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Negative regulation of innate lymphoid cell responses in inflammation and cancer

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ABSTRACT

The immune system employs an array of effector cells to ensure tissue homeostasis and protection against pathogens. Lymphocytes belonging to both the adaptive and innate branches share several functions, comprising the ability to directly kill stressed or transformed cells, and to provide helper responses through specific production of cytokines. These properties are regulated by distinct sets of soluble molecules, receptors, and intracellular factors, which altogether tune the functional output of effector lymphocytes and their final activation state. In contrast to adaptive T cells, innate lymphoid cells (ILCs) do not require antigen receptors and are characterized for their ability to provide rapid immune responses. While the factors underlying functional diversification and the main principles leading to ILC activation have been dissected, our understanding of the mechanisms underlying termination of ILC effector functions is still in its infancy. Herein, we discuss the recent findings describing how ILC responses are turned off in the context of inflammation and cancer.

1. Introduction

The relevance of innate lymphocytes in host defense drew the attention of the immunologists 10 years ago, following the evidence that typical helper responses could be potently induced in non-T lymphocytes, or occurred in absence of adaptive immunity [1]. Since then, the link connecting adaptive and innate functions has been corroborated by the identification of distinct innate lymphoid cell (ILC) populations, which ultimately have the ability to mirror most of the T cell properties [2–5]. Based on the spectrum of cytokine expression and lineage-defining transcription factor (LDTF) requirement, ILCs have been divided in three major groups and, at least, five prototypical subsets [6]. Type 1 ILCs include two populations, namely Natural Killer (NK) cells and ILC1, skewed to production of the signature cytokine interferon (IFN)-γ, and involved in providing protection against bacterial and viral infections [7,8]. NK cells are characterized by the ability to directly kill transformed or infected cells through perforin and granzymes. In contrast, ILC1 have a limited killing potential, and are mainly located in the tissues where they are specialized in a fast and potent release of type 1 cytokines. Despite the differences described above, transition from NK cells to ILC1 occurs both in homeostatic and pathological conditions [9–11]. Along with type 1 cells, the ILC scenario can count on type 2 ILCs, or ILC2, able to produce IL-13, IL-5 and IL-9. These cells play key roles in amplification of T helper (Th)2 responses and provide protection against worm infections [12–14]. Finally, ILCs belonging to the type 3 group are associated with Th17/22-related immune functions and are characterized by differential ability to produce IL-22 and IL-17. Lymphoid tissue inducer (LTi) cells, recognized for their role in the development of secondary lymphoid organs, are also included in this group [15–17].

Mature ILCs express four main LDTFs, EOMES, T-BET, GATA-3 and RORγt, which determine both the fate of NK, ILC1, ILC2 and ILC3, respectively, and their pre-poised effector functions [18,19]. The distinct ILC subsets originate in the bone marrow from an array of multipotent ILC precursors [11,20]. These cells progressively lose their multipotentiality through a programmed expression of transcription factors (TFs) and a sequential acquisition of specific epigenetic traits, giving rise to distinct functional ILC subsets in absence of pathogens [21–23]. These hard-wired features make ILCs key regulators of the immune responses and allow their typical fast activation occurring upon pathogen entry.

Activation of NK cells and other ILCs relies on different soluble factors, and on a complex equilibrium between activating and inhibitory receptors [24–29]. The latter bind molecules present on

Abbreviations: APC, antigen presenting cell; IFN, interferon; IL, interleukin; ILC, innate lymphoid cell; LDTF, lineage defining transcription factor; MCA, methylcholanthrene; NCRs, natural cytotoxicity triggering receptors; NK, natural killer; SDTF, signal dependent transcription factor; Th, T helper

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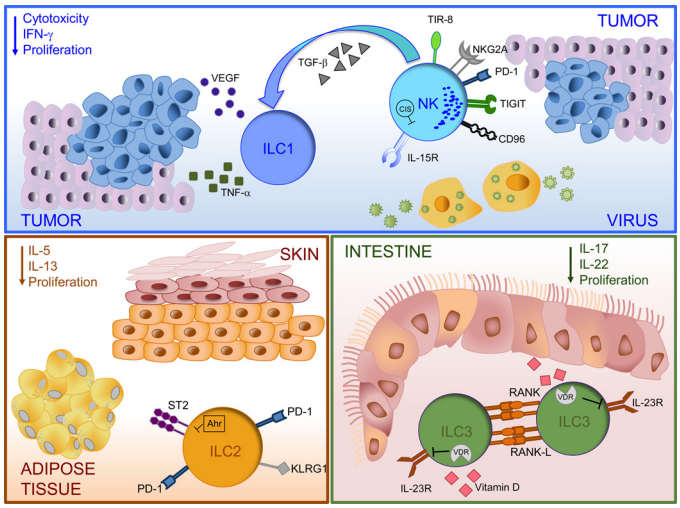

Fig. 1. Mechanisms regulating termination of ILC activation. Distinct mechanisms of feedback regulation are engaged on ILCs upon activation. Among those, PD-1 expression restrains NK cell and ILC2 functions in the context of infection and cancer. Other two receptors negatively regulate NK cell activity, namely TIGIT and CD96, competing with the activating receptor DNAM-1 for binding to PVR and Nectin-2. Modulation of ILC effector functions also occurs by inhibition of cytokine signaling. For instance, CIS is upregulated on NK cells upon activation, and inhibits IL-15 signaling as a mechanism of negative feedback regulation; while IL-1R8 is associated with inhibition of IL-18 functions in NK cells. Activation of NK cells and other ILCs can be inhibited directly by cytokines, including TGF-β and IL-25. TGF-β acts on NK cells driving transition to ILC1 favoring tumor growth, while IL-25, a cytokine inducing type 2 functions, also limits ILC3 numbers. In contrast to IL-25 effect, Ahr enhances type 3 features and limits ILC2 activity. Finally, ILC3-ILC3 interactions negatively regulate LTi-like ILC3 functions via RANK-RANKL axis.

healthy cells, including major histocompatibility complex (MHC) class I molecules, cadherins and glycoproteins. While mechanisms underlying NK cell and ILC activation have been extensively examined, here, we discuss recent findings describing how ILC responses can be terminated. In particular, we focus on the molecular mechanisms of ILC inhibition by immune checkpoints and cytokine signaling in the context of inflammation and cancer (Fig. 1).

2. NK cells and ILC1: regulation by immune checkpoints in viral infection and cancer

Several mechanisms of feedback regulation are engaged on activated NK cells to terminate effector responses, comprising an increased expression of a variety of immune checkpoints [30]. Among those, PD-1 (programmed cell death protein 1; also known as CD279) represents a critical regulator of T cell responses [31], and recent findings have extended its action on NK cells and other ILC subsets. PD-1 is a tyrosine-based inhibitory motif (ITIM)-containing receptor which binds to two ligands, PD-L1 (also called CD274 and B7-H1) and PD-L2 (also called CD273 and B7-DC), which are expressed on antigen presenting cells (APC) and several types of cancer and infected cells [32,33]. Distinct NK cell subsets can express this receptor in different clinical settings, including chronic infection or cancer. In the onset of mouse cytomegalovirus (MCMV), the negative regulation of NK cells by PD-1 has protective roles [34]. Endogenous glucocorticoids, and cytokines released upon viral infection, specifically induce PD-1 on splenic NK cells, limiting IFN-γ production and preventing immunopathology in the spleen without compromising viral clearance [34]. High levels of PD-1 can be found on a subset of peripheral blood NK cells in healthy subjects, which are serologically positive for human cytomegalovirus (HCMV). PD-1^{high} NK cells are functionally defective, having low cytolytic activity and altered ability to produce cytokines. This functional impairment can be partially reverted by usage of mAbs specific for PD-L1/PD-L2 [35]. The expression of PD-1 on NK cells has been observed in several types of cancer, and it is thought to be driven by the cytokine milieu in the tumor microenvironment and the chronic stimulation provided by the presence of activating ligands on tumor cells [35–40]. *In vivo* studies have corroborated evidence showing that NK cells play an important role in the therapeutic efficacy of PD-1/PD-L1 blockade. Indeed, PD-1 is expressed on the most activated NK cells, which are inhibited by PD-L1 expressed by tumor cells, resulting in suppression of anti-tumor immunity and tumor escape. In two mouse models of cancer, the protective effect of PD-1/PD-L1 blockade was abolished, at least in part, by depleting NK cells [39]. In this regard, the efficacy of the antitumor response obtained by blocking PD-1 can be further enhanced by the combined blockade NKG2A and PD-1 axis, which reduces tumor growth and increases survival by unleashing both NK and CD8$^+$ T cell functions [41]. Recent findings have provided novel mechanistic evidence on the functional impairment of NK cells mediated by PD-1, consisting on the inhibition of lytic granule polarization to the NK cell immunological synapse occurring along with impairment of integrin outside-in signaling [42]. PI3K/AKT signaling might also play a role in these mechanisms, since PD-1/PD-L1 blockade potentiates the activation of this pathway in NK cells [36]. In addition, STAT-1 and PI3K/AKT-Foxo1 activation by IL-21 is critical for the ability of this cytokine to reverse functional defects of intratumoral PD-1$^+$ NK cells [37].

Recently, other two receptors have been associated with negative regulation of NK cell function, namely TIGIT (T cell immunoglobulin and immunoreceptor tyrosine based inhibitory motif domain) and CD96 (or TACTILE). These two molecules belong to the immunoglobulin superfamily and are characterized by an ITIM domain, which delivers inhibitory signals upon ligand interaction. These surface proteins compete with the activating receptor DNAM-1 (CD226) for binding to the same ligands, PVR (CD155) and Nectin-2 (CD112) [43,44]. Both receptors play an important role in counterbalancing DNAM-1-mediated NK cell activation in the context of tumor microenvironment and during microbial infection [45–47]. Indeed, absence of CD96 causes an hyperinflammatory response and lowers survival in a murine model of LPS-induced endotoxicosis, which is associated with uncontrolled production of IFN-γ in NK cells. On the other hand, *Cd96*$^{-/-}$ mice are more resistant to methylcholanthrene (MCA)-induced fibrosarcoma and experimental lung metastasis than wild-type mice [46]. Tumor-infiltrating NK cells expressing high levels of TIGIT display low cytotoxicity, an impaired ability to release cytokines, and an overall hypofunctional and exhausted state [45]. Genetic ablation of TIGIT slows tumor growth and metastasis, prolongs survival of tumor-bearing mice, and leads to higher frequency of NK cells expressing CD226. Consistently, these effects can be reproduced by treatment of tumor-bearing mice with a blocking anti-TIGIT mAb in the absence of T cells. Moreover, NK cell deficiency abolishes the therapeutic effect of this mAb even in conditions where CD8$^+$ T cells are present, indicating that in the setting of TIGIT blockade NK cells have a direct anticancer activity and can support CD8$^+$ T cell-mediated response. TIGIT exerts inhibitory effects on NK cells also during viral infection [48]. As regard, NK cells from HIV-infected individuals display higher levels of TIGIT compared to healthy donors and, its expression correlates with disease progression. Increased levels of this receptor were specifically found on CD56^{dim}CD226$^+$ NK cells and, considering the higher affinity of TIGIT for binding to the ligand CD155, this could lead to reduced activation of NK cells [48].

Modulation of ILC activity can also occur by interfering with the signaling of activating cytokines. Distinct TFs can act as intracellular

checkpoints able to literally shut down effector functions. Among those, members of the suppressor of cytokine signaling (SOCS) family represent natural inhibitors of cytokine signaling and their expression and activation raise quickly upon activation [49]. The role of SOCS proteins has been mainly dissected in T cells, while their function in ILCs has remained mainly unexplored. Recently, evidence for a negative role of cytokine-inducible SH2-containing protein (CIS, encoded by *Cish*), a SOCS family member, has been provided in NK cells downstream of IL-15 signaling [50]. In homeostatic conditions, NK cells express very low levels of *Cish*, while after activation with IL-15 and recruitment of STAT5 to the *Cish* locus, a strong increase of both mRNA and protein expression occurs [50,51]. In absence of CIS, NK cells show hyperproliferation and increased IFN-γ production upon activation with IL-15 *in vitro*, which is associated with protection against cancer metastasis, *in vivo* [50,52].

Another pathway with a very promising impact in cancer therapy implies the Interleukin-1 receptor 8 (IL-1R8, also known as SIGIRR, single immunoglobulin IL-1R-related receptor or TIR8) in regulation of NK cell functions. IL-1R8 belongs to the IL-1 receptor family and interferes with the IL-18 signaling in NK cells. *Il1r8*$^{-/-}$ NK cells show an increased activation, higher expression of NKG2D, DNAM-1 and Ly49H, and increased IFN-γ production upon IL-18 stimulation *in vitro*. This phenotype leads to a higher resistance to hepatic carcinogenesis, metastasis, as well as, viral infection in *Il1r8*$^{-/-}$ mice [53].

Termination of ILC activity also involves the action of immunomodulatory cytokines. The transforming growth factor (TGF)-β has pleiotropic effects in regulation of cell functions, and it is generally viewed as a key cytokine in controlling immune homeostasis and preventing autoimmunity [54]. This cytokine has been recognized for its ability to suppress NK cell functions by regulating key effector genes [55–59] and repressing the mTOR pathway [60]. As well, during homeostasis, TGF-β is involved in regulation of NK cell differentiation, which proceeds faster in the absence of TGF-β-signaling [61]. In salivary glands, TGF-β-signaling induces loss of the NK cell properties associated with a phenotypic transition towards the ILC1 fate, which includes downregulation of Eomes and cytotoxic effector genes [62]. This feature has important implications for cancer biology, since transition from NK to ILC1 can be induced by the tumor microenvironment and can favor tumor escape of the immune surveillance. This mechanism involves production of tumor necrosis factor (TNF)-α and vascular endothelial growth factor (VEGF) by ILC1 [63]. Interestingly, the selective deletion in NK cells and ILC1 of SMAD4, a key molecule in transmitting the canonical signaling of all cytokines of the TGF-β family, highly impairs the ability of these cells to provide protection against tumor metastasis and viral infection [64]. *Smad4* deletion does not affect ILC1 but mainly impacts the phenotype of NK cells, which surprisingly become hyper-responsive to TGF-β, revealing that SMAD4 activity negatively regulates the non-canonical TGF-β signaling in NK cells [64].

3. Inhibition of ILC2 functions during homeostasis and inflammation

ILC2 activation is sustained by several cytokines (comprising IL-25, IL-33, IL-7 and TSLP), lipid mediators, neuropeptides, and hormones [14,65,66]. In contrast, players and mechanisms underlying negative regulation of ILC2 functions are less characterized and have emerged only recently. As for NK cells, PD-1 represents a critical negative regulator of ILC2 activation, both in mice and humans. Single cell (sc)RNA-seq experiments have helped to reveal the expression of PD-1 as an early checkpoint in murine ILC2 development [67,68]. However, its function does not affect ILC2 differentiation but mainly their proliferative properties and expansion. PD-1 is expressed at basal levels on murine mature ILC2 and further enhanced upon activation with IL-2, IL-7 or IL-33. Mice deficient for PD-1 (*Pdcd1*$^{-/-}$) display higher ILC2 frequencies in the lung and skin than controls. Moreover, these cells are able to produce larger amounts of type-2 cytokines, associated with a higher STAT5 phosphorylation [69]. Accordingly, transcriptomic analysis on PD-1 deficient ILC2 revealed an increased expression of effector genes and, in particular, STAT5 target genes [69]. Upon parasitic helminth infection, *Pdcd1*$^{-/-}$ ILC2 are more efficient in clearing worm burden, because of their massive expansion near the site of infection and their higher production of IL-5 and IL-13. Importantly, PD-1 blockade potentiates ILC2 function in mouse models of infection, such as influenza and *Nippostrongylus brasiliensis*, and papain-induced acute lung inflammation [67,69]. The molecular mechanisms triggering PD-1 signaling in ILC2 at the site of infections remain unclear. However, there is a strong interest on the therapeutic benefits of targeting this receptor in contexts where ILC2 functions need to be restrained, since both expression and its negative effect are conserved on human ILC2. The PD-1/PD-L1 axis plays also an important role in molecular mechanisms causing ILC2 dysfunctions in the adipose tissue of obese mice [70]. These cells are key regulators of adipose tissue homeostasis and their number and function are strongly impaired in obese humans and mice [71–73]. In a mouse model of obesity, TNF-α induces pre-adipocytes to produce IL-33 which is able to increase both PD-1 expression on ILC2 and differentiation of PD-L1^{+} M1-type macrophages. This interaction leads to a reduced ILC2 function which alters adipose tissue homeostasis. PD-1 blockade *in vivo* increases the proportion of ILC2 expressing IL-13, ameliorates glucose intolerance and partially restores the axis involving ILC2, eosinophils and activation of the alternative pathway in macrophages [70].

Mature ILC2 also express high levels of the Killer cell lectin-like receptor subfamily G member 1 (KLRG1), which limits ILC2 functions through interaction with E-cadherin [74–76]. As shown in *in vitro* experiments, E-cadherin has a negative role in regulation of GATA-3 and expression of type 2 cytokines, as well as, cell proliferation. The effect of this interaction has not been studied *in vivo*, however, the reduction of E-cadherin expression levels in the inflamed skin in settings of atopic dermatitis could be associated with unrestricted release of type 2 cytokines and to excessive production of wound healing regulators by ILC2 [76].

Inhibition of ILC2 responses comprises also distinct molecular pathways which involve the aryl hydrocarbon receptor (AHR), cytokines and lipid mediators. AHR is highly expressed by ILC2, inhibiting IL-33 receptor (ST2) expression, and type 2 cytokine/amphiregulin production, in favour of type 3 responses [77,78]. Absence of *Ahr* in mice enhances ILC2 functions and protection against helminth infection [78]. Cytokines activating STAT1 have potent effects in suppressing ILC2 effector properties. Among those, type 1 and type 2 IFNs, and IL-27 represent potent inhibitors of proliferation and production of type 2 cytokines [79–83]. Finally, lipid mediators produced upon inflammation can act limiting ILC2 responses, as demonstrated for prostaglandin E2 (PGE2), which is able to suppress cytokine-induced activation of ILC2 [84,85].

4. Restraining ILC3 activation: the RANK/RANKL axis

The type 3 group is highly heterogeneous and at least five different transcriptional states have been defined for intestinal ILC3, in mice, using scRNA-seq approach [86]. In the adult, ILC3 are divided in two major subsets, namely, LTi-like cells and natural cytotoxicity receptor-expressing (NCR^{+}) ILC3 [15–17,87–89]. Activation of ILC3 is mainly driven by cytokines, such as IL-23 and IL-1β, as well as, AHR activation and dietary signals [17]. On the other hand, evidence for negative regulation is currently limited. In this context, alterations of symbiotic microbiota highly affects transcriptomes and functions of ILCs, and a microbiota-dependent mechanism of negative feedback has been shown in mice, occurring through epithelial expression of IL-25 [86,90]. ILC3 stimulation with IL-23 induces high levels of *Socs3* in mice [91], arguing for a role of this molecule in termination of ILC3 responses. Moreover, human ILC3 activated with IL-23 and IL-1β upregulate the vitamin D receptor (VDR), which in presence of Vitamin D drives

suppression of IL-23R expression, along with inhibition of IL-22, IL-17 F, and GM-CSF production [92]. The high ILC3 number and IL-22 expression observed in VDR deficient mice provide further evidence in support of the role of vitamin D in negative regulation of ILC3 responses [93].

Recently, Bando and colleagues identified a negative role for RANKL, a TNF superfamily member, in regulation of intestinal ILC3 activity [94]. Among murine ILC3 subsets, RANKL remarkably inhibits proliferation and effector functions of LTi-like ILC3. Of consequence, RANKL deficient mice have an increased number of this ILC3 subset, which also expresses higher amounts of IL-17 and IL-22. These differences persist during infection with *Citrobacter rodentium* and are reproduced by treatment of wild-type mice with an anti-RANKL blocking Ab, indicating that RANKL can negatively affect ILC3 activity during both homeostasis and infection. Surprisingly, RANKL-mediated suppression of LTi-like ILC3 depends on ILC3-ILC3 interactions, since RANKL and RANK are co-expressed in these cells. At mechanistic level, this interaction inhibits both the expression of *Rorc*, the LDTF for ILC3, and the LTi-like ILC3 hyperresponsiveness observed in RANKL deficient mice [94].

5. Regulatory function in ILCs

While T cells have a dedicated subset able to terminate effector responses, namely T regulatory cells (T-regs), the innate counterpart has been only recently added in the ILC context [95]. Although confirmatory studies are still missing, regulatory ILCs (ILCregs) are able to release inhibitory cytokines, including IL-10 and TGF-β, and play an immunoregulatory role in mouse models of intestinal inflammation. ILCregs have distinct transcriptional programs as compared to T-regs and other known ILC subsets. Indeed, neither FoxP3 or key LDTFs previously associated to other ILC lineages are found in ILCregs [95]. It has been proposed that the IL-10 produced by these cells suppresses the functions of ILC1 and ILC3 during inflammation, while the TGF-β1 expressed during inflammation can regulate the maintenance and expansion of ILCreg in an autocrine manner [95]. An ILC population able to suppress the function of tumor-infiltrating lymphocytes from high-grade serous tumors has been recently described in humans [96]. However, by a transcriptional point of view, these cells share several traits with NK cells and other ILCs, suggesting that they do not represent a separated lineage. Although presence of these ILCs is associated with a strong reduction in the time to disease recurrence and with suppression of proliferation and functions of tumor-associated T cells, the proposed mechanisms are independent on the IL-10 and TGF-β produced by these regulatory ILCs [96].

Expression of IL-10 has been previously observed in other innate lymphocytes, such as NK cells and ILC2 [14,97–99]. While the *Il10* locus is not accessible in resting NK cells, the proliferation driven by MCMV infection is able to induce an epigenetic reprogramming of the *Il10* locus, followed by IL-10 expression [97]. Under conditions of uncontrolled viral infection, the IL-10 produced by NK cells is able to modulate $CD8^+$ T cell functions [98]. Despite production, comprehensive studies evaluating the role of IL-10 on NK cell function are still missing. The effects of IL-10 cytokine have been evaluated on ILC2, even if its suppressive activity appears limited and depends on the cytokine cocktail used for ILC2 activation [79,100,101].

6. Conclusion

ILCs are now considered key players of the immune response ensuring early host defense, maintenance of the mucosal barrier integrity, and lymphoid organogenesis. More recently, the ILC functions have been extended to other contexts, including regulation of metabolic homeostasis and activity of the enteric nervous system [1]. Mechanisms limiting ILC responses take part to processes involved in the maintenance of immune homeostasis, preventing autoimmunity. In this regard, an increasing number of findings have linked NK cell and ILC functions with chronic inflammation and autoimmunity [13,102–105]. In light of these observations, understanding the mechanisms underlying termination of ILC responses can have a huge impact in controlling the balance between immunity and immunopathology. In particular, the efficacy to target ILC2 functions can be applied in several type 2 inflammatory diseases, like allergy, asthma, and chronic rhinosinusitis. On the other hand, the identification of novel inhibitory pathways in ILC3 opens new possibility toward therapeutic strategies for regulation of intestinal inflammation in patients with inflammatory bowel disease (IBD). Immune checkpoints take part to the “physiological” termination of inflammatory responses, as well, these molecules and their pathways are evoked by cancer cells to evade the immune-surveillance [31]. Immune checkpoint inhibitors have now been employed for the control of several types of cancer, and we have discussed in this review several studies describing the role of NK cells in the therapeutic efficacy of immune checkpoint blockade, in several mouse models. Overall, because of the wide range of activities, strategical localization in distinct tissues, and ability to provide potent inflammatory responses, ILCs represent a useful and appealing target for several pathological conditions.

Author contributions

The final manuscript was a result of the joint efforts of all the authors.

Declarations of interest

None.

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