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Review article

SOCS-mediated immunomodulation of natural killer cells

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ABSTRACT

Natural killer (NK) cells are innate immune cells with an intrinsic ability to detect and kill infected and cancerous cells. The success of therapies targeting immune checkpoints on CD8 cells has intensified interest in harnessing the cytolytic effector functions of NK cells for new cancer treatments. NK cell development, survival and effector activity is dependent on exposure to the cytokine interleukin (IL)-15. The suppressor of cytokine (SOCS) proteins (CIS; SOCS1-7) are important negative regulators of cytokine signaling, and both CIS and SOCS2 are reported to have roles in regulating NK cell responses. Their immunomodulatory effects on NK cells suggest that these SOCS proteins are promising targets that can potentially form the basis of novel cancer therapies. Here we discuss the role of NK cells in tumor immunity as well as review the role of the SOCS proteins in regulating IL-15 signaling and NK cell function.

1. Introduction

Cancer is a major cause of disease burden worldwide, with an estimated 8.2 million cancer-related deaths in 2012 [1] and 1,735,000 new cases expected in 2018 in the United States alone [2]. While the human immune system can detect and eliminate transformed cells, cancers often acquire mutations that result in suppression of the immune system (immune tolerance), aiding their survival. Similarly, the development of drug resistance and severe off-target effects limit our use of conventional treatments such as chemotherapy and radiotherapy. The discovery of 'immune checkpoints' has enabled the development of highly successful therapeutic approaches, especially for the treatment of haematological malignancies [3]. These include antibody-based therapies such as Keytruda and Ipilimumab, which inhibit the immune checkpoints programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), on the surface of CD8 T cells, to enhance tumor immunity. However, despite substantial advances and markedly improved patient outcomes [4], some cancer-types types are refractory to treatment and there is a need for more targeted therapeutic options.

Natural killer (NK) cells are an important component of the innate immune response and have gained considerable attention as therapeutic tools due to their intrinsic ability to kill cancerous cells [5]. The success of the immune checkpoint inhibitors has stimulated efforts to harness the anti-tumor effector functions of NK cells. Whilst CTLA-4 is expressed on the surface of activated murine NK cells, it does not appear to be expressed on human NK cells [6]. In contrast, PD-1 is found on a subset of human NK cells in ~25% of the population and found more frequently in patients with ovarian cancer [7], with the ability of the PD-1 inhibitor Pembrozilumab to reverse NK cell exhaustion currently being assessed in a phase II clinical trial (NCT03241927). Several other NK cell-based immunotherapies are also in clinical trials and these will be discussed briefly throughout this review. Molecules involved in the intracellular signaling pathways downstream of NK cell surface receptors also represent attractive points for therapeutic intervention. In particular, two members of the suppressor of cytokine signaling (SOCS) family, SOCS2 and cytokine-inducible Src homology-2 (SH2)-containing protein (CIS), are reported to regulate NK cell differentiation and activity. This review will analyse the role of SOCS-mediated NK cell immunomodulation and discuss how these SOCS might be exploited for the development of novel cancer immunotherapies.

2. Natural killer cells

NK cells have important roles in immune defence against both

Abbreviations: CIS, cytokine-inducible SH2-containing protein; CTLA4, cytotoxic T-lymphocyte-associated antigen 4; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; JAK, Janus kinase; KIR, killer immunoglobulin-like receptor; KIR, kinase inhibitory region; MHC, major histocompatibility complex; NCR (NKp46), natural cytotoxicity triggering receptor 1; NK, Natural killer; NKG2A, natural killer cell receptor group 2-member A; PD-1, programmed cell death protein 1; PEST, sequence rich in proline (P), glutamic acid (G), serine (S) and threonine (T); RBX2, RING (Really Interesting New Gene) box protein 2; SH2, Src homology-2; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription; SUMO, small-ubiquitin like modifier; TNF, tumor necrosis factor

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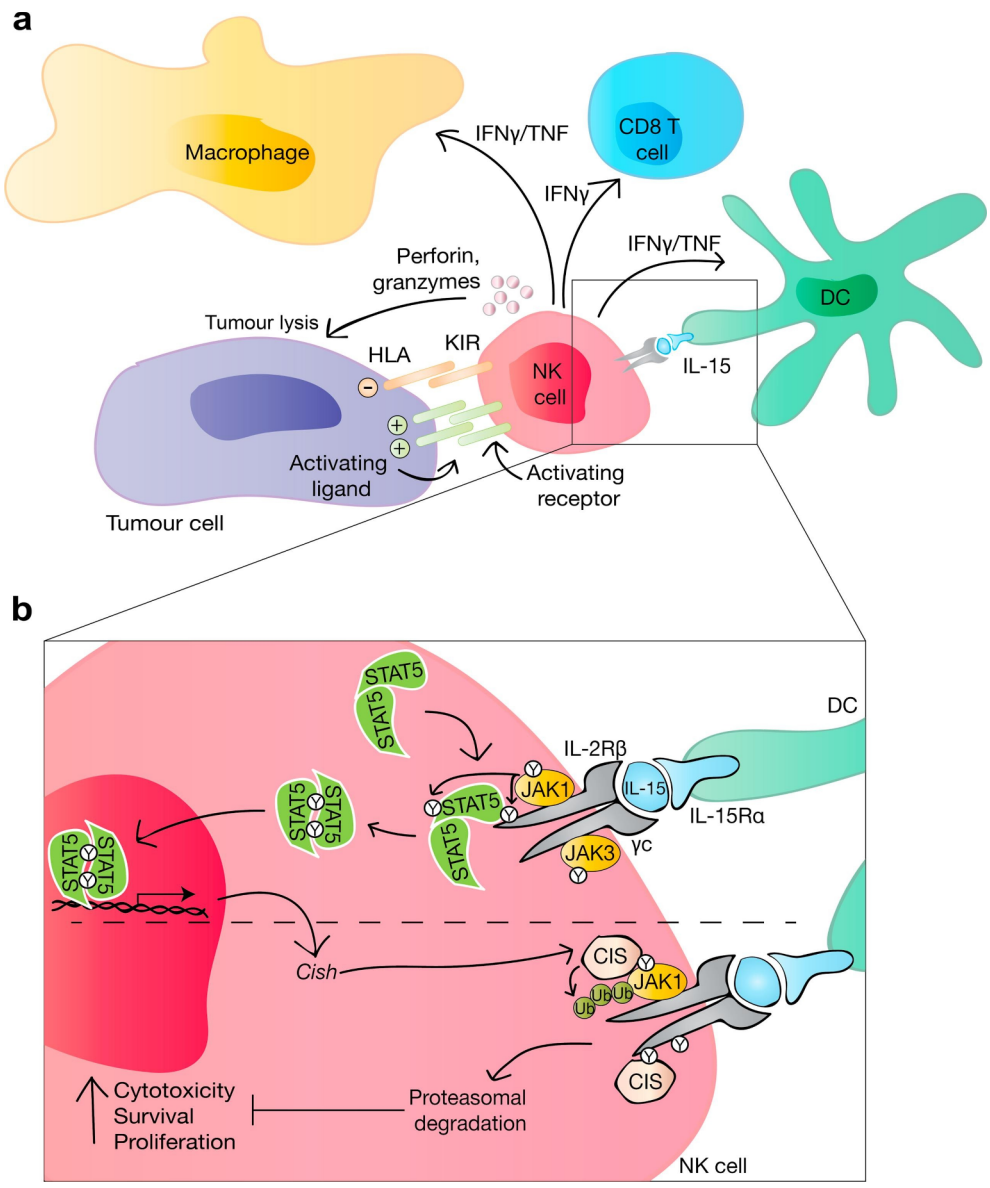

Fig. 1. CIS inhibits IL-15 signaling to regulate NK cell-mediated anti-tumor activity. A: Inhibitory MHC class I receptors maintain NK cell tolerance. MHC ligands are reduced or lost in the transformation of healthy cells into tumor cells, removing NK inhibitory signals. Simultaneously, cellular stress causes the tumor to upregulate ligands that engage activating NK cell receptors. Both events contribute to activation of NK cytolytic effector functions. NK cells also regulate responses of other immune cells, promoting the maturation and activation of dendritic cells (DC)s, macrophages and T cells, by release of TNF-α and/or IFNγ. B: IL-15 is trans-presented to NK cells by DCs or monocytes. In response to IL-15 binding to the IL-2Rβ/γc subunits, JAK1 and JAK3 are activated by cross-phosphorylation and subsequently phosphorylate tyrosine residues within the receptor subunits. These create docking sites for the STAT proteins. Tyrosine phosphorylation of STAT dimers enables their translocation to the nucleus, promoting transcription of target genes that drive NK cell survival, proliferation and cytotoxicity. *Cish* is a STAT5 responsive gene and acts in a negative feedback loop to inhibit JAK-STAT5 signaling by binding to IL-2Rβ and JAK1, targeting them for proteasomal degradation to reduce NK cell proliferation, cytotoxicity and survival. Abbreviations: interferon-gamma, IFNγ; tumour necrosis factor, TNF; human leukocyte antigen, HLA; killer immunoglobulin-like receptor.

infection and cancer. Since their discovery in the 1970s [8–10], it has become clear that reduced NK cell number and function results in an increased risk of infection [11,12]. This was highlighted in 1989, when a patient suffering from severe herpesvirus infections was discovered to have severely reduced NK cell numbers and effector activity [13]. Importantly, the presence of tumor-infiltrating NK cells is associated with a better prognostic outcome for various cancers [14–16]. Moreover, a prospective 11-year study demonstrated a correlation between NK cell activity *in vitro* and clinical prognosis, with low NK cell cytotoxic activity associated with a higher incidence of cancer [17,18]. Enhancing the ability of NK cells to proliferate, survive and overcome the tumor microenvironment has unsurprisingly become an attractive therapeutic avenue for new cancer treatments.

NK cells are classed as a group 1 innate lymphoid cell (ILC) and can be activated without prior antigen sensitization, distinguishing them from adaptive immune cells such as B and T cells [19]. NK cell activation or tolerance of self is determined by the integration of signals from activating and inhibitory receptors (Fig. 1a) (reviewed extensively in [20;21]). The major histocompatibility complex (MHC) class I is an important inhibitory ligand which is often reduced or lost as healthy cells transform into tumor cells. NK cell receptors that detect MHC class I and maintain NK cell tolerance in humans include the killer immunoglobulin-like receptors (KIRs), the leukocyte Ig-like receptors (LIRs) and the CD94/natural killer cell receptor group 2-member A (NKG2A) heterodimer. Various clinical trials, most in combination with other therapies, are underway to assess the effects of drugs such as Lirilumab and Monalizumab that respectively, block the KIR and NKG2A receptors, promoting NK and CD8 T cell activation [22].

Simultaneously with reduced MHC I expression, cellular stress can result in the upregulation of ligands on the surface of tumor cells that engage activating receptors such as NKG2D, NKp46, NKp30, NKp44 and CD226 (DNAM-1) on NK cells [21]. A shift in the balance towards activating signals induces NK cytolytic effector functions, allowing spontaneous lysis of target cells by release of effector molecules such as granzymes and perforin [23]. NK cells can also be activated by antibody crosslinking of the Fc receptor CD16 to the target cell, resulting in antibody-dependent cellular cytotoxicity (ADCC) and subsequent lysis of the target cell. In addition, NK cells promote the anti-tumor responses of other immune cells, including T cells and dendritic cells, by secreting cytokines such as interferon-gamma (IFNγ) [24], tumor necrosis factor-alpha (TNF-α) [25] (Fig. 1a) and other growth factors such a granulocyte/monocyte colony-stimulating factor (GM-CSF) [26].

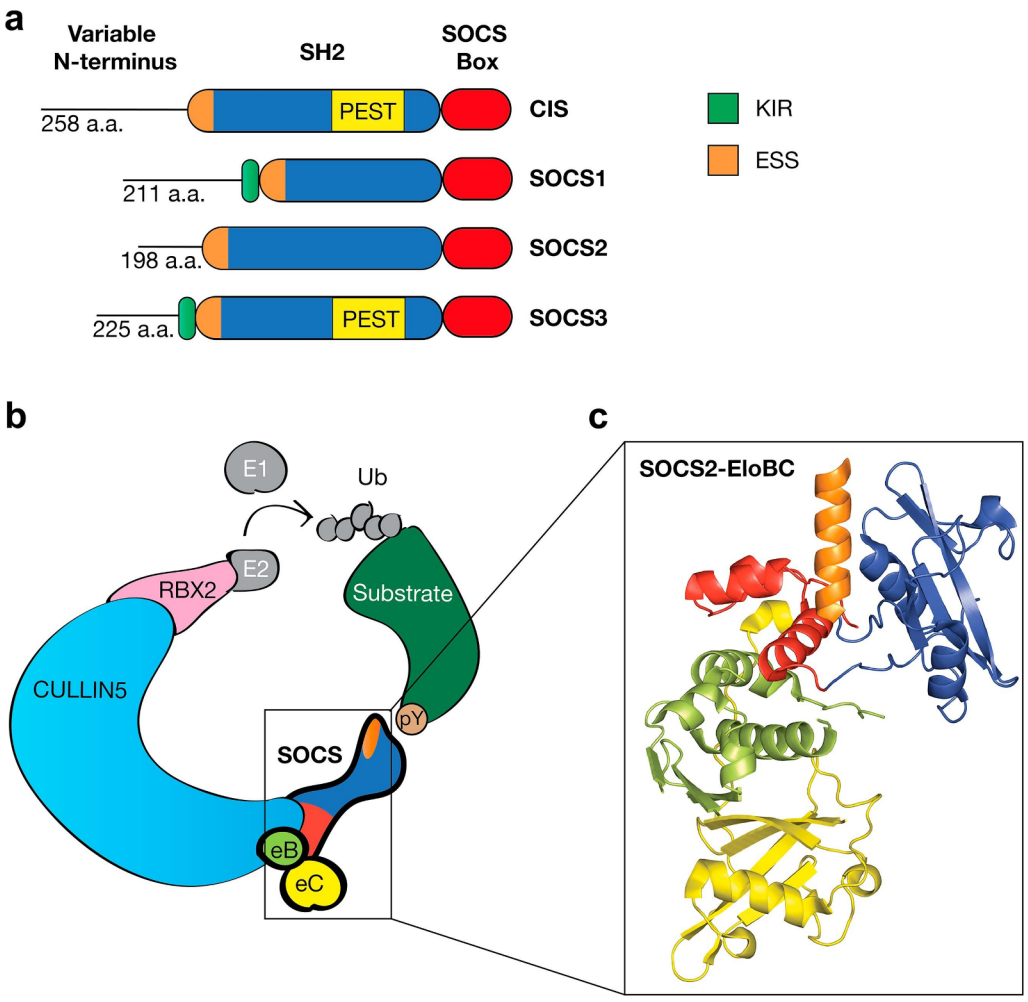

Fig. 2. SOCS domain architecture and structure. A: Domain architecture of CIS and SOCS1-SOCS3. SOCS proteins share an SH2 domain (blue), including an extended-SH2 subdomain (orange; ESS), and SOCS box (red). The N-terminus (black line) varies in length and amino acid sequence. CIS and SOCS3 contain a PEST motif (yellow; rich in proline, glutamic acid, serine and threonine), present as an unstructured 15-residue insertion in the SOCS2 BG loop. SOCS1 and SOCS3 contain a kinase-inhibitory region (green; KIR) that interacts with a unique motif on JAK1, JAK2 and TYK2, inhibiting JAK catalytic activity. B: Schematic of the SOCS-E3 ligase complex. The SOCS-SH2 domain targets tyrosine-phosphorylated (pY) substrates. The SOCS box recruits Elongins B and C, Cullin5 and RBX2 to form an active E3 ubiquitin ligase complex. An E2 enzyme mediates transferral of ubiquitin from the E1 enzyme to the SH2-bound protein, targeting it for proteasomal degradation. C: Ribbon diagram of the SOCS2-elongin BC crystal structure. The SOCS2-SH2 domain is shown in blue, the ESS in orange, the SOCS box in red, and Elongins B and C in green and yellow, respectively (PDB ID code 2C9W) [52]. Abbreviations: ubiquitin, Ub; amino acid, a.a.

3. IL-15 regulates NK cell development and effector functions

NK cell development, survival, proliferation and cytotoxicity are highly dependent on the cytokine interleukin (IL)-15, a member of the IL-2 superfamily [27]. IL-15 is primarily produced by monocytes and dendritic cells in response to IFN and signals through a trimeric receptor complex consisting of a specific α subunit, a *β* subunit shared by IL-15 and IL-2, and a common-gamma chain (γc) subunit shared by all IL-2 family cytokines. Unlike most IL-2 family cytokines, the IL-15/IL-15Rα complex is predominantly trans-presented from the surface of monocytes and dendritic cells to the high-affinity IL-2R*β*/γ receptor complex on the surface of NK cells [28]. Noguchi *et al.* demonstrated that patients with X-linked severe combined immunodeficiency (X-SCID) resulting from loss-of-function mutations in the γc subunit, had severely reduced T and NK cell numbers [29]. In addition, γc-deficient ($\gamma c^{-/-}$) mice have reduced NK cell numbers [30], further highlighting the dependence of NK cell development on IL-2 related cytokines. Moreover, both *Il-2rβ* $^{-/-}$ and *Il-15rα*$^{-/-}$ mice lack mature NK cells [31], whereas mice transgenic for IL-15 show a dramatic increase in NK cell cytolytic effector functions [32], collectively revealing IL-15 as the dominant cytokine required for NK cell development and effector activity.

Current NK cell-based cancer therapies include administration of recombinant IL-2 or IL-15 to extend endogenous NK cell function. IL-2 treatment is unfortunately associated with high levels of toxicity, mostly due to release of the pro-inflammatory cytokines IFNγ, IL-6, TNFα and GM-CSF [33]. Co-administration of IL-15 with adoptive NK cell transfer is currently in clinical trials (clinical trials NCT01385423 and NCT01875601). However, the poor bioavailability and short half-life of IL-15, and the low expression of IL-15Rα may restrict its therapeutic potential. The super-agonist IL-15–IL-15Rα–Sushi-Fc fusion complex, also in clinical trials, may address some of these issues (ALT-803; clinical trial NCT02099539).

4. IL-15 signaling

Once IL-15 signaling is initiated by ligand binding, the receptor-associated Janus kinases (JAK), JAK1 and JAK3 cross-phosphorylate, initiating a tyrosine-phosphorylation cascade and creating docking sites within the cytoplasmic regions of the *β*/γ receptors for signaling intermediates such as the signal transducers and activators of transcription (STAT) proteins. The JAKs then phosphorylate and activate STAT3 and STAT5, enabling STAT-conformational change and translocation to the nucleus to initiate a transcriptional program driving NK cell proliferation, survival and function. STAT5 is indispensable for NK cell development, with a targeted deletion of *Stat5a* resulting in reduced NK cell number and cytolytic responses, whilst *Stat5b* deletion results in complete loss of peripheral NK cells [34–36]. In contrast, deletion of *Stat3* in NK cells resulted in enhanced cytotoxicity in melanoma and leukaemia models, together with increased NK cell production of perforin and granzyme B [37,38]. In addition, STAT5 expression was up-regulated in *Stat3*$^{-/-}$ NK cells [38], leading to speculation that STAT3 plays a suppressive role, preventing over-activation of STAT5-mediated NK cell immunity [39].

Natural biological immunomodulation is critical to ensure that immune signaling is tightly regulated and prevent over activation of the

immune response. The JAK-STAT pathway is controlled at multiple levels, including receptor internalisation and trafficking and by interaction with regulatory proteins. Phosphatases, such as CD45 [40], protein tyrosine phosphatase 1B (PTP1B) [41] and TC-PTP [42] inactivate JAKs and STATs by dephosphorylation. Potent inhibitors of PTP1B have been synthesized for the treatment of metabolic disorders and inflammation, however, the efficacy of the most active compounds have yet to be assessed *in vivo* [43]. Protein inhibitors of activated STAT (PIAS) proteins inhibit STAT-mediated transcription by blocking DNA binding, altering cellular localisation and/or introducing SUMO modifications [44–46]. Lastly, the STATs induce expression of the SOCS proteins, a family of critical negative regulators that inhibit JAK-STAT signaling in a classic negative feedback loop (Fig. 1b).

5. Suppressors of cytokine signaling

There are eight SOCS family members, including CIS and SOCS1-7 [47]. CIS (encoded by *Cish* gene) was discovered in 1995 by Yoshimura and colleagues as a regulator of IL-3 and erythropoietin signaling [48], whilst SOCS1 was discovered concurrently by three laboratories as an inhibitor of JAK signaling [49–51]. The SOCS are characterized by a variable N-terminal region, central SH2 domain and a highly conserved C-terminal SOCS box (Fig. 2a) [47]. The SOCS box recruits an active E3 ubiquitin ligase complex consisting of Elongins B and C [52,53], RING box protein 2 (RBX2) and the scaffold Cullin-5 [54], which targets bound proteins for ubiquitination and subsequent proteasomal degradation (Fig. 2b) [53].

The ability of the SOCS proteins to recognize and recruit their specific target(s) relies heavily on an interaction between the SH2 domain and a tyrosine-phosphorylated substrate. The classic SH2 domain consists of three antiparallel beta sheets flanked by two alpha helices. SOCS-SH2 domains also include a unique extended SH2 sub-domain (ESS) that forms an α-helix, which, in part determines the positioning of the phosphotyrosine binding loop, whilst residues both N- and C-terminal to the target phosphotyrosine contribute to the binding interface [55,56] (Fig. 2c). Additional features of the SOCS proteins include a PEST motif present as an unstructured insert in the CIS and SOCS3-SH2 domains, as well as a kinase inhibitory region (KIR) that immediately precedes the SH2 domain in SOCS1 and SOCS3. Whilst the PEST motif in SOCS3 has been shown to be a true PEST motif (rich in proline, glutamic acid, serine and threonine residues) in that it regulates SOCS3 stability [55], the function of this insert in CIS is unknown. The kinase inhibitory region is required by SOCS1 and SOCS3 to exert their primary function [57]; inhibiting the enzymatic activity of JAK1, JAK2 and TYK2 by blocking access to the substrate binding groove [58,59].

The SOCS proteins have an important regulatory role in a variety of immune responses, with careful analysis of *Socs*-deficient mice elucidating specific roles for each SOCS *in vivo* [60–63]. *Socs1*-deficient (*Socs1*$^{-/-}$) mice die shortly after birth due to excessive IFNγ signaling [60,64,65]. Further *in vivo* studies revealed that SOCS1 also regulated IFNα/β signaling [65] as well as IL-2 related cytokines, such as IL-4, which signal through the γc receptor subunit [66]. *Socs2*-deficient (*Socs2*$^{-/-}$) mice display a gigantic phenotype due to excessive growth hormone (GH) signaling [62], whilst *Socs3*-deficient (*Socs3*$^{-/-}$) mice are embryonic lethal, resulting from placental failure caused by dysregulated leukaemia inhibitory factor (LIF) signaling [63]. Conditional deletion of *Socs3* revealed a role in regulating other gp130 cytokines such as IL-6, and G-CSF [67,68]. SOCS4-7 are generally induced to a lesser extent than CIS and SOCS1-3, and are often constitutively expressed in the steady-state. SOCS4 remains the least studied member of the SOCS family, but has been suggested to be a critical regulator of anti-viral immunity, with *Socs4*-deficient (*Socs4*$^{-/-}$) mice more susceptible to influenza infection [69]. Similarly, SOCS5 has a role in restricting influenza infection via inhibition of epidermal growth factor receptor (EGFR) signaling [70–72]. SOCS5 has also been reported to regulate IL-4R signaling [73], although mice lacking SOCS5 do not display any obvious IL-4-related defects [74]. There has been limited examination of the roles that SOCS6 and SOCS7 play in human disease, but both have been shown to regulate insulin receptor signaling pathways [75,76].

6. CIS

Cish is a STAT5 target gene and was initially shown to be induced in response to IL-3 [48], IL-2 [77], and erythropoietin [48], with exogenous expression of CIS able to inhibit signaling through these receptors [48,78]. In general, *Cish*-deficient (*Cish*$^{-/-}$) mice have no major phenotype in the steady-state [61,79,80], with the exception of a modest inflammatory lung condition observed in aged mice [81]. However, when challenged, *Cish*$^{-/-}$ mice displayed altered CD4 T helper cell differentiation and enhanced IL-2 and IL-4 responses leading to exacerbated allergic asthma [81]. Several studies have now revealed a role for CIS in anti-tumor immunity.

In vitro, Cish$^{-/-}$ NK cells are hypersensitive to IL-15 stimulation, resulting in enhanced NK cell proliferation, survival and cytotoxicity [61]. CIS was shown to regulate IL-2Rβ levels and phosphorylated-JAK1 by either ubiquitination and proteasomal degradation or direct inhibition of JAK1 kinase activity. Importantly, *Cish*-deletion and/or the adoptive transfer of *Cish*$^{-/-}$ NK cells provided protection against tumor metastasis in multiple experimental models, restricting the metastatic growth of melanoma, prostate cancer and breast cancer lines [61,82]. Moreover, *Cish*-deficiency combined with immune checkpoint inhibitors anti-PD1 and anti-CTLA4 was significantly more effective at reducing tumor metastases than treatment with immune checkpoint inhibitors or *Cish* deletion alone [61], highlighting the benefit of combinatorial targeting of immune checkpoints.

CIS also appears to be a key regulator of CD8 T cell biology with a role in antigen-mediated T cell receptor (TCR) signaling, although somewhat surprisingly, this was independent of the JAK-STAT pathway [79]. Palmer *et al.* [79] concluded that CIS interacted with phospholipase C gamma 1 (PLCG1), targeting it for proteasomal degradation to inhibit TCR signaling and revealing potentially distinct target proteins for CIS in different cell-types. The authors showed that *Cish*-deletion enhanced T cell expansion and tumor immunity in antigen-specific experimental models, and analogous to the NK cell data published by Delconte *et al*, adoptive transfer of *Cish*$^{-/-}$ CD8 T cells was sufficient to protect against subcutaneous B16 melanoma experimental metastases. Importantly, the authors showed that reduced *Cish* expression enhanced IFNγ production in human CD8 T cells [79].

CIS appears to be a promising immunotherapeutic target in primary mouse NK and T cells but it is important to confirm that CIS inhibition can also enhance anti-tumor immunity in human cells. Definitive evidence that the enhanced NK or T cell anti-tumor activities conferred by *Cish*-deletion can be directly attributed to loss of either JAK1 or PLCG1 regulation, is also lacking. In addition, exactly how CIS inhibits JAK1 kinase activity remains unclear, given that unlike SOCS1 or SOCS3, CIS lacks a kinase inhibitory region. Finally, whilst it is known that CIS turnover is regulated by the proteasome [61], the E3 ligases and deubiquitinases which govern the tight regulation of CIS protein expression are not known. In order to understand how CIS is regulated and/or how blocking CIS therapeutically could affect other biological functions, it will be critical to determine the full complement of CIS interactors in different immune cell-types.

7. SOCS2

SOCS2 is most closely related to CIS [83] and has also been suggested to regulate tumor immunity, with roles in NK cells [84], dendritic cells [85,86] and CD4 T cells [87]. SOCS2 is a key negative regulator of the GH, insulin-like growth factor (IGF) [88], and prolactin [89] signaling cascades; consistent with the enhanced growth of

Socs2$^{-/-}$ mice [62]. GH signals through JAK2 and STAT5, to promote the transcription of numerous GH-regulated genes, including the expression of SOCS2, which subsequently inhibits signaling by targeting the GH receptor complex for degradation [90,91]. However, a dualistic regulatory role has been described for SOCS2, which can either positively or negatively regulate GH signaling, depending on the amount of SOCS2 present and the cellular context [89,92,93]. Interestingly, exogenous SOCS2 expression has also been shown to antagonise other SOCS members such as SOCS1 [92] and SOCS3 [94], although at least for the latter, this does not appear to be borne out at the level of the endogenous proteins, with no obvious SOCS3-linked phenotype in *Socs2*-deficient cells [90]. Despite this, the mechanism by which transgenic expression of SOCS2 enhances growth hormone signaling *in vivo* [95] remains unclear and given the role of growth hormone in promoting certain cancers [96], will be an important factor in assessing SOCS2 as a target for immunotherapy.

SOCS2 is induced by IL-15 in both human and mouse NK cells. However, while knockdown of *Socs2* in a human NK cell line resulted in defective effector functions, it did not affect IL-15R signaling or IL-15-mediated differentiation and survival [84]. The decreased effector activity was credited to increased levels of phosphorylated proline-rich tyrosine kinase 2 (Pyk2) which was suggested to be a target for SOCS2-mediated proteasomal degradation [84]. Interestingly, a recent study by the same group showed increased numbers of NK cells in *Socs2*$^{-/-}$ mice, with a corresponding increase in IL-15-driven JAK2-STAT5 activity, but no increase in NK cell cytotoxicity *per se* [97]. *Socs2*$^{-/-}$ mice were protected in an experimental model of lung metastasis, and this correlated with an increased number of NK cells in the lung. The authors further suggested that JAK2 was a direct target for SOCS2 inhibition, by a rather unusual interaction with the JAK2 FERM domain [97]. Paradoxically, the authors didn't comment on the IL-15 activation of JAK2, given that the IL-2 receptor complex is conventionally thought to signal through JAK1 and JAK3.

The differences between the two studies were attributed to intrinsic differences between mouse and human cells [97], although the limitations of using leukemic NK cell lines as predictors of normal NK cell function should also be acknowledged. However, these findings potentially indicate a differential role for CIS and SOCS2 in NK cell regulation. It is interesting that both *Cish* and *Socs2* are STAT5 target genes, and it may be useful to understand the possible relationship between CIS and SOCS2-mediated NK cell regulation at various stages of differentiation and activation, particularly in the context of therapeutic inhibition of either or both SOCS family members.

SOCS2 has also been reported to play an important role in dendritic cell (DC) activation [86]. DCs coordinate a cascade of immune responses through antigen presentation and interaction with effector innate and adaptive lymphocytes such as NK cells and T cells. Nirschl and colleagues have shown that during early melanoma formation, IFNγ induces SOCS2 expression in mononuclear phagocytes infiltrating the tumor. Further, SOCS2 was shown to restrict DC-based priming of CD8 T cells, and mice lacking SOCS2 showed reduced intradermal tumor growth associated with increased CD8 infiltration [86].

Given the *in vivo* complexities of tumor immunity, the interplay between DC and NK cell activation may contribute to the enhanced tumor immunity observed in *Socs2*$^{-/-}$ mice [86,97]. Again, whilst SOCS2 is expressed in tissue migratory murine DCs and in tumor-infiltrating human CD11c^{+} mononuclear phagocytes [86], the consequence of *Socs2*-deletion in human DCs requires further investigation.

8. Targeting the SOCS proteins for cancer immunotherapies

Despite the potential that the SOCS family have as immunotherapeutic targets, there are many barriers to overcome. Historically, E3 ligases are difficult to drug as they lack a prototypical enzymatic pocket in which a small-molecule can bind. Similarly, targeting SH2 domains has been problematic due to the conserved mode of phosphotyrosine binding. While blockade of CIS or SOCS2 to enhance NK cell effector functions appear promising as novel immunotherapies, precisely defining how the SOCS achieve specificity will be extremely important. For example, SOCS proteins are often induced by the same cytokines, yet target related but distinct pathways. Since CIS and SOCS2 share the highest degree of amino acid similarity compared to other SOCS members, it is unclear whether target-selectivity can be achieved. Moreover, given that they both have the potential to negatively regulate NK cell responses, a dual inhibitor that blocked both proteins could be beneficial. However, given the catastrophic phenotypes observed in *Socs1* and *Socs3* deficient mice, it is clear that any inhibitor will need to avoid off-target effects on other SOCS family members.

The T cell-based immunotherapies have revolutionized cancer treatment and there is no doubt that new NK cell-based therapeutics could also significantly improve patient outcomes. The observation that, at least in mice, loss of CIS or SOCS2 can enhance tumor immunity is encouraging. Additionally, the immunomodulation exerted by CIS in CD8 T cells suggests that inhibition of CIS could improve the immune response by harnessing the cytotoxicity of both NK cells and T cells. The poor ability of NK cells to infiltrate solid tumors due to chronic immunosuppressive signals in the tumor environment [98] may mean that NK cell-based therapeutics are more effective in treating metastases or haematological cancers, and are most likely to be effective as co-modalities. Regardless, there is much work to be done to determine the appropriate clinical context and aspects such as the apparent discrepancies between mouse and human will need to be carefully considered.

Overall, targeting intracellular immune checkpoints such as SOCS2 or CIS represent a novel treatment strategy that may complement the standard management of various cancers and improve patient outcomes.

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