moreover, SOCS1 expression was negatively related to hypereosinophilia and T2 gene signature. As shown in other studies, increased SOCS1 levels in epithelial cells from asthmatic patients impair type I and type III IFN induction suppressing antiviral pathways. This represents a novel mechanism explaining IFN deficiency in asthmatic patients [20]. Therefore, modulation of SOCS1 function is worthy of investigation as a new therapeutic approach.

In conclusion, the study presented by DORAN *et al.* [19] highlights a novel role for SOCS proteins in severe eosinophilic asthma but their action is highly context dependent. Hence, it would be necessary to better define the physiological function of SOCS proteins by identifying the inducing stimuli, the relevant cell type, the SOCS substrate(s) and the biological context in which SOCS regulation is critical. SOCS proteins are potential new candidates for the treatment of asthma but their precise role in this disease should be clarified according to the different phenotypes and endotypes of asthma.

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