How CD4+ T-cell help shapes functional and dysfunctional CD8+ T-cell differentiation

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Chapter 6

The importance of type I interferon in orchestrating the cytotoxic T-cell response to cancer

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Abstract

Both type I interferon (IFN-I) and $CD4^+$ T-cell help are required to generate effective $CD8^+$ T-cell responses to cancer. We here outline based on existing literature how IFN-I signaling and $CD4^+$ T-cell help are connected. Both impact on the functional state of dendritic cells (DCs), particularly conventional (c)DC1. The cDC1s are critical for crosspresentation of cell-associated antigens and for delivery of $CD4^+$ T-cell help for cytotoxic T-lymphocyte (CTL) effector and memory differentiation. In infection, production of IFN-I is prompted by pathogen-associated molecular patterns (PAMPs), while in cancer it relies on danger-associated molecular patterns (DAMPs). IFN-I production by tumor cells and pDCs in the tumor micro-environment (TME) is often limited. IFN-I signals increase the ability of migratory cDC1 and cDC2 to transport tumor antigens to tumor-draining lymph nodes (tdLNs). IFN-I also enables cDC1 to form and sustain the platform for help delivery by stimulating the production of chemokines that attract $CD4^+$ and $CD8^+$ T cells. IFN-I promotes delivery of help in concert with CD40 signals by additive and synergistic impact on cross-presentation and provision of critical costimulatory and cytokine signals for CTL effector and memory differentiation. The scenario of $CD4^+$ T-cell help therefore depends on IFN-I signaling. This scenario can play out in tdLNs as well as in the TME, thereby contributing to the cancer immunity cycle. The collective observations may explain why both IFN-I and $CD4^+$ T-cell help signatures in the TME correlate with good prognosis and response to PD-1 targeting immunotherapy in human cancer. They also may explain why a variety of tumor types in which IFN-I signaling is attenuated, remain devoid of functional CTLs.

Introduction

Early studies in mice identified that type I and -II interferon (IFN) contribute to tumor rejection[1,2]. In agreement, the "inflamed" or "hot" tumor micro-environment (TME) in mouse melanoma, qualified by presence of $CD8^+$ T cells in the tumor core, had an IFN-associated transcriptional profile[3]. In human, histology identified the inflamed TME with presence of $CD8^+$ T cells in many cancer types associated with better prognosis[4]. $CD8^+$ T cells play a central role in anti-tumor immunity because they can recognize and kill virtually all cell types upon recognition of antigens in the context of major histocompatibility complex I (MHC-I) molecules. Immunogenic tumors can spontaneously raise tumor-specific cytotoxic T lymphocyte (CTL) responses that are initiated by migratory dendritic cells (DCs) that bring tumor antigens to tumor-draining lymph nodes (tdLNs). $CD4^+$ helper T cells recognize antigens in context of MHC-II primarily on professional antigen-presenting cells (APCs) and have immunomodulatory roles. While $CD4^+$ T cells therefore generally do not play a direct role in elimination of tumor cells, they are critical for optimal differentiation of $CD8^+$ T cells into primary effector and effector memory CTLs.

Until recently, the conventional (c)DC1 was thought to be essential for anti-tumor immunity mainly due to its optimal capacity to process and cross-present tumor antigens. However, the cDC1 also performs a unique function among other DC types in relaying $CD4^+$ T-cell help for the CTL response[5,6]. For optimal activation and maturation of cDC1s, both IFN-I and help signals from $CD4^+$ T cells are essential. Early studies have demonstrated that IFN-I production by host hematopoietic cells[1] and IFN-I signaling into cDC1s[7,8] are critical for spontaneous CTL priming against immunogenic tumors. IFN-I signaling optimizes cDC1s to support tumor-specific CTL responses by multiple mechanisms (reviewed in[9,10]). Since these mechanisms are also activated by $CD4^+$ T-cell help, help was originally proposed as an amplification signal of the innate IFN-I stimulus[11]. In this review, we provide an update on the mechanisms that connect IFN-I signaling with $CD4^+$ T-cell help, and propose a model explaining how lack of IFN-I signals in tumors may contribute to failed CTL-based tumor control.

CTL priming, role of cDCs and $CD4^+$ T-cell help

CTL priming in LNs

The cDCs comprise two lineages, namely cDC1 ($XCR1^+$/$CD103^+$) and cDC2 ($CD11b^+$/$SIRP\alpha^+$)[12]. In both mouse and human, cDC1 are discerned from cDC2 by cell surface markers XCR1 and Clec9A. In the mouse, cDC2 are commonly defined by cell surface markers CD11b/SIRPα and in human by CD11c/CD1c[13,14]. Each lineage is subdivided into migratory and lymph-node resident populations. After collection of antigens and activation in the TME, cDCs rely on chemokine receptor CCR7 for migration to tdLN[15]. Early *in vivo* experiments showed that cDC1s are more

efficient than cDC2s in antigen cross-presentation, i.e. loading exogenous antigens into MHC-I molecules and presenting them to CD8$^+$ T cells[16]. In agreement with this unique function of cDC1s, they proved to be critical for tumor control in mouse models[17,18]. cDC2s are reportedly more prone to stimulate CD4$^+$ T cells[19,20].

When cDCs encounter infected or damaged cells in peripheral tissues, they can be activated via multiple types of pathogen- or "danger" associated molecular patterns (PAMPs or DAMPs) that can bind to a variety of plasma membrane, endosomal and cytoplasmic sensors, that we collectively call pattern recognition receptors (PRRs). Activated migratory cDC have optimized antigen presentation, as well as expression of costimulatory ligands including CD80/86 and CD70 and make specific cytokines including IL-12 or IL-15 that collectively induce initial T-cell activation and effector differentiation. According to intravital imaging of the murine immune response to virus infection, the first step of CD8$^+$ and CD4$^+$ T-cell priming occurs in spatially segregated regions of the lymph node (LN) by migratory cDCs[21–23]. In this initial activation step, CD4$^+$ T cells recognize with their T-cell receptor (TCR) antigen presented in MHC-II on cDC2s, while CD8$^+$ T cells recognize antigen in the context of MHC-I on cDC1s.

CD4$^+$ T-cell help for the CTL response

In what we have termed the second step of T-cell priming, CD4$^+$ T cells help CD8$^+$ T cells to become competent cytotoxic effector- and effector-memory cells[24]. The capacity of cDC1s to present antigens in both MHC-I and MHC-II enables them to act as a bridge between CD8$^+$ and CD4$^+$ T cells[6,21,22]. In mice, help delivery has been shown to be performed by migratory cDC1s[5], or by LN-resident (CD8a$^+$) cDC1s that can receive antigen from migratory DCs via synaptic transfer[22,25]. Using mice lacking MHC-II on cDC1s, it was proven that help delivery relies on cDC1s and contributes to optimal priming of CD8$^+$ and CD4$^+$ T cells[5]. In this second step of priming, not PRRs, but CD4$^+$ T cells activate the cDC1. Earlier, CD4$^+$ T cells were shown to activate cDCs via CD40 ligand (L) that is expressed on upon TCR stimulation and engages CD40 on the cDC[26–28]. CD40 signaling into DCs induces the production of cytokines IL-12 and IL-15[29,30], which both promote CTL differentiation [31,32]. CD40 signaling also upregulates co-stimulatory molecules CD80, CD86 and CD70 on cDC, which engage costimulatory receptors CD28 and CD27 on the CD8$^+$ T-cell[33,34]. Recently, the cDC1 in both mouse and human was shown to be the specific responder to these CD40 signals downstream of CD4$^+$ T-cell help[6,35] (Figure 1). The collective input of CD4$^+$ T-cell help into the cDC1, also termed "licensing", induces gene expression programs in cDC1s[6,35,36] that promote CTL effector and memory differentiation by multiple mechanisms[37,38]. In addition, IL-21 produced by CD4$^+$ T cells plays a role in sustaining CD8$^+$ T-cell effector functions in mouse models of chronic infection [39–41], but this mechanism likely takes place after initial priming. Without "help" signals, clonal expansion of primed T cells is limited and effector and memory differentiation of CD8$^+$ T cells is incomplete[37,38]. Helpless CD8$^+$ T cells have limited cytotoxicity and express diverse coinhibitory receptors such as PD-1 and BTLA that impede their function[37,42].

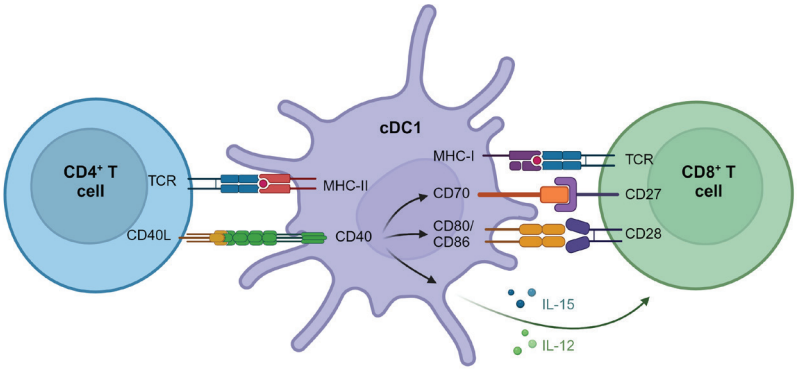

Figure 1. Pathways underlying CD4⁺ T-cell help delivery to CD8⁺ T cells during priming. Upon antigen recognition via the TCR, CD40L is upregulated on the activated CD4⁺ T-cell and binds the CD40 on the cDC1.These interactions promote antigen cross-presentation on cDC1 and production of cytokines such as IL-12 and IL-15, which support the differentiation of CD8⁺ T cells into effector CTLs. Additionally, cDC1s upregulate co-stimulatory ligands CD80/86 and CD70, which bind to respectively CD28 and CD27 on the CD8⁺ T cell. The combined signals delivered during CD4⁺ T- cell help result in the priming of optimally differentiated, 'helped' CTLs [24]. cDC1: conventional dendritic cell type I; CTL: cytotoxic T lymphocyte; MHC: major histocompatibility complex; TCR: T-cell receptor.

Spatial aspects of T-cell priming

Optimal signal exchange between players in CD4⁺ T-cell help delivery requires their proximal localization in the LN, which is regulated by chemokines. In settings where DCs are not infected, such as in cancer, initial activation of murine CD8⁺ T cells depends on cross-presentation by migratory or resident cDC1s, which are located in the LN paracortex[22,23,25,43]. In vaccination and infection mouse models, CCR5 and CXCR3 chemokine gradients were shown to attract initially activated CD8⁺ T cells from the paracortex into the interfollicular region (IFR) of the LN, which likely represents the secondary priming site[44]. The CXCR3-dependent migration of CD4⁺ T cells into the IFR was also shown to be essential for T helper (h)1 differentiation in response to viral infection and vaccination[45], indicating that interactions at the secondary priming site contribute to CD4⁺ T-cell priming and effector differentiation as well.

CTL priming in cancer

Stem-like and exhausted CD8⁺ T cells

The generation of an effective CTL response against cancer is often impaired, resulting in tumor progression. It may be that no CTL response to the cancer is initiated, or that the CTL response is ineffective. Regularly, dysfunctional or exhausted CD8⁺ T cells are found within the TME, characterized by high expression of inhibitory receptors and impaired proliferation and effector function[46]. Initially, it was thought that exhausted CD8⁺ T cells stem from previously active effector cells that become exhausted due to chronic antigen stimulation. However, various studies

both in mouse and human have shown that exhausted CD8$^+$ T cells instead derive from PD-1$^+$ TCF-1$^+$ progenitor exhausted (Tpex) or 'stem-like' CD8$^+$ T cells, which are poorly differentiated, 'predysfunctional' cells that arise early after tumorigenesis. While some stem-like cells can be maintained in the tdLN or specific intratumoral niches, chronic antigen stimulation in the TME drives the progression of stem-like cells into exhausted T cells[47,48]. In both mouse and human, the CD8$^+$ T-cell differentiation trajectory from stem-like to terminally exhausted is described as a spectrum which consists of different subpopulations of exhausted cells, including early effector-like and intermediate or transitional exhausted populations which still have some cytolytic capacity[49–52]. In mouse tumor models, stem-like CD8$^+$ T cells in the tdLN display a more memory-like functional state than those in the TME[53,54], and are suggested to be bona-fide memory cells, which could maintain a memory phenotype when shielded from antigen exposure[50,54].

Help delivery in cancer

Fewer studies have focused on the process of CD4$^+$ T-cell help delivery in the context of a tumor compared to viral infection, but it is clear that the cDC1 is responsible for help delivery to tumor-specific CD8$^+$ T cells[5,6]. In a mouse tumor model, it has been suggested that the initial priming of both CD4$^+$ and CD8$^+$ T cells takes place on cDC1[5]. This indicates the importance of cDC1-CD4$^+$ T-cell interactions for the CD4$^+$ T-cell response, but this study did not rule out initial CD4$^+$ T-cell activation by cDC2s.

While initial priming of tumor-specific CD8$^+$ T cells depends on their activation in the tdLN, increasing evidence supports the idea that help delivery may also occur in the TME. In a pan-cancer analysis of 16 human carcinoma types, co-localization of CD8$^+$ T cells, CD4$^+$ T cells and cDC1s within the TME was observed in a subset of tumor samples[55]. In such tumors, local help delivery may take place, according to the identification of the "helped" cDC1 signature in these tumors[6]. Additionally, intratumoral so-called 'triads' of DC, CD4$^+$ Th cells, and CD8$^+$ T cells, which likely represent CD4$^+$ T-cell help delivery, were associated with better response to ICB treatment in hepatocellular carcinoma patients[56]. Also larger, more complex immune structures in close localization to the tumor, so-called tertiary lymphoid structures (TLS), where DCs and T cells colocalize, have been associated with better prognosis and response to ICB therapy (reviewed by[57,58]).

Based on transcriptomic analyses of the predysfunctional / stem-like CD8$^+$ T-cell population in cancer and supported by literature, our group proposed a new model arguing that stem-like cells equal 'helpless' cells, generated as a result of priming in the absence of CD4$^+$ T-cell help[59]. Helpless CD8$^+$ T cells have not received all the required signals to complete their CTL effector differentiation, but instead are arrested in the PD-1$^+$TCF-1$^+$ stem-like state. Our model proposes that in the absence of 'helped' effector CTLs, cellular sources of antigen are insufficiently removed, leading to continuous antigen stimulation of the stem-like population which eventually drives their conversion into exhausted cells. Thus, helpless priming may be an important underlying mechanism for the occurrence of stem-like and exhausted CD8$^+$ T cells in cancer.

Help and IFN-I signals

Not only in cancer, but also in virus infection, IFN-I has been identified as key signal for CTL responses, which impinges on the functional state of cDC1s[60]. IFN-I signaling into cDC1s, as well as delivery of $CD4^+$ T-cell help signals to cDC1 are decisive for the CTL response to cancer. In virus infection models, $CD4^+$ T-cell help signals were suggested to amplify IFN-I signals in cDC1 licensing[11], but recently gene expression studies have led to an alternative model of signal integration[36]. Recently, human $CD4^+$ T cells were shown to deliver IFNb to the cDC1 during the "licensing" process, which acted in a partially non-redundant manner with CD40 ligand to optimize CTL priming *in vitro*[61]. These data explain the unique role of the $CD4^+$ T-cell help process in optimization of CTL responses. Below, we will describe that IFN-I plays a key role in CTL priming to cancer, not only for initial DC activation but also via orchestrating the platform for $CD4^+$ T-cell help delivery and making additive and synergistic contributions to cDC1 licensing.

Type I IFN production and signaling

IFN-I induction

The IFN-I family comprises as major species one IFNb protein produced by many cell types and multiple homologous IFNα proteins produced primarily by hematopoietic cells[62]. While most cell types can produce IFNβ, hematopoietic cells and in particular pDCs produce also IFNα. A primary role of IFN-I signaling is to provoke antiviral states in infected and neighboring cells and to limit their proliferation. However, IFN-I also has a multitude of immunomodulatory roles[63], of which specific ones will be addressed here. The key stimuli that lead to IFN-I production are RNA or DNA derived from pathogens upon infection or from endogenous sources after cell damage or death. These PAMPs or DAMPs are recognized by a number of PRRs that induce IFN-I gene expression. Toll-like receptor family members TLR3, 7, 8 and 9 can recognize specific DNA or RNA patterns in endosomes. TLR4 that recognizes bacterial lipopolysaccharide at the cell surface can also induce IFN-I. Furthermore, the cytosolic RIG-I family of RNA sensors can do so, as well as several cytosolic DNA sensors, among which cGAS. This enzyme produces the cyclic dinucleotide cGAMP that activates Stimulator of Interferon Genes (STING) at the endoplastic reticulum (Figure 2). In the context of cancer, where PAMPs are lacking, IFN-I production can be induced in tumor cells themselves by self-derived DNA, such as endogenous retroviral elements, mitochondrial DNA and micronuclei that reach the cytosol upon upon cellular damage or stress[64]. Tumor cell-derived DNA or RNA released into the extracellular environment may also be sensed in particular by phagocytic immune cells such as DCs via TLRs, or by cytoplasmic sensors upon transfer from endosomes to cytosol[65]. The different PRRs mentioned activate kinases that phosphorylate IFN regulatory factor 3 (IRF3) or IRF7. These factors then locate to the nucleus and activate IFNA and IFNB gene transcription[63].

IFN-I signaling

IFNα and IFNβ both signal via the IFNα/β receptor (IFNAR) that is composed of IFNAR1 and -2 subunits. IFNAR activates the tyrosine kinases JAK1 and TYK2 are that phosphorylate and activate STAT1, -2 in the cytosol. Upon dimerization and nuclear translocation, these transcription factors form a trimeric complex with IRF9, called ISGF3. This complex binds to cognate IFN-stimulated response elements (ISREs) in the DNA, resulting in the transcription hundreds of interferon-stimulated genes (ISGs)[66]. These ISGs restrict pathogen replication and spread by diverse mechanisms[67]. In addition, STAT1 homodimers bind to gamma-activated sequences (GAS), which leads to expression of pro-inflammatory genes. IFNAR signaling is subject to positive and negative regulation and crosstalk with signaling components activated by other membrane receptors. E.g. STAT1 levels and activity can be amplified by diverse cytokine- and chemokine signaling pathways and ISGF3 complex formation is regulated by Tumor Necrosis Factor (TNF) receptor signaling[66].

IFN-I production in cancer

IFN-I production by tumor cells

In tumor cells, DNA damage and genomic instability lead to DNA leakage into the cytosol and activation of the cGAS-STING pathway. Therefore, tumor cells are potential IFN-I producers. However, in a variety of human cancers, the STING pathway is suppressed or defective due to epigenetic silencing, loss-of-function mutations or overexpression of inhibitory factors[68–71]. As a result, spontaneous IFN-I production by tumor cells is rare, and has been mainly reported to occur after treatment with STING- or TLR agonists[10]. In a recent study, murine metastatic breast cancer cells showed active cGAS-STING signaling and IFN-I production *in vitro*, but this response was dampened when these cells formed a tumor *in vivo*[72]. Overexpression of the MYC oncogene in mouse breast cancer models downregulated various STING pathway-related genes and ISGs, resulting in immune cell exclusion[71]. In breast cancer and melanoma patients, lower IFN-I or ISG expression signatures in the tumor correlated with reduced T-cell infiltration and worse prognosis[8,72,73]. These results suggest that in the TME, tumor cells suppress their own IFN-I production in order to evade antitumor immune responses. In a spontaneously regressing fibrosarcoma mouse model, constitutive IFN-I production by tumor cells induced an intratumoral ISG^+ DC population, which was required for tumor control[74]. Interestingly, this ISG^+ DC population consisted not of cross-presenting cDC1s, but of $CD11b^+$ cDC2s that gained the capacity to prime $CD8^+$ T cells via MHC-I cross-dressing, the presentation of intact tumor-derived peptide-MHC-I complexes. The ISG^+ DC state has not been widely described in the context of progressing tumors, consistent with tumor-intrinsic IFN-I production being a rather rare phenotype[74].

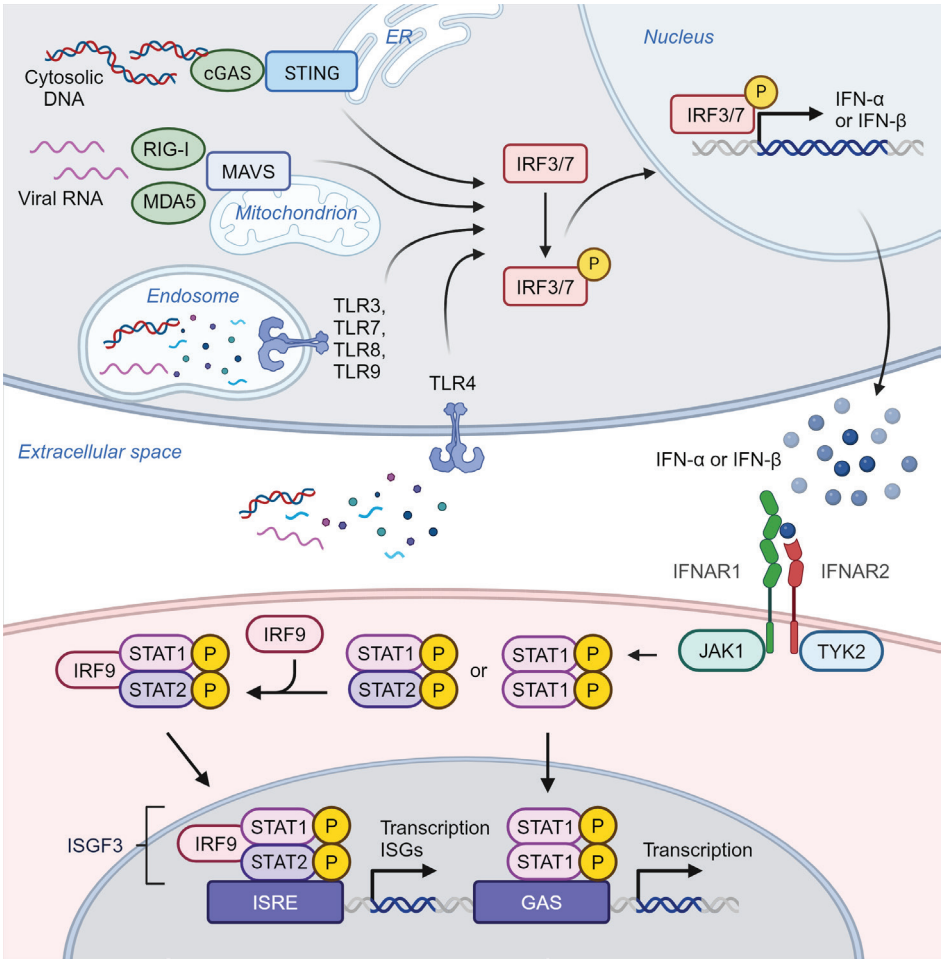

Figure 2. IFN-I production and signaling pathway. Extracellular and endosomal DNA, RNA and microbial molecules are sensed by TLRs on immune cells. Cytosolic DNA is sensed by the cGAS-STING pathway in immune cells and tumor cells. Viral RNA is sensed by cytosolic RIG-I-like sensors, which signal via MAVS. This causes the phosphorylation of IRF3/7, which subsequently translocates to the nucleus and induces the transcription of IFN-α and IFN-β. IFN-I binds to IFNAR, resulting in activation of JAK1 and TYK2. Consequently, STAT1 and STAT2 are phosphorylated and bind IRF9, which together form a heterodimer ISGF3. ISGF3 translocates to the nucleus where it can induce the transcription of a wide range of ISGs by binding to ISRE. In addition, STAT1 homodimers can bind to GAS to induce transcription of pro-inflammatory genes [66]. GAS: gamma-activated sequences; IFN: interferon; IFNAR; interferon α receptor; IRF: interferon regulatory factor; ISG: interferon-stimulated gene; ISGF3: interferon-stimulated gene factor 3; ISRE: interferon-stimulated response element; JAK1; Janus kinase 1; MAVS: mitochondrial antiviral-signaling protein; MDA5: melanoma differentiation-associated protein 5; RIG: retinoic acid-inducible gene; STAT: signal transducer and activator of transcription; STING stimulator of interferon genes; TLR: Toll-like receptor; TYK2: tyrosine kinase 2.

IFN-I production by DCs

In immunogenic fibrosarcoma, IFNAR signaling into hematopoietic cells rather than the cancer cells themselves proved important for immunosurveillance[1]. Pioneering studies demonstrated that IFN-I signaling into cDC1s is critical for antigen crosspresentation and CTL-mediated rejection of spontanously immunogenic tumors in mice[7,8]. In these models, cGAS/STING rather than TLR- of RIG-I-like receptors were decisive for spontaneous CTL priming by the tumor cells[65,75]. Reporter mice identified in the key model of immunogenic fibrosarcoma $CD11c^+$ cDCs and more specifically $CD11b^+$ DCs, likely cDC2, as the main source of IFN-I (IFNβ) in the TME[75], in agreement with earlier findings[8]. Both studies argue that cDC-derived rather than tumor-derived IFN-I was the decisive factor for tumor rejection.

During steady state, tonic IFN-I produced by pDCs instructs a basal cDC state permissive for $CD8^+$ T-cell priming[76]. In infection, when PAMPs are abundant, PRR stimulation evokes robust IFN-I production by pDCs. In cancer, however, PAMPs are generally lacking and the TME is often highly infiltrated by dysfunctional pDCs. Such pDCs display impaired IFNα production and are associated with tumor progression (reviewed by[77]). For example, pDCs in the TME of breast- and ovarian cancer patients did not produce IFNα, unlike circulating pDCs[78,79]. Inhibition of IFN-I production by intratumoral pDCs has been mainly attributed to TGF-β produced by tumor cells, both in mouse and in human[80,81]. In breast cancer patients, dysfunctional pDCs co-localized with regulatory T cells (Tregs) and were shown to promote Treg proliferation *ex vivo*[78]. This effect could be reversed by administration of IFN-I, suggesting that the lack of IFN-I production by pDCs is an important underlying mechanism for Treg maintenance and the establishment of an all-over immunosuppressive environment in the TME. Taken together, impaired IFN-I production both by tumor cells and by tumor-infiltrating pDCs contribute to the IFN-I poor environment of the TME that impedes initial cDC activation for the initiation of antitumor T-cell responses. In mouse models where immune-mediated tumor rejection takes place, the necessary IFN-I to drive CTL priming by cDC1s is most likely produced by cDC2s in the TME.

While the tdLN likely embodies a less immunosuppressive environment than the TME, often without the constant presence of (derivates of) tumor cells, the environment of the tdLN may also lack sufficient IFN-I signals for cDC1 activation. In a mouse model of viral infection, functional pDCs provide the cDC1 with IFN-I within the LN, which optimizes cDC1 functionality and establishment of the $CD4^+$ T-cell help delivery platform[82]. However, in a mouse melanoma model a subset of pDCs in the tdLN adopted a suppressive phenotype via expression of indoleamine 2,3-dioxygenase (IDO), which inhibited T-cell responses via activation of mature Tregs[83,84]. Until now, limited literature has touched upon the activation mechanisms and IFN-I production of non-suppressive pDCs in the tdLN. Therefore, it remains unclear whether pDCs in the tdLN are typically capable of producing sufficient IFN-I for cDC1 optimization and delivery of $CD4^+$ T-cell help.

IFN-I production by CD4$^+$ T cells

In this context, it is of interest that activated CD4$^+$ T cells can be a source of IFN-I that contributes to cDC1 functionality, as we have recently documented[61]. Unlike myeloid cells, T cells are generally not considered major producers of IFN-I due to a more strictly regulated cGAS-STING pathway[85]. However, upon stimulation via CD3 and CD28, mimicking initial T-cell activation, human CD4$^+$ T cells produced IFNβ via the cGAS-STING pathway and delivered it to cDC1 in a human *in vitro* model of CTL priming, which optimized cDC1 for CTL crosspriming to tumor antigens[61]. IFN-I production was also observed in human CD4$^+$ T cells with a tumor antigen-specific phenotype in the TME[61]. Thus, in the TME where IFN-I inducing signals and IFN-I production by pDCs are scarce, IFN-I production by tumor-specific CD4$^+$ T cells may play a role in cDC stimulation.

Effects of IFN-I on cDC1s

Given the convergence of IFN-I signals into the CD4$^+$ T-cell help scenario, we focus on how IFN-I has been described to impact on cDC1s, CD4$^+$ and CD8$^+$ T-cell functions and may shape their mutual interactions (Figure 3). Between the cell types that make up the help delivery platform, most effects of IFN-I signaling have been described for cDC1s. As shown in various studies in mouse and human, IFN-I improves the survival of cDC1s, as well as all three T-cell activating signals: 1) antigen presentation by MHC, 2) co-stimulation, and 3) specific cytokine production. In addition, IFN-I induces specific chemokine expression in cDC1, which is important for T-cell recruitment, as will be further discussed later.

Antigen presentation

Several studies in both mouse and human have shown that IFN-I promotes antigen cross-presentation by cDC1s (reviewed in[86]). In a murine thymoma model, IFN-I promoted survival of CD8α$^+$ DCs, MHC-I expression and cross-presentation of tumor cell-associated antigens by prolonging antigen persistence within the DCs[87]. Antigen presentation on MHC-II in murine DCs was also upregulated by IFN-I, improving the interaction with CD4$^+$ T cells[88]. In a viral infection model, IFN-I optimized cross-presentation of antigens by cDC1 to CD8$^+$ T cells in the context of CD4$^+$ T-cell help delivery in the LN[82]. In another study, upregulation of MHC-II on CD8α$^+$ cDC1s upon viral infection relied on IFNAR signaling[36]. Recently, our group showed that IFN-I stimulation of human cDC1s increased their expression of both MHC-I and MHC-II, as well as proteosome subunits and TAP1 and -2 that transport antigen into the ER for MHC-I loading[61]. Furthermore, IFN-I upregulated CD83 that promotes cell surface expression of MHC-II[89]. Taken together, IFN-I signaling in cDC1s enhances antigen processing and presentation on both MHC-I and MHC-II. In this way, it contributes to cognate interactions and synaptic communication with both CD4$^+$ and CD8$^+$ T cells.

Costimulation

IFN-I also promotes T-cell costimulatory capacity of cDC1s. Early *in vitro* experiments showed that IFN-I stimulation upregulated CD86 on mouse CD8α⁺ DCs and CD80 and CD86 on primary human DCs [87,88,90]. Selective deletion of IFNAR on cDCs led to reduced expression of CD80 and CD86 on non-infected cDC1s in a viral infection mouse model, where pDCs delivered IFN-I[82]. In human cDC1, IFN-I signaling enhanced expression of CD80, CD86 and CD70[61], of which the latter was shown to be important for CTL differentiation in both mouse and human[6,35,37]. IFN-I signaling also upregulated PD-L1 [61] that can form a costimulatory heterodimer with CD80[91–93]. Interestingly, IFN-I stimulation of murine and human cDC1s also results in upregulation of CD40 [61,87]. In a viral infection model, mice that specifically lacked IFNAR1 on cDCs showed a striking reduction in CD40 expression on cDC1s [82]. These results indicate that IFN-I signaling *in vivo* leads to upregulation of CD40 on cDC1s, which promotes their ability to receive help signals from CD4⁺ T cells via CD40L.

Integration of IFN-I and CD40 signals

Many effects of IFN-I on cDC1s are comparable to those of CD40 signaling and it has been questioned whether these signals are additive or synergistic[11]. Similar to IFN-I signaling[87], CD40 signaling into cDC1 increases survival, MHC-I expression and cross-presentation of antigens[35,94]. In a mouse tumor model, adenoviral delivery of membrane-stable CD40L and IFNβ increased the expression of CD80 and CD86 on migratory cDC1s, while this effect was diminished upon delivery of either stimulus alone[95]. Treatment of mice with IFN-I and CD40 agonist, but not either of these strategies alone, resulted in upregulation of CD70 on CD8α⁺ cDC1s, and a CD70-dependent enhanced CTL response[96].

Gressier *et al*. have recently illuminated how cDC1s integrate IFN-I and CD40 signals by transcriptomics. Treating murine bone-marrow-derived cDC1-like cells with CD40 agonist and/or IFNα/β indicated that CD40 signaling can amplify IFN-I induced signals, but also that the combined signals activate specific transcriptional programs, by integration of transcription factor activity[36]. By comparing different stimulation regimens, the authors demonstrated that cDC1s first need to be exposed to IFN-I in order to become receptive to CD40 signals. Thus, IFN-I signaling conditions the cDC1 to become receptive to CD4⁺ T-cell help mediated through CD40L-CD40 interactions and shapes the transcriptional response to CD40 stimulation.

Cytokines

IFN-I stimulation also induces the expression of specific cytokines by cDC1s, improving their function as mediator of CD4⁺ T-cell help. Stimulation with either agonistic anti-CD40 or IFN-I alone was not sufficient to induce production of IL-15 or IL-6 by *in vitro* generated murine cDCs, but upon dual stimulation their expression was amplified[60]. The same paper also demonstrated that CD8α⁺ cDC1 relied on IFNAR expression for IL-15 production that was required for HSV-specific CD8⁺ T-cell priming[60]. IL-15, produced by cDC1, is known to be required for CTL

differentiation and long-lived memory T-cell maintenance[30,97]. In mice, IL-6 has been reported for its anti-apoptotic functions in activated CD8$^+$ T cells, even in the presence of IL-15[97]. Thus, both cytokines exhibit distinct roles in improving CD8$^+$ T-cell survival and CTL differentiation, and they are produced by DCs only when both CD40 and IFN-I signals are present.

Direct effects of IFN-I on T cells

Effects of IFN-I *in vivo* can be indirect, but direct effects of IFN-I on T cells have been identified in mice with T-cell specific deletion of IFNAR. In this way, IFNAR signaling into antigen-specific CD8$^+$ T cells was found to dictate their survival during clonal expansion and formation of a memory pool after infection with *lymphocytic choriomeningitis virus* (LCMV)[98]. This agrees with earlier *in vitro* data showing that IFN-I promotes survival of activated T cells[99]. However, this effect may depend on the *in vivo* context, since IFNAR-proficient and deficient CD4$^+$ and CD8$^+$ T cells were found expand equally upon *vaccina virus* or *vesicular stomatitis virus* (VSV) infection in mice[82,100].

CD8$^+$ T cells

Recently, IFN-I was found to promote survival and activation potential of naïve CD8$^+$ T cells in mice. IFNα signals induced and sustained a Ly6C$^+$ subpopulation of naïve CD8$^+$ T cells via MHC-I upregulation and induction of tonic TCR signaling. IFN-I-induced Ly6C$^+$ naïve CD8$^+$ T cells responded more rapidly upon specific interaction with cognate antigen *in vivo*, and expressed higher levels of effector molecules such as IFNγ[101]. Earlier data also show that murine CD8$^+$ T-cell differentiation into effector cells depends greatly on IFN-I signaling directly to CD8$^+$ T cells[98,102]. IFN-I signals promote the production of effector molecules such as IFNγ and Granzyme-B by CD8$^+$ T cells and increase their cytolytic activity[102,103]. Moreover, IFN-I can prevent the elimination of antigen-activated CTLs by natural killer cells[104,105]. Thus, IFN-I signaling directly to CD8$^+$ T cells contributes to their survival, clonal expansion and effector differentiation upon activation (Figure 3).

CD4$^+$ T cells

Early research showed that direct stimulation of human CD4$^+$ T cells with IFNα, in the context of TCR triggering, drives an IFNγ$^+$ Th1 phenotype[106] (Figure 3). In a mouse infection model, IFN-I and IL-12 signaling on CD4$^+$ T cells showed synergistic effects for the promotion of Th1 differentiation[107]. Direct IFN-I signaling into CD4$^+$ T cells has also been demonstrated to support CD4$^+$ T-cell expansion and survival in a mouse model of acute viral infection[108]. A rapid IFN-I response promoted T follicular helper (Tfh) differentiation of CD4$^+$ T cells after VSV infection, while a later, prolonged IFN-I response resulted in more Th1 differentiation after LCMV infection. However, these effects did not result from direct IFN-I signaling into CD4$^+$ T cells, since Tfh and Th1 polarization was comparable in wild-type and IFNAR$^{-/-}$ CD4$^+$ T cells[100].

Tregs

IFN-I also affects CD4⁺ Treg differentiation and function. In a human *in vitro* setting, addition of IFNα to a co-culture of APCs and CD4⁺ T cells prevented IL-2-driven Treg proliferation and suppressive capacity, and this effect was dependent on IFNAR expression on both on APCs and Tregs[109]. Mice that specifically lacked IFNAR expression in Tregs showed increased Treg activity and decreased CD8⁺ and CD4⁺ T-cell responses upon viral infection, indicating that IFN-I signaling in Tregs dampens their suppressive capacity[110]. It has been described that IFN-I can inactivate the suppressive function of human Tregs through activation of phosphodiesterase 4 and the consequent depletion of cyclic AMP[111]. Thus, apart from acting via cDC, IFN-I can also promote effector T-cell responses by direct effects on conventional CD4⁺ T cells, CD8⁺ T cells and Tregs.

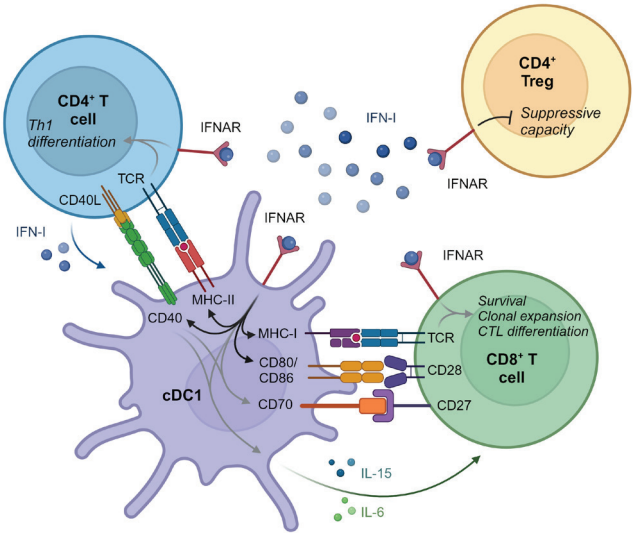

Figure 3. Effects of IFN-I on cells in the help delivery platform. On cDC1, direct IFN-I signaling (black arrows) induces upregulation of both MHC-II and MHC-I, thereby promoting interactions with both CD8⁺ and CD4⁺ T cells[36,61,82,87,88]. Also, IFN-I upregulates co-stimulatory molecules CD80/86 and CD40 on cDC1[61,82,87,88]. Combined stimulation of cDC1 with IFN-I and CD40L (grey arrows) results in a synergistic upregulation of CD70 and production of IL-6 and IL-15, which all contribute to optimal CD8⁺ T-cell functionality[60,96]. On CD4⁺ T cells, IFN-I stimulation during activation contributes to Th1 differentiation[106,107]. On CD8⁺ T cells, direct stimulation with IFN-I in the context of TCR stimulation contributes to clonal expansion and optimal CTL differentiation[98,102,103,112]. On Tregs, IFNAR signaling dampens their suppressive capacity[109–111]. cDC1: conventional dendritic cell type I; CTL: cytotoxic T lymphocyte; MHC: major histocompatibility complex; pDC: plasmacytoid dendritic cell; IFNAR: interferon α receptor; IFN-I: type I interferon; Treg: regulatory T cell.

Effects of IFN-I on cDC and T-cell migration and localization in LNs

Chemokines play a crucial role in cell migration and localization of cDCs and T cells towards and within LNs and tumor and between these compartments. In this section, we will describe the role of IFN-I in inducing chemokine gradients that contribute to the communication between T cells and cDCs and organization of the help delivery platform (Figure 4).

CCR7

In human cDC1s, *in vitro* stimulation with IFN-I resulted in upregulation of CCR7[61], which is the key chemokine receptor that enables trafficking of cDCs to LNs[113]. Expression of CCR7 ligands CCL19 and CCL21 in the LN recruites mature CCR7$^+$ cDCs to the LN, a process which is essential for anti-tumor CTL priming[23,114]. Under steady-state conditions, immature cDCs also express CCR7, allowing them to migrate to the LN and activate Tregs for the maintenance of immunological tolerance[114]. In a melanoma mouse model, intratumoral delivery of IFNβ contributed to CCR7 upregulation on migratory cDC1s[95]. cDCs from IFNAR$^{-/-}$ mice failed to upregulate CCR7 upon infection and showed impaired migration to the LN upon adoptive transfer[115]. Localization to the T-cell zone within the LN was also impaired in IFNAR$^{-/-}$ cDCs[115], which suggests an additional role of IFN-I, possibly via CCR7, for intranodal migration[15]. Thus, IFN-I signals in the TME are important for CCR7 upregulation on cDCs and their migration to the TdLN, thus allowing T-cell priming.

CCR5 ligands

IFN-I alone or in combination with CD40 signaling induced in murine cDCs the production of CCL3, CCL4 and CCL5, ligands for chemokine receptor CCR5[36,60]. CCL3 and CCL4 have been reported to orchestrate CD4$^+$ T-cell help delivery[97,116]. After vaccination, CCL3/4 was produced at sites of CD4$^+$ T cell-DC interactions in the IFR of the LN, which attracted CCR5$^+$ CD8$^+$ T cells and was crucial for CTL differentiation. In a mouse infection model, the gradient of CCL3 and CCL4 produced at the DC-CD8$^+$ T-cell interface was crucial for the migration of CCR5$^+$ pDCs to the CD8$^+$ T-cell priming site in the IFR. IFN-I produced by the pDCs optimized CD8$^+$ T-cell priming by improving cDC1 function[82]. Taken together, CCR5 ligands are likely important to spatially orchestrate the second step of T-cell priming. CCL4 and CCL5 have also been shown to enable DC migration into the TME[117] .

CXCR3 ligands

CXCR3 ligands CXCL9, -10 and -11 are differentially regulated and display individual binding characteristics which may result in distinct signal transduction upon CXCR3 engagement[118]. Humans express CXCL9, -10 and -11, of which the latter is suggested to induce a tolerizing state. C57BL/6 mice lack CXCL11 expression due to several mutations, but restoration of CXCL11 in these animals resulted in similar responses to viral infection as compared to wildtype mice[119]. Addition of IFN-I to human cDC1s led to increased expression of CXCL9, -10 and -11. Furthermore, human cDC1s produced CXCL9/10 in an IFNAR-dependent manner upon stimulation with CD4$^+$ T cells[61].

CXCL10 was also upregulated at the mRNA level in murine cDC1-like cells upon combined IFN-I and CD40 stimulation[36]. The common receptor for these chemokines is CXCR3 that enables T cells to migrate into non-lymphoid tissues, but also regulates their positioning within LNs during priming (reviewed by[120]).

In a viral infection model, IFN-I signaling proved crucial to induce CXCL10 expression within the LN[121]. After LCMV infection, cDC1s and stromal cells in the LN center predominantly expressed CXCL9, while CXCL9 and CXCL10 were produced by cDC2s, inflammatory monocytes and stromal cells in the periphery of the LN, including the IFR where "help" has been localized in vaccination models[44]. IFN-I-induced CXCL10 but not CXCL9 was required for $CD8^+$ T cells to migrate to the IFR in a CXCR3-dependent manner in order to undergo full effector differentiation[122]. $CXCR3^{-/-}$ $CD8^+$ T cells were retained in the LN paracortex and showed impaired effector functions, in line with earlier observations[122,123]. A recent study showed that early IFNAR blockade during acute viral infection in mice increased the stem-like phenotype of $CD8^+$ T cells and their localization in the LN paracortex[124]. Taken together, IFN-I signaling in the LN likely plays an important role in the induction of CXCR3 ligands for the intranodal localization and differentiation of CTLs. Also the CXCL10/CXCR3-dependent migration of $CD4^+$ T cells into the IFR was shown to be essential for Th1 differentiation in response to viral infection and vaccination[45]. Thus, IFN-I-induced CXCL10 expression in the IFR of the LN results in optimized priming, likely by facilitating optimal positioning of $CD4^+$ and $CD8^+$ T cells for help delivery. Upon CD70/CD27 co-stimulation, which is an important signal in help delivery, $CD8^+$ T cells produced CXCL10 themselves, acting as a chemoattractant for other activated $CD8^+$ T cells[125]. Thus, the accumulation of CXCR3 ligands locally surrounding the $CD4^+$ T-cell help platform may additionally attract other activated $CD4^+$ and $CD8^+$ T cells for help delivery.

Summary and proposed model

In the TME, IFN-I is required for the activation of migratory cDC1s and their localization to the LN to initiate the first step of T-cell priming. In addition, IFN-I also acts during the second step of T-cell priming, where delivery of $CD4^+$ T-cell help to $CD8^+$ T cells takes place. While it is commonly accepted both $CD4^+$ T-cell help and innate signals such as IFN-I are crucial for raising an effective anti-tumor $CD8^+$ T-cell response (reviewed in[9,10,24], thus far it has remained unclear how IFN-I affects all players deemed important for help delivery. In the sections above, we have provided an integrated view of the effects of IFN-I on all participants in help delivery, as well as on their spatial organization within the LN. In summary, IFN-I optimizes the cDC1 as mediator to transduce $CD4^+$ T-cell signals to $CD8^+$ T cells in various ways: 1) enhancing survival of the cDC1, 2) improving antigen presentation on both MHC-I and MHC-II, 3) upregulating co-stimulatory molecules, such as CD70 and CD80/86, 4) inducing the production of cytokines, such as IL-15 and IL-6, and 5) inducing the secretion of chemokines, such as CCR5 and CXCR3 ligands. Thus, IFN-I facilitates initial

cDC1 activation and direct interactions between cells in the help delivery platform, via antigen presentation, co-stimulatory molecules and cytokines, as well as their proximal localization in the IFR of the LN, via chemokines. This creates an optimal communication platform for the cDC1 to interact with $CD4^+$ and $CD8^+$ T cells, which ultimately results in the generation of optimally differentiated effector and memory CTLs. While presumably many effects of IFN-I on T cells are indirect because of the interaction with the optimized cDC, IFN-I has also been shown to act directly on T cells. It promotes $CD8^+$ T-cell survival and effector differentiation, and $CD4^+$ T-cell differentiation into the Th1 phenotype. Thus, the scenario of $CD4^+$ T-cell help depends on IFN-I for raising optimally differentiated effector CTLs against tumor antigens.

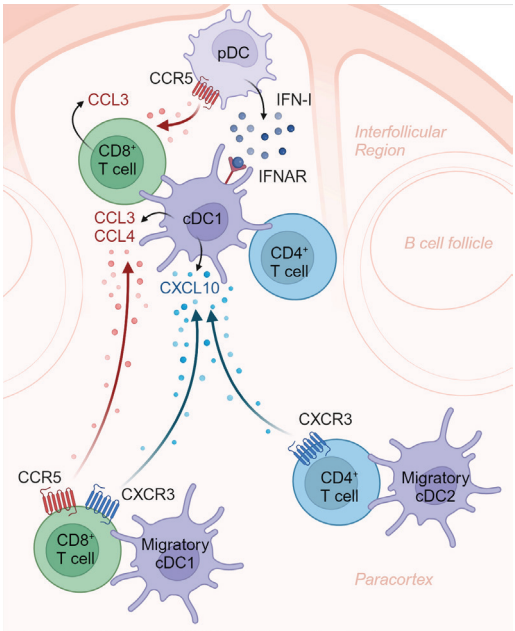

Figure 4: IFN-I induced chemokines in the LN involved in spatial organization of the help delivery platform. IFN-I promotes the production of CCR5 ligands (CCL3 and CCL4) and CXCR3 ligand (CXCL10) by the cDC1[36,60,121,122]. As a result, $CD4^+$ and $CD8^+$ T cells, initially activated in the paracortex, are attracted to the IFR via CXCR3 ligands, and $CD8^+$ T cells are additionally attracted via CCR5 ligands[45,116,122]. This facilitates the proximal localization of all participating cell types in $CD4^+$ T-cell help delivery. In virus infection, IFN-I producing pDCs are attracted to the secondary priming site by cDC1-derived and/or $CD8^+$ T cell-derived CCR5 ligands, leading to locally increased levels of IFN-I [82]. CCL3/4: CC-chemokine ligand 3/4; CCR5: CC-chemokine receptor 5; CXCL10: CXC-motif chemokine ligand 10; CXCR3: CXC-motif chemokine receptor 3; cDC1: conventional dendritic cell type 1; IFN-I: type I interferon; IFNAR: interferon α receptor; IFR: interfollicular region; LN: lymh node; pDC: plasmacytoid dendritic cell.

However, tumors often represent an IFN-I-poor environment. The strong induction of IFN-I by PAMPs as seen in viral infection is lacking in non-viral tumor settings, instead IFN-I induction relies on sensing of DAMPs. The main pathway driving IFN-I production in tumor settings is the cGAS-STING pathway, which can sense cytosolic DNA as a result of DNA damage, mitochondrial stress and

genomic instability in tumor cells. This pathway is defective or downregulated in many tumor cells. Also pDCs, which are the most important IFN-I producers in viral infections, are often dysfunctional in the TME. In parallel, T-cell infiltrated tumors often accommodate exhausted, or predysfunctional / stem-like $CD8^+$ T cells, with impaired effector function. Previous work from our group postulated that these stem-like T cells equal helpless $CD8^+$ T cells, generated after priming in absence of $CD4^+$ T-cell help[59]. Combining these observations, we propose that the IFN-I-poor environment of the TME is an important underlying mechanism for impaired $CD4^+$ T-cell help delivery to tumor-specific $CD8^+$ T cells. We argue that by removing IFN-I from the TME, tumors prevent the proper priming of CTLs not only by impaired DC activation, but also by impaired delivery of $CD4^+$ T-cell help, thereby impacting all steps in the cancer-immunity cycle[126,127] (Figure 5). This explains why tumors in which IFN-I signaling is attenuated, remain devoid of functional CTLs.

Clinical data support the importance of IFN-I in anticancer immunity. In breast cancer and melanoma patients, higher expression of IFN-I-related genes or ISGs in the tumor correlated with increased T-cell infiltration and better prognosis [8,72,73,128]. An increased IFN-I gene signature in intratumoral myeloid cells predicted better response to PD-1 blockade therapy in basal cell carcinoma patients [129]. Also, the presence of functional pDCs in the TME, considered the main producers of IFN-I, correlated with increased survival of patients with colon cancer and follicular lymphoma [130,131]. In a pan-cancer analysis of 16 solid tumor types, carcinoma ecotypes showing co-localization of $CD8^+$ T cells, $CD4^+$ T cells and cDC1s were associated with the highest overall survival and response to PD-1 blockade therapy [55]. In these tumors help delivery likely takes place, as testified by the helped cDC1 gene expression signature in the TME [6]. Since effective anti-tumor CTL priming requires IFN-I signaling to cDC1s [1,7,8], in these types of tumors there must be cell types in the TME or tdLN that can produce IFN-I. The most likely candidates for this are cDC2s in the TME, which can produce IFNβ in mouse tumor models, possibly via STING-mediated sensing of tumor-derived DNA in their cytosol [65,75]. Also DCs in the tdLN have been described to produce IFNβ in immunogenic mouse models [8], however the type of DCs or the precise role of IFN-I signaling within the tdLN has not been further elucidated. pDCs in the tdLN have been suggested to produce IFN-I and contribute to spontaneous CTL priming, but this hypothesis has not yet been formally addressed [132]. Another outstanding question remains if in cancer, cDC1s are capable of producing IFN-I in an autocrine manner, whether as a first signal or as an amplifying response to IFN-I derived from other sources. Our recent findings suggest that once $CD4^+$ T cells have been primed, they may also provide IFN-I to cDC1s to further optimize help delivery [61]. Taken together, understanding the role of IFN-I signaling, $CD4^+$ T-cell help and how these mechanisms are connected, will contribute to better insights into the conditions required for effective CTL priming in cancer.

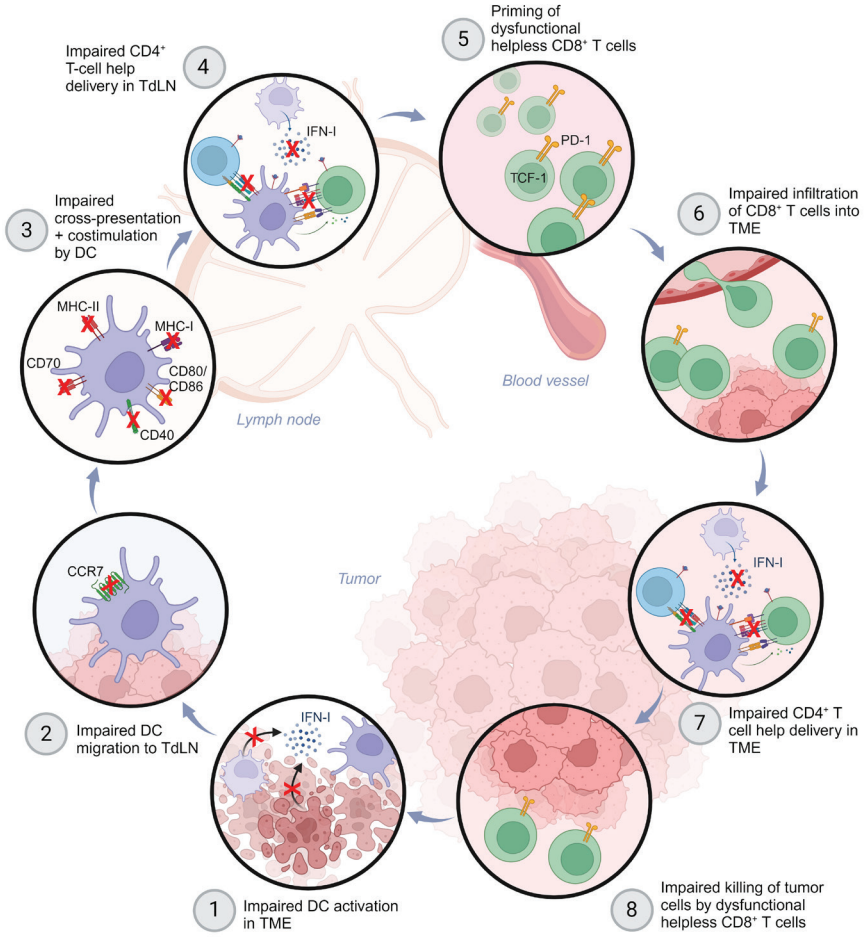

Figure 5. The effects of lack of IFN-I on the cancer-immunity cycle[126,127]. Step 1) Lack of IFN-I production by tumor cells and intratumoral pDCs leads to impaired cDC activation in the TME, and potentially impaired cDC infiltration into the TME. Step 2) Lack of IFN-I signaling in cDC results in lower expression of CCR7, which leads to impaired LN homing of the DC. Step 3) Cross-presentation of tumor antigens and expression of MHC-I, MHC-II and co-stimulatory ligands is decreased as a result of insufficient IFN-I-mediated activation of cDCs. Step 4) $CD4^+$ T-cell help delivery is hindered by the impaired initial cDC activation in the TME. pDCs in the TdLN may also be partly dysfunctional, potentially leading to a decrease in local IFN-I production within the TdLN. Step 5) As a result of impaired $CD4^+$ T-cell help delivery, helpless $CD8^+$ T cells are primed. Step 6) Helpless $CD8^+$ T cells display impaired migratory capacities and tumor infiltration. The absence of IFN-I in the TME may also result in a lack of chemokines, such as CXCR3 and CCR5 ligands, which are responsible for T-cell infiltration into the TME. Consequently, T cells are hindered to infiltrate the tumor. Step 7) $CD4^+$ T-cell help cannot be delivered as a result of the lack of IFN-I in the TME. The close localization of the participating cells, as well as their maturation, cannot be established. Step 8) Dysfunctional helpless $CD8^+$ T cells exhibit impaired effector potential, which results in decreased tumor killing. CCR5: CC-chemokine receptor 5; CCR7: CC-chemokine receptor 7; cDC: conventional dendritic cell; CXCR3: CXC-motif chemokine receptor 3; IFN-I: type I interferon; LN: lymph node; MHC: major histocompatibility complex; pDC: plasmacytoid dendritic cell; TdLN: tumor-draining lymph node; TME: tumor-microenvironment.

Competing Interests

The authors declare no competing interests.

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