Molecular Immunology 110 (2019) 48–56

Contents lists available at ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm

The expanding role of innate lymphoid cells and their T-cell counterparts in gastrointestinal cancers

Ka Yee Fung[a,b], Paul M. Nguyen[a,b], Tracy Putoczki[a,b,*]

[a] Walter and Eliza Hall Institute of Medical Research, Victoria, 3052 Australia
[b] Department of Medical Biology, University of Melbourne, Victoria, 3052 Australia

ARTICLE INFO

Keywords:
Gastrointestinal
ILCs
Th17 cells
Colorectal cancer
IBD

ABSTRACT

Innate lymphoid cells (ILCs) contribute to the regulation of gastrointestinal (GI) homeostasis. Over the past 15 years, there has been a large effort to dissect the mechanisms required for GI homeostasis, with a major focus on different immune cell populations and the cytokines that they produce. In contrast to T-helper (Th) cells, ILCs respond rapidly to cytokines in their microenvironment in the absence of specific antigens; however, once activated both cell populations have similar effector functions. Two effector cytokines produced by both ILC3 and Th17 cell populations, Interleukin (IL)-17 and IL-22, have taken center stage for their ability to signal directly to GI epithelial cells and promote epithelial cell survival. In this review, we outline our current understanding of ILCs in the GI tract, and focus on GI cancers associated with aberrant production of IL-17 and IL-22. We highlight evidence from both mouse and patient-based analyses and discuss how tumor cells may hijack the potential evolutionary redundancy of these two cell populations.

1. Introduction

The innate immune system is our first line of defense against pathogens. The main cellular components of the innate immune response include macrophages, monocytes, neutrophils, natural killer cells (NK) and their relatives, innate lymphoid cells (ILCs). The second arm of our defense system is governed by the adaptive immune response, which consists of B lymphocytes and T lymphocytes, including both CD4+ T-helper (Th) cells and CD8+ cytotoxic T-cells. In a number of solid tumor types, neoplastic cells can hijack the natural function of both the innate and adaptive immune system to avoid destruction and fuel their growth (Grivennikov et al., 2010; Pardoll, 2012).

At the onset of tumorigenesis, when cell intrinsic tumor suppressor mechanisms have failed, the innate immune system activates a cascade of events that are designed to eradicate neoplastic cells. In the initial response, the immune surveillance governed by sub-types of macrophages and other tissue resident immune cells results in either the direct destruction of a neoplastic cell, or the production of chemokines to attract additional innate immune cells, including NK cells that can directly lyse the tumor cells (Georgoudaki et al., 2016; Dahlberg et al., 2015). In the second phase of immune surveillance, dendritic cells (DCs) bridge the innate and adaptive immune response by collecting tumor antigens and presenting them to naïve T-cells, resulting in the activation of cytotoxic CD8+ T-cells that complete tumor destruction (Palucka and Banchereau, 2012).

Over the past 10 years, it has become clear that tumor cells have devised mechanisms to overcome immune editing, and hijack the effector functions of both innate and adaptive immune cells. Here we will discuss recent literature for two previously under-characterized immune cell populations, ILCs and CD4+ Th17 cells, both of which are present in the tumor microenvironment. We will review our current understanding of how ILCs, in particular the ILC3 subgroup, inadvertently contribute to the initiation and progression of gastrointestinal (GI) cancers and compare this to our knowledge of the overlapping function of Th17 cells. We focus on GI cancers, as these cell types are critical in host defense to infections and the control of chronic inflammation, both of which increase the risk of colorectal cancer (CRC) development (Kim and Chang, 2014; Dejea et al., 2013).

2. Innate lymphoid cells are primarily localized to mucosal surfaces

The GI tract contains the largest concentration of immune cells in the body. Sheltered by the mucosal barrier, an immune response can be triggered by exposure to ingested antigens, chemical irritants, and dysregulation of commensal bacteria. In a thought provoking review of

Abbreviations: CRC, colorectal cancer; DSS, dextran sulfate sodium; GI, gastrointestinal; IBD, inflammatory bowel disease; ILC, innate lymphoid cell; IL, interleukin; Th, T-helper

* Corresponding author.
E-mail address: putoczki.t@wehi.edu.au (T. Putoczki).

https://doi.org/10.1016/j.molimm.2017.11.013
Received 3 August 2017; Accepted 14 November 2017
Available online 27 November 2017

'The Hallmarks of Cancer', Hanahan and Weinberg discuss our emerging scientific appreciation of the extrinsic tumor-suppressive role the immune system can play, with disruption of the normal immune function capable of promoting tumor development (Hanahan and Weinberg, 2011). It is now well established that communication within the tumor microenvironment between neoplastic cells, fibroblasts, endothelial cells, and immune cells can fuel tumor progression (Klemm and Joyce, 2015). In light of this, reprograming the tumor microenvironment, through immunotherapy, is currently a major area of research. This in principle, allows for utilization of the immune system beyond the intrinsic tumoricidal capacity of NK cells. Here we focus on the NK cell family, and more specifically the recent extension to include ILCs, with the role of this sub-family in cancer onset, progression and response to immunotherapy not clear.

ILCs develop from common lymphoid progenitors (CLP) present in the bone marrow, and require the expression of IL-2Rγc and inhibitor of DNA-binding 2 (Id2) for their maturation (Yang et al., 2011; Yokota et al., 1999; Klose et al., 2014). ILCs have a lymphoid-like morphology and are defined by the absence of surface markers for myeloid and DCs, and the lack of antigen receptors (Spits and Cupedo, 2012). While they can be detected in a number of tissues, they are relatively rare, and comprise only 0.1-13% of CD45+ leukocytes depending on the tissue examined (Kim et al., 2016). ILCs are unique in that they primarily exist as tissue resident cells at mucosal surfaces, and thus much of our basic knowledge of their function is derived from the GI tract. Here we will outline our current understanding of ILCs in IBD and GI malignancies.

3. Our current understanding of the function of ILCs in the gastrointestinal mucosa

ILCs are subdivided into three groups, based on their known transcription factor and cytokine profiles (Spits et al., 2013). This subclassification parallels the descriptors for their adaptive Th-cell counterparts (Fig. 1). In contrast to Th-cells, ILCs can respond rapidly to cytokines present in the microenvironment without the need for specific antigens, providing an immediate outlet for tissue defense systems against pathogens, maintenance of epithelial homeostasis, and repair at mucosal barriers. However, once activated their effector functions mirror that of Th-cells, a functional redundancy that tumor cells can readily hijack.

Our understanding of why ILC populations home to the GI tract is still evolving. They are thought to be present in large numbers at mucosal surfaces because their precursors express CXCR6, which is necessary for migration to the intestine, and integrin α4β7, which binds to MADCAM-1, an adhesion molecule expressed within Peyer's patches (Klose et al., 2014; Satoh-Takayama et al., 2014). In adults, the lymphatic network provides a means to migrate between the mesenteric lymph node and the GI lamina propria, a mechanism by which CCR6+ ILC3s are known to assist with the removal of auto-reactive T-cells (Hepworth et al., 2015; Kim et al., 2015). However, at early stages in life, retinoic acid (RA) has been shown to induce the expression of integrin α4β7 and CCR9, and reduce the expression of CCR7 on ILC1s and ILC3s resulting in their propensity to travel to the GI tract (Kim et al., 2015). In contrast, ILC2s express CCR9 facilitating direct migration to the GI tract (Kim et al., 2015). The stage of embryogenesis where the decision to migrate to the GI tract as a final destination has yet to be revealed. The proliferation of tissue-resident progenitor cells in the GI tract is able to promote self-renewal to maintain or increase ILC numbers as required (Gasteiger et al., 2015).

3.1. ILC1s are associated with inflammatory bowel disease

Group 1 ILCs are most similar to NK cells, which upon activation release perforin and granzyme molecules to directly lyse cancer cells (Vivier et al., 2008). ILC1s can be subdivided into NK cells, CD127- ILC1 cells which are functionally similar to CD4+ Th1 cells, and CD127+ ILC1 cells which have cytotoxic abilities similar to CD8+ T-cells (Klose et al., 2014; Robinette et al., 2015). ILC1s respond to IL-12, IL-15, and IL-18 within the mucosal environment (Spits et al., 2016; Klose et al., 2014; Klose et al., 2013). Additionally, it has recently been shown that ILCs are present in the small intestinal lamina propria of mice in the absence of IL-7Rα, with IL-15 able to compensate for deficiency in IL-7R (Robinette et al., 2017). ILC1s require the transcription factor T-box factor (T-bet) (Klose et al., 2014), while NK cells and intraepithelial ILC1 cells also require eomesodermin (Eomes) (Spits et al., 2016). ILC1s are best defined by their production of Interferon-γ

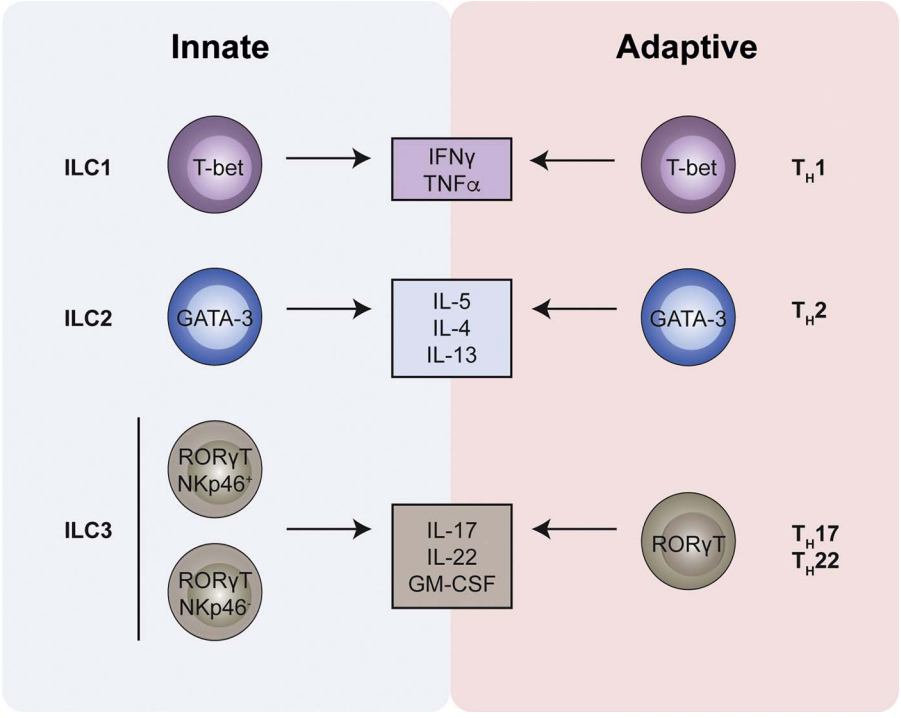

Fig. 1. Redundancy between ILC and Th populations is exemplified by cytokine signatures.
The innate ILC populations (left) and Th populations (right) share common transcription factors and cytokine expression profiles. The significance of these common signatures may relate to evolutionary pressure to rapidly respond to pathogens and maintain epithelial barrier function.

(IFNγ) and tumor necrosis factor-α (TNFα), similar to their Th1 counterparts (Fig. 1). ILC1s are present in both the lamina propria and intraepithelial spaces within the intestine, with elevated numbers associated with Crohn's disease, a type of IBD associated with aberrant IFN-γ expression (Fuchs et al., 2013; Bernink et al., 2013). Animal models suggest that ILC1s contribute to the pathogenesis of IBD, with depletion of ILCs and NK cells resulting in increased inflammation and epithelial damage in the intestine of *Rag1*$^{-/-}$ mice treated with anti-CD40, a mouse model of colitis with enhanced IFN-γ production (Fuchs et al., 2013).

3.2. ILC2s contribute to the development of specialized gastrointestinal cells

ILC2s are activated in response to epithelial cell derived cytokines including IL-25, IL-33, alarmins, prostaglandin D2 (PGD2), and thymic stromal lymphopoietin (TSLP) during inflammation and infection (Kim et al., 2013; Monticelli et al., 2015). In culture, they have also been shown to expand in response to Notch ligands, which are stem cell factors secreted by stromal cells (Zhang et al., 2017). ILC2s are dependent on the transcription factors gata binding protein-3 (GATA3) and retinoic acid receptor-related orphan receptor-α (RORα) for their maturation and development (Hoyler et al., 2012; Wong et al., 2012). Small numbers of ILC2s can be detected in the blood, with the majority localized to the mucosal surfaces of the lung, skin, and GI tract (Mjosberg et al., 2011). ILC2s are primarily known for their secretion of IL-13 and IL-15, similar to their Th2 counterparts (Fig. 1); however, they have also been shown to secrete IL-4, IL-5, IL-6, IL-8, IL-9, and GM-CSF (Walker and McKenzie, 2013). ILC2s can also secrete amphiregulin (Areg), a member of EGF family, that is linked to colon cancer (Ciardiello et al., 1991). Interestingly, it has been shown that after dextran sulfate sodium (DSS)-induced colitis, mice deficient for *Areg* were more susceptible to inflammation and epithelial damage, suggesting that ILC2s may contribute to a wound healing response (Monticelli et al., 2015). Importantly, ILC2s contribute to the development of a specialized population of epithelial cells, called tuft cells, which are a source of IL-25 that may have a fundamental role in the detection and expulsion of worms (von Moltke et al., 2016). Indeed, ILC2s are well characterized for their protective immune response against helminth parasites (Neill et al., 2010).

3.3. ILC3s are essential to management of the gastrointestinal microbiome

In humans, ILC3s are divided into two primary sub-types based on their expression of CCR6: fetal lymphoid tissue induced cells (LTi) are CCR6+, while post-natal ILC3s are CCR6-(Spits et al., 2013). The subclassification of ILC3s is further delineated based on expression of the activating NK cell receptor (NCR) NKp44 in humans, and NKp46 in mice (Hoorweg et al., 2012). Adult ILC3s respond to IL-1β and IL-23 (Kim et al., 2014), and similar to Th17 cells, are defined by the requirement of the transcription factor RAR-related orphan receptor gamma (Rorγt) for development (Fig. 1) (Spits et al., 2013). Rorγt also regulates aryl hydrocarbon receptor (AHR), a transcription factor necessary for Th17 function and the survival of ILC3s (Hughes et al., 2014; Qiu et al., 2012). The ligand for AHR is available through food by-products and the microflora, thus linking ILC3s to the microbiome (Qiu and Zhou, 2013; Zelante et al., 2013). ILC3s produce Th17-type cytokines including IL-17A, IL-17F and IL-22 either alone or in combination (Buonocore et al., 2010; Hughes et al., 2010). In some instances, ILC3s can also produce TNFα and IFNγ in addition to Th17 cytokines, consistent with the Th17/Th1 plasticity of their adaptive counterparts (Spits et al., 2013). However, the level of expression of these cytokines differs between ILC3 populations, with NCR+ ILC3 cells known to produce IL-22, but very little IL-17, while NCR- cells produce mainly IL-17 and GM-CSF (Vonarbourg et al., 2010; Glatzer et al., 2013). In some human NCR+ ILC3 cells, upon stimulation with IL-23, a potent pro-inflammatory response ensues resulting in the release of TNFα as opposed to the release of IL-22 (Glatzer et al., 2013). Like ILC2s, NCR- ILC3s express MHCII, and can present antigen in the absence of costimulatory molecules (Hepworth et al., 2015; Hepworth et al., 2013). However, only splenic ILC3s are able to induce T-cell responses (von Burg et al., 2014). Instead, intestinal ILC3s can outcompete T-cells for IL-2, resulting in T-cell death (Hepworth et al., 2015). This provides a mechanism to limit commensal bacteria-specific CD4 T-cell responses and chronic intestinal inflammation, which together can provide a microenvironment that supports cancer development (Hepworth et al., 2015; Hepworth et al., 2013).

ILC3s are the most abundant ILC in the human intestine at steady state, and are found in cryptopatches, lymphoid follicles, and throughout the lamina propria (Bernink et al., 2013; Klose and Artis, 2016). ILC3s constitute the majority of the ILCs in the lamina propria of the ileum of mice, with corresponding characterization of the healthy human colon not yet described (Bernink et al., 2013). In Crohn's disease patients, IL-17A and IL-17F are elevated in CD3- cells, which are most likely to be ILC3s (Geremia et al., 2011). It is believed that ILCs contribute to an inflammatory feedback loop in Crohn's disease, with the loss of mucosal barrier function and exposure to microbial antigens resulting in a chronic state of inflammation. This would prolong the activation of ILC3s, resulting in an increase in IL-17 that could repair the epithelial barrier (Geremia et al., 2011), although, the persistent increase in IFNγ secreting ILC1s are known to enhance the inflammatory response that contributes to the disease (Bernink et al., 2013). A current thought is that a switch between IFNγ to IL-22 producing ILCs could have therapeutic utility in Crohn's disease (Bernink et al., 2015).

ILC3 s are best characterized for their roles in anti-bacterial immunity, tissue homeostasis, and repair following chronic inflammation (Buonocore et al., 2010; Mortha et al., 2014). However, different ILC3 subsets appear to have different functions within this context. NCR+ IL-22-producing ILC3 cells prevent colonization by pathogenic bacteria, and can signal directly the colonic stem cell compartments to maintain epithelial integrity (Satoh-Takayama et al., 2008; Sanos et al., 2009). This is achieved in part through IL-22 mediated induction of the expression of the antimicrobial peptide RegIIIγ and α(1,2)-fucosylation of intestinal epithelial cells, which maintain homeostatic interactions with the microbiota (Pham et al., 2014). On the other hand, NCR- IL17-producing ILC3s have a pathogenic role in colitis, facilitated by their expression of GM-CSF in response to IL-1β secretion by macrophages and DC derived IL-23 (Mortha et al., 2014; Pearson et al., 2016). Moreover, blockade of IL-17 and IFNγ using neutralizing antibodies in *Rag*$^{-/-}$ mice infected with *H. hepaticus* resulted in reduced colitis pathology (Buonocore et al., 2010). Understanding the balance between these two populations will be essential to understanding the maintenance of the epithelial barrier. A simple explanation may stem from the tissue localization of ILC3s, with NCR-ILC3s located below crypts in cryptopatches and thus may be involved directly in epithelial maintenance, while NCR+ ILC3s are found throughout the lamina propria and thus are able to respond rapidly to pathogen infection (Eberl et al., 2004).

3.4. Cross talk between ILCs and the relationship to epithelial cells

There is increasing evidence that there is cross-regulation between ILC subsets. In the steady state GI tract, the microbiota can induce the differentiation of Th17 cells (Ivanov et al., 2008), and alter the number of IL-22 producing ILC3 cells, with the number of IL-22-producing ILC3s lower in germ free mice after weaning (Sawa et al., 2011). The repression of ILC3s is believed to be mediated by the epithelial cell derived IL-25 (also termed, IL-17E), which acts on IL-17BR + ILC2 or CD11c + DCs (Sawa et al., 2011). Consistently, IL-25 expression is reduced and IL-22 producing ILC3s are expanded following epithelial damage by DSS-induced colitis (Sawa et al., 2011). Moreover, mice with epithelial-deletion of IKKα (a noncanonical NFκB-dependent gene)

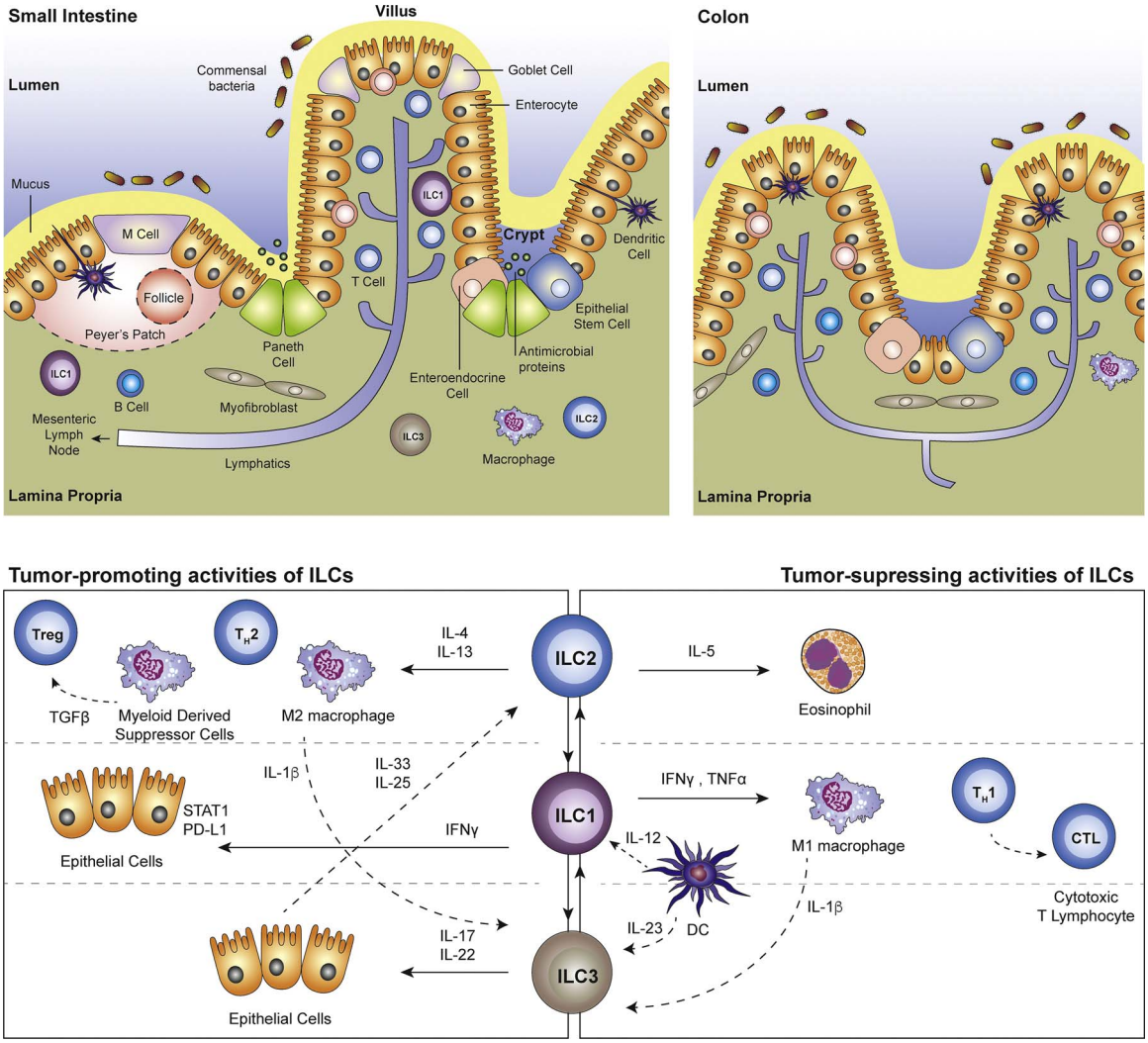

Fig. 2. ILCs are located throughout the gastrointestinal mucosa.
In the adult mouse, ILC1s, ILC2 s, and ILC3 s are present throughout the intestine (top panel, left), and are less well characterised in the colon (top panel, right). They traffic to the intestinal tract through the mesenteric lymph node, where they take up residence within the lamina propria. In gastrointestinal cancers, which arise within the colon, ILCs may have both pro- and anti-tumorigenic roles (bottom panel), which primarily stems from their known cytokine expression profiles. How this relates to their Th-counterparts has yet to be clearly defined.

are highly susceptible to *C.rodentium* infection and DSS-induced colitis,which was associated with less IL-22-producing ILC3 infiltration and the subsequent reduction of antimicrobial peptide expression (Giacomin et al., 2015). Mechanistically, deficiency of IKKα leads to elevated TSLP which can promote the function of ILC2. These results further highlight the relationship between ILC subsets and epithelial cells. However, the interaction whether direct or indirect between ILC2 and ILC3 remains to be elucidated. Since both ILC2 and ILC3 have been shown to be anti-and pro-tumorigenic, it will become increasingly important to further delineate their role in CRC (Fig. 2).

4. Link between innate lymphoid cells and the progression of gastrointestinal cancers

It is now well appreciated that the growth and progression of cancers of the GI tract can be fueled by cytokines produced within the tumor microenvironment. It is clear from the overlap in localization, transcriptional activity, cytokine profiles and effector functions that ILCs strongly resemble different Th-cell subsets. Here we will summarize our understanding of the role of ILCs in GI cancers, and how they, together with their Th counterparts, may inadvertently aid tumor growth.

4.1. ILC1s may be associated with colitis-associated cancer

A direct role for ILC1s in CRC has not been explored. Given the link between IBD, which has a dominant ILC1 signature (Bernink et al., 2013), and increased risk of CRC (Karvellas et al., 2007) it is likely that ILC1s may contribute to the early onset and growth of GI tumors. It could be argued that this may be associated with IFNγ, the dominant cytokine produced by ILC1s, which has known functions in CRC progression. However, a contribution of IFNγ to tumorigenesis is not likely to be black and white. *In vitro* IFNγ has been shown to promote apoptosis (O'Connell et al., 2000), inhibit angiogenesis (Beatty and Paterson, 2001), and inhibit proliferation (Wang et al., 2015) of CRC cells. *In vivo*, IFNγ has also been shown to promote colon epithelial apoptosis and inhibit proliferation, which was linked to attenuated chronic inflammation (Schmitt et al., 2012). Similarly, using the Apc^{Min} mouse model of familial adenomatous polyposis, the genetic deletion of a single *Ifn*γ allele was attributed to augmented CRC progression (Wang et al., 2015). Since IFNγ is required for the Th1 response, which is known to enhance the activity of cytotoxic effector cells, including CD8+ T-cells, NK cells, and macrophages (Whitmire et al., 2005; Reiter, 1993; Haabeth et al., 2011; Hoepner et al., 2013), it is possible that lack of an immune mediated lyses of tumor cells attributed to this

observation. Indeed, IFNγ is able to upregulate MHC class I expression on tumor cells which in turn promotes a CD8 T-cell medicated cytotoxic response (Martini et al., 2010). IFNγ is also a potent mediator of signal transducer and activator of transcription-1 (STAT1) activation, which is linked to the upregulation of PD-L1 expression on tumor cells, and their ability to evade cytotoxic T-cells (Garcia-Diaz et al., 2017). Indeed, ILC1s have been shown to play a role in immune surveillance in other cancers, including non-small-cell lung cancer (Djenidi et al., 2015). How ILC1 derived IFNγ may contribute to the success or failure of current cancer immunotherapy approaches will be an interesting area of research.

Along a similar line of thought, TNFα is associated with the pathogenesis of IBD, with biological inhibitors of this cytokine a major pharmaceutical success story (Levin et al., 2016). Like IFNγ, TNFα also has a role in anti-tumor immunity, through the recruitment of macrophages and DCs (Villeneuve et al., 2005). However, like IFNγ, this is not a simple correlation as dysregulated TNFα can also promote tumor formation and growth in CRC models, where therapeutic blockade of TNFα has been shown to prevent tumor formation (Popivanova et al., 2008). The disparity in our understanding of the role of each of these cytokines in CRC may stem from our understanding of the dominant source, and location, of the cells actively secreting and responding to them. Clarification of the presence and function of ILC1s in this context may assist with delineating the pro and ant-tumorigenic properties of IFNγ and TNFα.

4.2. ILC2s may support pro-tumorigenic immune cells in gastrointestinal cancers

While direct investigations into the role of ILC2s in CRC have yet to be performed, the frequency of ILC2s in peripheral blood mononuclear cells is increased in gastric cancer patients compared to healthy controls (Bie et al., 2014). There is emerging evidence that prototypical ILC2-type cytokines may play a significant role in CRC, since IL-4, IL-15 and IL-33 have been detected in CRC cells (Di Stefano et al., 2010; Kuniyasu et al., 2001; Zhou et al., 2013), and can promote the secretion of IL-13, which has been suggested to trigger tumor promoting myeloid derived suppressor cells to secrete TGFβ or polarize macrophages towards their pro-tumorigenic M2 phenotype (Dhakal et al., 2014; Gabrilovich and Nagaraj, 2009). However, *Il13*$^{-/-}$ mice have comparable colonic tumor formation to wild-type mice, suggesting that IL-13 secretion does not contribute directly to CRC (Ingram et al., 2013). IL-15 has been shown to suppress colitis-associated cancer (CAC) by promoting anti-tumor immunity (Bahri et al., 2015). In contrast, IL-4 deficient mice developed fewer CRC tumors compared to wild-type mice (Osawa et al., 2006). IL-33-induced ILC2s have been shown to protect against acute colitis, which was associated with Areg, since *Areg*^{KO} mice had increased disease (Monticelli et al., 2015). Depletion of Areg in *Apc*^{Min} mice can also lead to reduced tumor burden compared to wild-type mice, implicating Areg in intestinal tumorigenesis (Guzman et al., 2013). TSLP has also been linked to CRC (Yue et al., 2016). Among the other cytokines secreted by ILC2s, clear roles for IL-6 and GM-CSF in CRC have been elucidated (Grivennikov et al., 2009; Wang et al., 2014a). However, the dominant cellular source of these cytokines driving tumor progression has yet to be determined. It is likely, that tumor cells have taken advantage of growth factors secreted by numerous cell types to ensure a growth advantage.

4.3. ILC3s stimulate the growth and expansion of neoplastic gastrointestinal cells

Among the three subsets of ILCs, the role of ILC3 is gaining increased research interest for its potential tumor promoting activities. The function of the NCR+ IL-22-producing ILC3 subset in preventing aberrant microbial colonization in the intestine is an evolutionary adaptation that may inadvertently promotes the growth of mutant epithelial cells that express the receptors needed for IL-17 and IL-22 mediated pro-tumorigenic STAT3 activation (Kirchberger et al., 2013). This line of thought has been further fueled by a recent observation, whereby tumor development was decreased in *Rag*$^{-/-}$*;Il17*$^{-/-}$ mice, while both *Rag*$^{-/-}$ and wild-type mice developed large tumors following IL-23 transgene injection (Chan et al., 2014). This observation suggests that IL-23 activates an innate source of IL-17, independent to T cells, that contributes to intestinal tumorgenesis. IL-22 producing ILCs have also been shown to promote tumor growth in a bacterial model of CRC, with depletion of IL-17+ and IL-22+ ILCs preventing tumor formation (Kirchberger et al., 2013). In this model; however, IL-17 played only a minor role in tumor growth, with inhibition of IL-17 resulting in reduced inflammation, while inhibition of IL-22 significantly reduced tumor burden. The discrepancies between the role of ILC derived IL-17 and IL-22 could potentially be explained by the differences in localization and function of the NCR+ and NCR- ILC3 subsets.

5. Is the evolutionary redundancy of ILC3s and Th17 cells hijacked by tumor cells?

The similarities between ILCs and their Th-cell counterparts leaves one to question when they arose during evolution, if they co-evolved to ensure robust immunity, or if selective pressure led to shared cytokine expression signatures that tumors use to their advantage. The substantial heterogeneity of both the ILC3 and Th17 lineages suggests that they may still be evolving under pressure from a changing microbial environment.

5.1. IL-17 produced by Th17 cells is associated with gastrointestinal cancer progression

Although both ILC3 and Th17 cells produce IL-17A, with the majority of the literature to date on IL-17A in CRC attributed to Th17 cells. Human tumor-infiltrating Th17 cells have been extensively documented in patients with CRC, and their polarization was found to be mediated by tumor-associated macrophages (Kryczek et al., 2009). An increase in Th17 cells has been linked to poor prognosis in CRC patients (Tosolini et al., 2011) and IL-17A can promote CAC, with *Il17*$^{-/-}$ mice having reduced tumor burden (Hyun et al., 2012). IL-17A deficiency has also been shown to alleviate CRC in *Apc*^{Min} mice (Chae et al., 2010).

Once IL-17A is secreted, it binds to IL-17 receptors A (IL-17RA) and C, with IL-17RA expressed on both hematopoietic cells and non-hematopoietic cells including colonic epithelial cells and cancer-associated fibroblasts (Wang et al., 2014b). Engagement of the receptor complex leads to activation of mitogen activated protein kinases (MAPK), NFκB and C/EBP signaling. This results in the production of chemokines that recruit neutrophils, T-cells, and myeloid cells (Laan et al., 1999). Additionally, IL-17A can induce the production of a range of anti-microbioal proteins including β-defensin, S100A7, S100A8, S1200A9 and lipocalin-2 (Kao et al., 2004; Liang et al., 2006). These observations suggest that IL-17 has a major role in inflammation and protection against infection. Indeed, *il17a*$^{-/-}$ mice are susceptible to *C. rodentium* infection, where the major source of IL-17A is T cells (Ishigame et al., 2009).

Both IL-17 producing CD3- and CD3+ cells are present in the intestine of IBD patients (Geremia et al., 2011), and the expression of IL-23 is known to be elevated in CRC patient tumors (Grivennikov et al., 2012; Langowski et al., 2006). IL-23 and IL-1β are essential to the development of both human ILC3s and Th17 cells, with both IL-23 and IL-1β derived from CX3CR1+ mononuclear phagocytes (MNPs) or CD14- dendritic cells in the human intestine (Bernink et al., 2015; Longman et al., 2014). Tumor infiltrating neutrophils and DCs have also been shown to secrete IL-23 in the GI tract (Kvedaraite et al., 2016). Following the observation that *Apc*^{Min}*;Il23p19*$^{-/-}$ mice have a reduced tumor burden, which correlated with reduced IL-17 expression in the

distal colon (Grivennikov et al., 2012), the pathogenesis of IL-23 was primarily linked to Th17 cells. This was further supported when *Il23p19*$^{-/-}$ mice were shown to be resistant to CAC, antibody-mediated inhibition of IL-23 reduced CAC burden, and syngeneic tumor transplants into mice deficient for IL-23R did not grow (Langowski et al., 2006; Wu et al., 2009). However, we now appreciate that IL-23 creates an environment that can readily prime ILC3 cells, and following antigen presentation fuel Th17 cells, suggesting that much of the IL-17 literature in GI cancers may need to be revisited.

5.2. IL-22 produced by ILCs is associated with gastrointestinal cancer progression

In naïve mice, ILC3s are the main source of IL-22, a cytokine that is known to stimulate the proliferation and survival of colonic epithelial cells (Kirchberger et al., 2013). Polymorphisms in *IL22* are associated with an increased risk of CRC (Thompson et al., 2010), although how these polymorphisms impact on protein expression levels and function is not clear. The level of IL-22 expressed in human colon tumors has been linked to tumor growth and metastasis, which is thought to be mediated by STAT3 activation and upregulation of associated anti-apoptotic and pro-proliferation genes (Jiang et al., 2013). In contrast to IL-17A producing Th17 cells, IL-22 producing Th17 cells have been less well documented in CRC.

Once IL-22 is secreted, it interacts with a heterodimeric receptor complex, consisting of IL-22R1 and IL-10R2, with IL-22R1 expressed exclusively by non-hematopoietic cells (Tachiiri et al., 2003). Engagement of the receptor complex results in the phosphorylation and activation of STAT3, which regulates the production of anti-microbial peptides such as RegIIIβ, RegIIIγ, S100A8, S100A9 and β-defensin in order to limit pathogen survival (Pickert et al., 2009; Zheng et al., 2008). This has been best demonstrated in the *C. rodentium* infection model, in which Rorγt ILC3 deficient mice rapidly succumb to infection, attributed to attenuated IL-22 signaling (Tumanov et al., 2011; Guo et al., 2014). Under homeostatic conditions, IL-22 signaling is inhibited by IL-22 binding protein (IL-22BP), a soluble receptor secreted by immature DCs (Martin et al., 2014). When tissue damage occurs, expression of IL-22BP is downregulated, allowing IL-22 exert its tissue repair functions (Martin et al., 2014). In a CAC model, IL-22BP deficient mice have accelerated tumor development (Huber et al., 2012). Most importantly, IL-22-driven STAT3 activation has been implicated in several mouse models of CRC including a bacterial-induced CRC mouse model, where depletion of ILC3 blocked the development of invasive CRC and neutralization of IL-22, to a greater extent than IL-17, resulted in less intestinal inflammation and reduced tumor burden (Kirchberger et al., 2013). However, the study did not address which sub-lineage of ILC3s were responsible for the tumor development. Other studies suggest that in the early stages of inflammation-associated CRC, IL-22 may protect against tumor development, while at later stages IL-22 evokes a pro-tumorigenic function (Huber et al., 2012). Our understanding of the source and function of IL-22 in CRC is really only just beginning to become clear.

6. Implications for the success and failures of cancer therapeutics

Pending the stage of CRC at the time of diagnosis, patients will undergo standard-of-care chemotherapeutic treatments. It is now appreciated that chemotherapy drastically alters the microbial environment (Roy and Trinchieri, 2017), which would indirectly alter the ILC and Th17 profiles of a patient. As a result of their location, ILCs would be the first population of cells to respond to chemotherapy induced changes to a microbial environment, in particular ILC3s, which would result in an increase in the presence of IL-17A and IL-22. NCR+ IL-22 producing ILC3 cells are essential to the proliferation of intestinal stem cells that express IL-22R (Lindemans et al., 2015), facilitating tissue repair and cancer growth, which one could predict would negate the intended function of a chemotherapeutic. Indeed, serum IL-22 levels correlate with chemoresistance in CRC patients, which was attributed to the induction of the IL-22 induced pro-survival activities of STAT3 (Wu et al., 2013; Wu et al., 2014). A similar scenario is emerging for IL-17, with expression levels shown to increase following Fluorouracil (5 FU) treatment, a standard of care chemotherapeutic in CRC, resulting in the activation of IL-17 mediated pro-survival pathways in colonic epithelial cells (Wang et al., 2014b). IL-17 also been shown to mediate resistance to anti-angiogenic therapies (Chung et al., 2013). Whether these observations relate solely to the innate response, or linger as a result of the adaptive response remain to be revealed. However, these observations warrant a better understanding of the innate and adaptive source of IL-17 and IL-22 following chemotherapeutic treatments. It is likely that their role in preventing bacterial infections, chronic inflammation and mediating repair of normal tissues following multiple rounds of chemotherapy will need to be weighed against their likelihood of promoting extrinsic resistance as reagents targeting these cytokines, and their associated transcription factors, are developed for clinical use.

7. Concluding remarks

Our understanding of the role of ILCs in the tumor microenvironment is only just beginning, with the relative contribution of ILC3s and Th17 cells to tumor progression not clear. ILCs are unique in that they do not need antigen sensing for their activation, and thus respond to environmental triggers more rapidly than T-cells. This distinctive feature also suggests that they may be the first to trigger the growth and progression of a tumor, which may be sustained by their adaptive T-cell counterparts. The tumor promoting functions shared by these cell populations are most likely related to cytokine secretion, which are amenable therapeutic targets. Thus, the success of anti-cytokine therapies alone or in combination with other treatment options will depend on our understanding of the timing of cytokine expression during tumor onset, progression, and standard-of-care therapeutic treatments.

Acknowledgements

The laboratory of TP is supported by Victorian State Government Operational Infrastructure Support and the National Health and Medical Research Council Australia (NHMRC) project grants APP1080498, and APP1098643, and Worldwide Cancer Research project grant no. 14-1197. PMN was supported by an Australian Postgraduate Scholarship and TP is a Victorian Cancer Agency Fellow, and a WEHI Centenary Fellow.

References

Bahri, R., Pateras, I.S., D'Orlando, O., Goyeneche-Patino, D.A., Campbell, M., Polansky, J.K., Sandig, H., Papaioannou, M., Evangelou, K., Foukas, P.G., Gorgoulis, V.G., Bulfone-Paus, S., 2015. IL-15 suppresses colitis-associated colon carcinogenesis by inducing antitumor immunity. Oncoimmunology 4, e1002721.

Beatty, G., Paterson, Y., 2001. IFN-gamma-dependent inhibition of tumor angiogenesis by tumor-infiltrating CD4+ T cells requires tumor responsiveness to IFN-gamma. J. Immunol. 166, 2276–2282.

Bernink, J.H., Peters, C.P., Munneke, M., te Velde, A.A., Meijer, S.L., Weijer, K., Hreggvidsdottir, H.S., Heinsbroek, S.E., Legrand, N., Buskens, C.J., Bemelman, W.A., Mjosberg, J.M., Spits, H., 2013. Human type 1 innate lymphoid cells accumulate in inflamed mucosal tissues. Nat. Immunol. 14, 221–229.

Bernink, J.H., Krabbendam, L., Germar, K., de Jong, E., Gronke, K., Kofoed-Nielsen, M., Munneke, J.M., Hazenberg, M.D., Villaudy, J., Buskens, C.J., Bemelman, W.A., Diefenbach, A., Blom, B., Spits, H., 2015. Interleukin-12 and −23 Control Plasticity of CD127(+) Group 1 and Group 3 Innate Lymphoid Cells in the Intestinal Lamina Propria. Immunity 43, 146–160.

Bie, Q., Zhang, P., Su, Z., Zheng, D., Ying, X., Wu, Y., Yang, H., Chen, D., Wang, S., Xu, H., 2014. Polarization of ILC2s in peripheral blood might contribute to immunosuppressive microenvironment in patients with gastric cancer. J. Immunol. Res. 2014, 923135.

Buonocore, S., Ahern, P.P., Uhlig, H.H., Ivanov, I.I., Littman, D.R., Maloy, K.J., Powrie, F., 2010. Innate lymphoid cells drive interleukin-23-dependent innate intestinal

pathology. Nature 464, 1371–1375.
Chae, W.J., Gibson, T.F., Zelterman, D., Hao, L., Henegariu, O., Bothwell, A.L., 2010. Ablation of IL-17A abrogates progression of spontaneous intestinal tumorigenesis. Proc. Natl. Acad. Sci. U. S. A. 107, 5540–5544.
Chan, I.H., Jain, R., Tessmer, M.S., Gorman, D., Mangadu, R., Sathe, M., Vives, F., Moon, C., Penaflor, E., Turner, S., Ayanoglu, G., Chang, C., Basham, B., Mumm, J.B., Pierce, R.H., Yearley, J.H., McClanahan, T.K., Phillips, J.H., Cua, D.J., Bowman, E.P., Kastelein, R.A., LaFace, D., 2014. Interleukin-23 is sufficient to induce rapid de novo gut tumorigenesis independent of carcinogens, through activation of innate lymphoid cells. Mucosal Immunol. 7, 842–856.
Chung, A.S., Wu, X., Zhuang, G., Ngu, H., Kasman, I., Zhang, J., Vernes, J.M., Jiang, Z., Meng, Y.G., Peale, F.V., Ouyang, W., Ferrara, N., 2013. An interleukin-17-mediated paracrine network promotes tumor resistance to anti-angiogenic therapy. Nat. Med. 19, 1114–1123.
Ciardiello, F., Kim, N., Saeki, T., Dono, R., Persico, M.G., Plowman, G.D., Garrigues, J., Radke, S., Todaro, G.J., Salomon, D.S., 1991. Differential expression of epidermal growth factor-related proteins in human colorectal tumors. Proc. Natl. Acad. Sci. U. S. A. 88, 7792–7796.
Dahlberg, C.I., Sarhan, D., Chrobok, M., Duru, A.D., Alici, E., 2015. Natural Killer Cell-Based Therapies Targeting Cancer: Possible Strategies to Gain and Sustain Anti-Tumor Activity. Front. Immunol. 6, 605.
Dejea, C., Wick, E., Sears, C.L., 2013. Bacterial oncogenesis in the colon. Future Microbiol. 8, 445–460.
Dhakal, M., Hardaway, J.C., Guloglu, F.B., Miller, M.M., Hoeman, C.M., Zaghouani, A.A., Wan, X., Rowland, L.M., Cascio, J.A., Sherman, M.P., Zaghouani, H., 2014. IL-13Ralpha1 is a surface marker for M2 macrophages influencing their differentiation and function. Eur. J. Immunol. 44, 842–855.
Di Stefano, A.B., Iovino, F., Lombardo, Y., Eterno, V., Hoger, T., Dieli, F., Stassi, G., Todaro, M., 2010. Survivin is regulated by interleukin-4 in colon cancer stem cells. J. Cell Physiol. 225, 555–561.
Djenidi, F., Adam, J., Goubar, A., Durgeau, A., Meurice, G., de Montpreville, V., Validire, P., Besse, B., Mami-Chouaib, F., 2015. CD8 + CD103+ tumor-infiltrating lymphocytes are tumor-specific tissue-resident memory T cells and a prognostic factor for survival in lung cancer patients. J. Immunol. 194, 3475–3486.
Eberl, G., Marmon, S., Sunshine, M.J., Rennert, P.D., Choi, Y., Littman, D.R., 2004. An essential function for the nuclear receptor RORgamma(t) in the generation of fetal lymphoid tissue inducer cells. Nat. Immunol. 5, 64–73.
Fuchs, A., Vermi, W., Lee, J.S., Lonardi, S., Gilfillan, S., Newberry, R.D., Cella, M., Colonna, M., 2013. Intraepithelial type 1 innate lymphoid cells are a unique subset of IL-12- and IL-15-responsive IFN-gamma-producing cells. Immunity 38, 769–781.
Gabrilovich, D.I., Nagaraj, S., 2009. Myeloid-derived suppressor cells as regulators of the immune system. Nat. Rev. Immunol. 9, 162–174.
Garcia-Diaz, A., Shin, D.S., Moreno, B.H., Saco, J., Escuin-Ordinas, H., Rodriguez, G.A., Zaretsky, J.M., Sun, L., Hugo, W., Wang, X., Parisi, G., Saus, C.P., Torrejon, D.Y., Graeber, T.G., Comin-Anduix, B., Hu-Lieskovan, S., Damoiseaux, R., Lo, R.S., Ribas, A., 2017. Interferon Receptor Signaling Pathways Regulating PD-L1 and PD-L2 Expression. Cell Rep. 19, 1189–1201.
Gasteiger, G., Fan, X., Dikiy, S., Lee, S.Y., Rudensky, A.Y., 2015. Tissue residency of innate lymphoid cells in lymphoid and nonlymphoid organs. Science 350, 981–985.
Georgoudaki, A.M., Prokopec, K.E., Boura, V.F., Hellqvist, E., Sohn, S., Ostling, J., Dahan, R., Harris, R.A., Rantalainen, M., Klevebring, D., Sund, M., Brage, S.E., Fuxe, J., Rolny, C., Li, F., Ravetch, J.V., Karlsson, M.C., 2016. Reprogramming Tumor-Associated Macrophages by Antibody Targeting Inhibits Cancer Progression and Metastasis. Cell Rep. 15, 2000–2011.
Geremia, A., Arancibia-Carcamo, C.V., Fleming, M.P., Rust, N., Singh, B., Mortensen, N.J., Travis, S.P., Powrie, F., 2011. IL-23-responsive innate lymphoid cells are increased in inflammatory bowel disease. J. Exp. Med. 208, 1127–1133.
Giacomin, P.R., Moy, R.H., Noti, M., Osborne, L.C., Siracusa, M.C., Alenghat, T., Liu, B., McCorkell, K.A., Troy, A.E., Rak, G.D., Hu, Y., May, M.J., Ma, H.L., Fouser, L.A., Sonnenberg, G.F., Artis, D., 2015. Epithelial-intrinsic IKKalpha expression regulates group 3 innate lymphoid cell responses and antibacterial immunity. J. Exp. Med. 212, 1513–1528.
Glatzer, T., Killig, M., Meisig, J., Ommert, I., Luetke-Eversloh, M., Babic, M., Paclik, D., Bluthgen, N., Seidl, R., Seifarth, C., Grone, J., Lenarz, M., Stolzel, K., Fugmann, D., Porgador, A., Hauser, A., Karlas, A., Romagnani, C., 2013. RORgammat(+) innate lymphoid cells acquire a proinflammatory program upon engagement of the activating receptor NKp44. Immunity 38, 1223–1235.
Grivennikov, S., Karin, E., Terzic, J., Mucida, D., Yu, G.Y., Vallabhapurapu, S., Scheller, J., Rose-John, S., Cheroutre, H., Eckmann, L., Karin, M., 2009. IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. Cancer Cell 15, 103–113.
Grivennikov, S.I., Greten, F.R., Karin, M., 2010. Immunity, inflammation, and cancer. Cell 140, 883–899.
Grivennikov, S.I., Wang, K., Mucida, D., Stewart, C.A., Schnabl, B., Jauch, D., Taniguchi, K., Yu, G.Y., Osterreicher, C.H., Hung, K.E., Datz, C., Feng, Y., Fearon, E.R., Oukka, M., Tessarollo, L., Coppola, V., Yarovinsky, F., Cheroutre, H., Eckmann, L., Trinchieri, G., Karin, M., 2012. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. Nature 491, 254–258.
Guo, X., Qiu, J., Tu, T., Yang, X., Deng, L., Anders, R.A., Zhou, L., Fu, Y.X., 2014. Induction of innate lymphoid cell-derived interleukin-22 by the transcription factor STAT3 mediates protection against intestinal infection. Immunity 40, 25–39.
Guzman, M.J., Shao, J., Sheng, H., 2013. Pro-neoplastic effects of amphiregulin in colorectal carcinogenesis. J. Gastrointest Cancer 44, 211–221.
Haabeth, O.A., Lorvik, K.B., Hammarstrom, C., Donaldson, I.M., Haraldsen, G., Bogen, B., Corthay, A., 2011. Inflammation driven by tumour-specific Th1 cells protects against B-cell cancer. Nat. Commun. 2, 240.
Hanahan, D., Weinberg, R.A., 2011. Hallmarks of cancer: the next generation. Cell 144, 646–674.
Hepworth, M.R., Monticelli, L.A., Fung, T.C., Ziegler, C.G., Grunberg, S., Sinha, R., Mantegazza, A.R., Ma, H.L., Crawford, A., Angelosanto, J.M., Wherry, E.J., Koni, P.A., Bushman, F.D., Elson, C.O., Eberl, G., Artis, D., Sonnenberg, G.F., 2013. Innate lymphoid cells regulate CD4+ T-cell responses to intestinal commensal bacteria. Nature 498, 113–117.
Hepworth, M.R., Fung, T.C., Masur, S.H., Kelsen, J.R., McConnell, F.M., Dubrot, J., Withers, D.R., Hugues, S., Farrar, M.A., Reith, W., Eberl, G., Baldassano, R.N., Laufer, T.M., Elson, C.O., Sonnenberg, G.F., 2015. Immune tolerance. Group 3 innate lymphoid cells mediate intestinal selection of commensal bacteria-specific CD4(+) T cells. Science 348, 1031–1035.
Hoepner, S., Loh, J.M., Riccadonna, C., Derouazi, M., Maroun, C.Y., Dietrich, P.Y., Walker, P.R., 2013. Synergy between CD8T cells and Th1 or Th2 polarised CD4T cells for adoptive immunotherapy of brain tumours. PLoS One 8, e63933.
Hoorweg, K., Peters, C.P., Cornelissen, F., Aparicio-Domingo, P., Papazian, N., Kazemier, G., Mjosberg, J.M., Spits, H., Cupedo, T., 2012. Functional differences between human NKp44(−) and NKp44(+) RORC(+) innate lymphoid Cells. Front. Immunol. 3, 72.
Hoyler, T., Klose, C.S., Souabni, A., Turqueti-Neves, A., Pfeifer, D., Rawlins, E.L., Voehringer, D., Busslinger, M., Diefenbach, A., 2012. The transcription factor GATA-3 controls cell fate and maintenance of type 2 innate lymphoid cells. Immunity 37, 634–648.
Huber, S., Gagliani, N., Zenewicz, L.A., Huber, F.J., Bosurgi, L., Hu, B., Hedl, M., Zhang, W., O'Connor Jr., W., Murphy, A.J., Valenzuela, D.M., Yancopoulos, G.D., Booth, C.J., Cho, J.H., Ouyang, W., Abraham, C., Flavell, R.A., 2012. IL-22BP is regulated by the inflammasome and modulates tumorigenesis in the intestine. Nature 491, 259–263.
Hughes, T., Becknell, B., Freud, A.G., McClory, S., Briercheck, E., Yu, J., Mao, C., Giovenzana, C., Nuovo, G., Wei, L., Zhang, X., Gavrilin, M.A., Wewers, M.D., Caligiuri, M.A., 2010. Interleukin-1beta selectively expands and sustains interleukin-22+ immature human natural killer cells in secondary lymphoid tissue. Immunity 32, 803–814.
Hughes, T., Briercheck, E.L., Freud, A.G., Trotta, R., McClory, S., Scoville, S.D., Keller, K., Deng, Y., Cole, J., Harrison, N., Mao, C., Zhang, J., Benson, D.M., Yu, J., Caligiuri, M.A., 2014. The transcription Factor AHR prevents the differentiation of a stage 3 innate lymphoid cell subset to natural killer cells. Cell Rep. 8, 150–162.
Hyun, Y.S., Han, D.S., Lee, A.R., Eun, C.S., Youn, J., Kim, H.Y., 2012. Role of IL-17A in the development of colitis-associated cancer. Carcinogenesis 33, 931–936.
Ingram, N., Northwood, E.L., Perry, S.L., Marston, G., Snowden, H., Taylor, J.C., Scott, N., Bishop, D.T., Coletta, P.L., Hull, M.A., 2013. Reduced type II interleukin-4 receptor signalling drives initiation, but not progression, of colorectal carcinogenesis: evidence from transgenic mouse models and human case-control epidemiological observations. Carcinogenesis 34, 2341–2349.
Ishigame, H., Kakuta, S., Nagai, T., Kadoki, M., Nambu, A., Komiyama, Y., Fujikado, N., Tanahashi, Y., Akitsu, A., Kotaki, H., Sudo, K., Nakae, S., Sasakawa, C., Iwakura, Y., 2009. Differential roles of interleukin-17A and −17F in host defense against mucoepithelial bacterial infection and allergic responses. Immunity 30, 108–119.
Ivanov, I.I., Frutos Rde, L., Manel, N., Yoshinaga, K., Rifkin, D.B., Sartor, R.B., Finlay, B.B., Littman, D.R., 2008. Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine. Cell Host Microbe 4, 337–349.
Jiang, R., Wang, H., Deng, L., Hou, J., Shi, R., Yao, M., Gao, Y., Yao, A., Wang, X., Yu, L., Sun, B., 2013. IL-22 is related to development of human colon cancer by activation of STAT3. BMC Cancer 13, 59.
Kao, C.Y., Chen, Y., Thai, P., Wachi, S., Huang, F., Kim, C., Harper, R.W., Wu, R., 2004. IL-17 markedly up-regulates beta-defensin-2 expression in human airway epithelium via JAK and NF-kappaB signaling pathways. J. Immunol. 173, 3482–3491.
Karvellas, C.J., Fedorak, R.N., Hanson, J., Wong, C.K., 2007. Increased risk of colorectal cancer in ulcerative colitis patients diagnosed after 40 years of age. Can. J. Gastroenterol. 21, 443–446.
Kim, E.R., Chang, D.K., 2014. Colorectal cancer in inflammatory bowel disease: the risk, pathogenesis, prevention and diagnosis. World J. Gastroenterol. 20, 9872–9881.
Kim, B.S., Siracusa, M.C., Saenz, S.A., Noti, M., Monticelli, L.A., Sonnenberg, G.F., Hepworth, M.R., Van Voorhees, A.S., Comeau, M.R., Artis, D., 2013. TSLP elicits IL-33-independent innate lymphoid cell responses to promote skin inflammation. Sci. Transl. Med. 5, 170ra116.
Kim, H.Y., Lee, H.J., Chang, Y.J., Pichavant, M., Shore, S.A., Fitzgerald, K.A., Iwakura, Y., Israel, E., Bolger, K., Faul, J., DeKruyff, R.H., Umetsu, D.T., 2014. Interleukin-17-producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity. Nat. Med. 20, 54–61.
Kim, M.H., Taparowsky, E.J., Kim, C.H., 2015. Retinoic Acid Differentially Regulates the Migration of Innate Lymphoid Cell Subsets to the Gut. Immunity 43, 107–119.
Kim, C.H., Hashimoto-Hill, S., Kim, M., 2016. Migration and Tissue Tropism of Innate Lymphoid Cells. Trends Immunol. 37, 68–79.
Kirchberger, S., Royston, D.J., Boulard, O., Thornton, E., Franchini, F., Szabady, R.L., Harrison, O., Powrie, F., 2013. Innate lymphoid cells sustain colon cancer through production of interleukin-22 in a mouse model. J. Exp. Med. 210, 917–931.
Klemm, F., Joyce, J.A., 2015. Microenvironmental regulation of therapeutic response in cancer. Trends Cell. Biol. 25, 198–213.
Klose, C.S., Artis, D., 2016. Innate lymphoid cells as regulators of immunity, inflammation and tissue homeostasis. Nat. Immunol. 17, 765–774.
Klose, C.S., Kiss, E.A., Schwierzeck, V., Ebert, K., Hoyler, T., d'Hargues, Y., Goppert, N., Croxford, A.L., Waisman, A., Tanriver, Y., Diefenbach, A., 2013. A T-bet gradient controls the fate and function of CCR6-RORgammat+ innate lymphoid cells. Nature 494, 261–265.
Klose, C.S.N., Flach, M., Mohle, L., Rogell, L., Hoyler, T., Ebert, K., Fabiunke, C., Pfeifer,

D., Sexl, V., Fonseca-Pereira, D., Domingues, R.G., Veiga-Fernandes, H., Arnold, S.J., Busslinger, M., Dunay, I.R., Tanriver, Y., Diefenbach, A., 2014. Differentiation of type 1 ILCs from a common progenitor to all helper-like innate lymphoid cell lineages. Cell 157, 340–356.
Kryczek, I., Banerjee, M., Cheng, P., Vatan, L., Szeliga, W., Wei, S., Huang, E., Finlayson, E., Simeone, D., Welling, T.H., Chang, A., Coukos, G., Liu, R., Zou, W., 2009. Phenotype, distribution, generation, and functional and clinical relevance of Th17 cells in the human tumor environments. Blood 114, 1141–1149.
Kuniyasu, H., Oue, N., Nakae, D., Tsutsumi, M., Denda, A., Tsujiuchi, T., Yokozaki, H., Yasui, W., 2001. Interleukin-15 expression is associated with malignant potential in colon cancer cells. Pathobiology 69, 86–95.
Kvedaraite, E., Lourda, M., Idestrom, M., Chen, P., Olsson-Akefeldt, S., Forkel, M., Gavhed, D., Lindforss, U., Mjosberg, J., Henter, J.I., Svensson, M., 2016. Tissue-infiltrating neutrophils represent the main source of IL-23 in the colon of patients with IBD. Gut 65, 1632–1641.
Laan, M., Cui, Z.H., Hoshino, H., Lotvall, J., Sjostrand, M., Gruenert, D.C., Skoogh, B.E., Linden, A., 1999. Neutrophil recruitment by human IL-17 via C-X-C chemokine release in the airways. J. Immunol. 162, 2347–2352.
Langowski, J.L., Zhang, X., Wu, L., Mattson, J.D., Chen, T., Smith, K., Basham, B., McClanahan, T., Kastelein, R.A., Oft, M., 2006. IL-23 promotes tumour incidence and growth. Nature 442, 461–465.
Levin, A.D., Wildenberg, M.E., van den Brink, G.R., 2016. Mechanism of Action of Anti-TNF Therapy in Inflammatory Bowel Disease. J. Crohns Colitis 10, 989–997.
Liang, S.C., Tan, X.Y., Luxenberg, D.P., Karim, R., Dunussi-Joannopoulos, K., Collins, M., Fouser, L.A., 2006. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. J. Exp. Med. 203, 2271–2279.
Lindemans, C.A., Calafiore, M., Mertelsmann, A.M., O'Connor, M.H., Dudakov, J.A., Jenq, R.R., Velardi, E., Young, L.F., Smith, O.M., Lawrence, G., Ivanov, J.A., Fu, Y.Y., Takashima, S., Hua, G., Martin, M.L., O'Rourke, K.P., Lo, Y.H., Mokry, M., Romera-Hernandez, M., Cupedo, T., Dow, L., Nieuwenhuis, E.E., Shroyer, N.F., Liu, C., Kolesnick, R., van den Brink, M.R.M., Hanash, A.M., 2015. Interleukin-22 promotes intestinal-stem-cell-mediated epithelial regeneration. Nature 528, 560–564.
Longman, R.S., Diehl, G.E., Victorio, D.A., Huh, J.R., Galan, C., Miraldi, E.R., Swaminath, A., Bonneau, R., Scherl, E.J., Littman, D.R., 2014. CX(3)CR1(+) mononuclear phagocytes support colitis-associated innate lymphoid cell production of IL-22. J. Exp. Med. 211, 1571–1583.
Martin, J.C., Beriou, G., Heslan, M., Chauvin, C., Utriainen, L., Aumeunier, A., Scott, C.L., Mowat, A., Cerovic, V., Houston, S.A., Leboeuf, M., Hubert, F.X., Hemont, C., Merad, M., Milling, S., Josien, R., 2014. Interleukin-22 binding protein (IL-22BP) is constitutively expressed by a subset of conventional dendritic cells and is strongly induced by retinoic acid. Mucosal Immunol. 7, 101–113.
Martini, M., Testi, M.G., Pasetto, M., Picchio, M.C., Innamorati, G., Mazzocco, M., Ugel, S., Cingarlini, S., Bronte, V., Zanovello, P., Krampera, M., Mosna, F., Cestari, T., Riviera, A.P., Brutti, N., Barbieri, O., Matera, L., Tridente, G., Colombatti, M., Sartoris, S., 2010. IFN-gamma-mediated upmodulation of MHC class I expression activates tumor-specific immune response in a mouse model of prostate cancer. Vaccine 28, 3548–3557.
Mjosberg, J.M., Trifari, S., Crellin, N.K., Peters, C.P., van Drunen, C.M., Piet, B., Fokkens, W.J., Cupedo, T., Spits, H., 2011. Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CRTH2 and CD161. Nat. Immunol. 12, 1055–1062.
Monticelli, L.A., Osborne, L.C., Noti, M., Tran, S.V., Zaiss, D.M., Artis, D., 2015. IL-33 promotes an innate immune pathway of intestinal tissue protection dependent on amphiregulin-EGFR interactions. Proc. Natl. Acad. Sci. U. S. A. 112, 10762–10767.
Mortha, A., Chudnovskiy, A., Hashimoto, D., Bogunovic, M., Spencer, S.P., Belkaid, Y., Merad, M., 2014. Microbiota-dependent crosstalk between macrophages and ILC3 promotes intestinal homeostasis. Science 343, 1249288.
Neill, D.R., Wong, S.H., Bellosi, A., Flynn, R.J., Daly, M., Langford, T.K., Bucks, C., Kane, C.M., Fallon, P.G., Pannell, R., Jolin, H.E., McKenzie, A.N., 2010. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. Nature 464, 1367–1370.
O'Connell, J., Bennett, M.W., Nally, K., O'Sullivan, G.C., Collins, J.K., Shanahan, F., 2000. Interferon-gamma sensitizes colonic epithelial cell lines to physiological and therapeutic inducers of colonocyte apoptosis. J. Cell Physiol. 185, 331–338.
Osawa, E., Nakajima, A., Fujisawa, T., Kawamura, Y.I., Toyama-Sorimachi, N., Nakagama, H., Dohi, T., 2006. Predominant T helper type 2-inflammatory responses promote murine colon cancers. Int. J. Cancer 118, 2232–2236.
Palucka, K., Banchereau, J., 2012. Cancer immunotherapy via dendritic cells. Nat. Rev. Cancer 12, 265–277.
Pardoll, D.M., 2012. The blockade of immune checkpoints in cancer immunotherapy. Nat. Rev. Cancer 12, 252–264.
Pearson, C., Thornton, E.E., McKenzie, B., Schaupp, A.L., Huskens, N., Griseri, T., West, N., Tung, S., Seddon, B.P., Uhlig, H.H., Powrie, F., 2016. ILC3 GM-CSF production and mobilisation orchestrate acute intestinal inflammation. Elife 5, e10066.
Pham, T.A., Clare, S., Goulding, D., Arasteh, J.M., Stares, M.D., Browne, H.P., Keane, J.A., Page, A.J., Kumasaka, N., Kane, L., Mottram, L., Harcourt, K., Hale, C., Arends, M.J., Gaffney, D.J., Sanger Mouse Genetics P, Dougan, G., Lawley, T.D., 2014. Epithelial IL-22RA1-mediated fucosylation promotes intestinal colonization resistance to an opportunistic pathogen. Cell Host Microbe 16, 504–516.
Pickert, G., Neufert, C., Leppkes, M., Zheng, Y., Wittkopf, N., Warntjen, M., Lehr, H.A., Hirth, S., Weigmann, B., Wirtz, S., Ouyang, W., Neurath, M.F., Becker, C., 2009. STAT3 links IL-22 signaling in intestinal epithelial cells to mucosal wound healing. J. Exp. Med. 206, 1465–1472.
Popivanova, B.K., Kitamura, K., Wu, Y., Kondo, T., Kagaya, T., Kaneko, S., Oshima, M., Fujii, C., Mukaida, N., 2008. Blocking TNF-alpha in mice reduces colorectal carcinogenesis associated with chronic colitis. J. Clin. Invest. 118, 560–570.
Qiu, J., Zhou, L., 2013. Aryl hydrocarbon receptor promotes RORgammat(+) group 3 ILCs and controls intestinal immunity and inflammation. Semin. Immunopathol. 35, 657–670.
Qiu, J., Heller, J.J., Guo, X., Chen, Z.M., Fish, K., Fu, Y.X., Zhou, L., 2012. The aryl hydrocarbon receptor regulates gut immunity through modulation of innate lymphoid cells. Immunity 36, 92–104.
Reiter, Z., 1993. Interferon?a major regulator of natural killer cell-mediated cytotoxicity. J. Interferon Res. 13, 247–257.
Robinette, M.L., Fuchs, A., Cortez, V.S., Lee, J.S., Wang, Y., Durum, S.K., Gilfillan, S., Colonna, M., Immunological Genome, C., 2015. Transcriptional programs define molecular characteristics of innate lymphoid cell classes and subsets. Nat. Immunol. 16, 306–317.
Robinette, M.L., Bando, J.K., Song, W., Ulland, T.K., Gilfillan, S., Colonna, M., 2017. IL-15 sustains IL-7R-independent ILC2 and ILC3 development. Nat. Commun. 8, 14601.
Roy, S., Trinchieri, G., 2017. Microbiota: a key orchestrator of cancer therapy. Nat. Rev. Cancer 17, 271–285.
Sanos, S.L., Bui, V.L., Mortha, A., Oberle, K., Heners, C., Johner, C., Diefenbach, A., 2009. RORgammat and commensal microflora are required for the differentiation of mucosal interleukin 22-producing NKp46+ cells. Nat. Immunol. 10, 83–91.
Satoh-Takayama, N., Vosshenrich, C.A., Lesjean-Pottier, S., Sawa, S., Lochner, M., Rattis, F., Mention, J.J., Thiam, K., Cerf-Bensussan, N., Mandelboim, O., Eberl, G., Di Santo, J.P., 2008. Microbial flora drives interleukin 22 production in intestinal NKp46+ cells that provide innate mucosal immune defense. Immunity 29, 958–970.
Satoh-Takayama, N., Serafini, N., Verrier, T., Rekiki, A., Renauld, J.C., Frankel, G., Di Santo, J.P., 2014. The chemokine receptor CXCR6 controls the functional topography of interleukin-22 producing intestinal innate lymphoid cells. Immunity 41, 776–788.
Sawa, S., Lochner, M., Satoh-Takayama, N., Dulauroy, S., Berard, M., Kleinschek, M., Cua, D., Di Santo, J.P., Eberl, G., 2011. RORgammat+ innate lymphoid cells regulate intestinal homeostasis by integrating negative signals from the symbiotic microbiota. Nat. Immunol. 12, 320–326.
Schmitt, M.J., Philippidou, D., Reinsbach, S.E., Margue, C., Wienecke-Baldacchino, A., Nashan, D., Behrmann, I., Kreis, S., 2012. Interferon-gamma-induced activation of Signal Transducer and Activator of Transcription 1 (STAT1) up-regulates the tumor suppressing microRNA-29 family in melanoma cells. Cell Commun. Signal. 10, 41.
Spits, H., Cupedo, T., 2012. Innate lymphoid cells: emerging insights in development, lineage relationships, and function. Annu. Rev. Immunol. 30, 647–675.
Spits, H., Artis, D., Colonna, M., Diefenbach, A., Di Santo, J.P., Eberl, G., Koyasu, S., Locksley, R.M., McKenzie, A.N., Mebius, R.E., Powrie, F., Vivier, E., 2013. Innate lymphoid cells?a proposal for uniform nomenclature. Nat. Rev. Immunol. 13, 145–149.
Spits, H., Bernink, J.H., Lanier, L., 2016. NK cells and type 1 innate lymphoid cells: partners in host defense. Nat. Immunol. 17, 758–764.
Tachiiri, A., Imamura, R., Wang, Y., Fukui, M., Umemura, M., Suda, T., 2003. Genomic structure and inducible expression of the IL-22 receptor alpha chain in mice. Genes Immun. 4, 153–159.
Thompson, C.L., Plummer, S.J., Tucker, T.C., Casey, G., Li, L., 2010. Interleukin-22 genetic polymorphisms and risk of colon cancer. Cancer Causes Control 21, 1165–1170.
Tosolini, M., Kirilovsky, A., Mlecnik, B., Fredriksen, T., Mauger, S., Bindea, G., Berger, A., Bruneval, P., Fridman, W.H., Pages, F., Galon, J., 2011. Clinical impact of different classes of infiltrating T cytotoxic and helper cells (Th1, th2, treg, th17) in patients with colorectal cancer. Cancer Res. 71, 1263–1271.
Tumanov, A.V., Koroleva, E.P., Guo, X., Wang, Y., Kruglov, A., Nedospasov, S., Fu, Y.X., 2011. Lymphotoxin controls the IL-22 protection pathway in gut innate lymphoid cells during mucosal pathogen challenge. Cell Host Microbe 10, 44–53.
Villeneuve, J., Tremblay, P., Vallieres, L., 2005. Tumor necrosis factor reduces brain tumor growth by enhancing macrophage recruitment and microcyst formation. Cancer Res. 65, 3928–3936.
Vivier, E., Tomasello, E., Baratin, M., Walzer, T., Ugolini, S., 2008. Functions of natural killer cells. Nat. Immunol. 9, 503–510.
Vonarbourg, C., Mortha, A., Bui, V.L., Hernandez, P.P., Kiss, E.A., Hoyler, T., Flach, M., Bengsch, B., Thimme, R., Holscher, C., Honig, M., Pannicke, U., Schwarz, K., Ware, C.F., Finke, D., Diefenbach, A., 2010. Regulated expression of nuclear receptor RORgammat confers distinct functional fates to NK cell receptor-expressing RORgammat(+) innate lymphocytes. Immunity 33, 736–751.
von Burg, N., Chappaz, S., Baerenwaldt, A., Horvath, E., Bose Dasgupta, S., Ashok, D., Pieters, J., Tacchini-Cottier, F., Rolink, A., Acha-Orbea, H., Finke, D., 2014. Activated group 3 innate lymphoid cells promote T-cell-mediated immune responses. Proc. Natl. Acad. Sci. U. S. A. 111, 12835–12840.
von Moltke, J., Ji, M., Liang, H.E., Locksley, R.M., 2016. Tuft-cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit. Nature 529, 221–225.
Walker, J.A., McKenzie, A.N., 2013. Development and function of group 2 innate lymphoid cells. Curr. Opin. Immunol. 25, 148–155.
Wang, Y., Han, G., Wang, K., Liu, G., Wang, R., Xiao, H., Li, X., Hou, C., Shen, B., Guo, R., Li, Y., Chen, G., 2014a. Tumor-derived GM-CSF promotes inflammatory colon carcinogenesis via stimulating epithelial release of VEGF. Cancer Res. 74, 716–726.
Wang, K., Kim, M.K., Di Caro, G., Wong, J., Shalapour, S., Wan, J., Zhang, W., Zhong, Z., Sanchez-Lopez, E., Wu, L.W., Taniguchi, K., Feng, Y., Fearon, E., Grivennikov, S.I., Karin, M., 2014b. Interleukin-17 receptor a signaling in transformed enterocytes promotes early colorectal tumorigenesis. Immunity 41, 1052–1063.
Wang, L., Wang, Y., Song, Z., Chu, J., Qu, X., 2015. Deficiency of interferon-gamma or its receptor promotes colorectal cancer development. J. Interferon Cytokine Res. 35, 273–280.
Whitmire, J.K., Tan, J.T., Whitton, J.L., 2005. Interferon-gamma acts directly on CD8+ T cells to increase their abundance during virus infection. J. Exp. Med. 201, 1053–1059.

Wong, S.H., Walker, J.A., Jolin, H.E., Drynan, L.F., Hams, E., Camelo, A., Barlow, J.L., Neill, D.R., Panova, V., Koch, U., Radtke, F., Hardman, C.S., Hwang, Y.Y., Fallon, P.G., McKenzie, A.N., 2012. Transcription factor RORalpha is critical for nuocyte development. Nat. Immunol. 13, 229–236.

Wu, S., Rhee, K.J., Albesiano, E., Rabizadeh, S., Wu, X., Yen, H.R., Huso, D.L., Brancati, F.L., Wick, E., McAllister, F., Housseau, F., Pardoll, D.M., Sears, C.L., 2009. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nat. Med. 15, 1016–1022.

Wu, T., Cui, L., Liang, Z., Liu, C., Liu, Y., Li, J., 2013. Elevated serum IL-22 levels correlate with chemoresistant condition of colorectal cancer. Clin. Immunol. 147, 38–39.

Wu, T., Wang, Z., Liu, Y., Mei, Z., Wang, G., Liang, Z., Cui, A., Hu, X., Cui, L., Yang, Y., Liu, C.Y., 2014. Interleukin 22 protects colorectal cancer cells from chemotherapy by activating the STAT3 pathway and inducing autocrine expression of interleukin 8. Clin. Immunol. 154, 116–126.

Yang, Q., Saenz, S.A., Zlotoff, D.A., Artis, D., Bhandoola, A., 2011. Cutting edge: Natural helper cells derive from lymphoid progenitors. J. Immunol. 187, 5505–5509.

Yokota, Y., Mansouri, A., Mori, S., Sugawara, S., Adachi, S., Nishikawa, S., Gruss, P., 1999. Development of peripheral lymphoid organs and natural killer cells depends on the helix-loop-helix inhibitor Id2. Nature 397, 702–706.

Yue, W., Lin, Y., Yang, X., Li, B., Liu, J., He, R., 2016. Thymic stromal lymphopoietin (TSLP) inhibits human colon tumor growth by promoting apoptosis of tumor cells. Oncotarget 7, 16840–16854.

Zelante, T., Iannitti, R.G., Cunha, C., De Luca, A., Giovannini, G., Pieraccini, G., Zecchi, R., D'Angelo, C., Massi-Benedetti, C., Fallarino, F., Carvalho, A., Puccetti, P., Romani, L., 2013. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. Immunity 39, 372–385.

Zhang, K., Xu, X., Pasha, M.A., Siebel, C.W., Costello, A., Haczku, A., MacNamara, K., Liang, T., Zhu, J., Bhandoola, A., Maillard, I., Yang, Q., 2017. Cutting Edge Notch Signaling Promotes the Plasticity of Group-2 Innate Lymphoid Cells. J. Immunol. 198, 1798–1803.

Zheng, Y.M., Li, X., Zhao, H.Y., Zhao, J.Y., 2008. Effect of matrine and oxymatrine on proliferation and expression of Stat3 and Stat5 in SMMC-7721 cell line. Zhongguo Zhong Yao Za Zhi 33, 2234–2237.

Zhou, R., Qian, S., Gu, X., Chen, Z., Xiang, J., 2013. Interleukin-13 and its receptors in colorectal cancer (Review). Biomed. Rep. 1, 687–690.