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Review

Tumoricidal activity of human dendritic cells

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Dendritic cells (DCs) are a family of professional antigen-presenting cells (APCs) that are able to initiate innate and adaptive immune responses against pathogens and tumor cells. The DC family is heterogeneous and is classically divided into two main subsets, each with its unique phenotypic and functional characteristics: myeloid DCs (mDCs) and plasmacytoid DCs (pDCs). Recent results have provided intriguing evidence that both DC subsets can also function as direct cytotoxic effector cells; in particular, against cancer cells. In this review, we delve into this understudied function of human DCs and discuss why these so-called killer DCs might become important tools in future cancer immunotherapies.

DCs: commanders-in-chief of the immune army

Forty years after their discovery by Zanvil Cohn and Ralph Steinman, DCs continue to fascinate and intrigue immunologists. Although the nomenclature of the DC system is still evolving and novel markers to identify and subclassify DCs are being continually identified, it is well established that the DC family constitutes a heterogeneous group of cells that can be categorized in two main subtypes: mDCs and pDCs. Despite the considerable heterogeneity between the different DC types in terms of phenotype, gene expression profile, and function, a common characteristic of all DCs is their capacity for antigen presentation and their unique ability to prime and activate naïve T lymphocytes. As the primary APCs of the immune system, DCs are pivotal in eliciting adaptive immune responses and, as such, in determining the balance between immunity and tolerance [1]. In addition to their central role in adaptive immunity, DCs also occupy a pre-eminent place within the innate immune system. In this context, DCs express Toll-like receptors (TLRs); a family of innate immune receptors involved in sensing viruses and other microbial stimuli. DCs are also capable of activating other innate immune cells, including natural killer (NK) cells.

Given their key role in regulating innate and adaptive immunity, DCs are critical for the induction of antitumor immunity [1]. Through their role in the induction of antigen-specific cytotoxic T lymphocytes (CTLs) and through their capacity to harness the cytotoxic activity of innate immune cells (NK cells, NKT cells, and γδ T cells), DCs can elicit potent cytotoxic immune responses towards tumor cells [2]. Evidence from animal and human studies indicates that DCs themselves can initiate cytotoxic effector function through which they directly contribute to tumor cell killing. These so-called killer DCs were first described in the mid-1990s, when a population of murine DCs was identified with the capacity to lyse $CD4^+$ T cells in a FAS–FAS ligand (FAS-L)-dependent fashion [3]. Almost one decade later, three research groups independently reported on the existence of a novel DC type within the murine immune system that bore phenotypic, molecular, and functional characteristics of both DCs and NK cells [4–6]. This DC subtype was termed natural killer dendritic cell (NKDC) or, alternatively, interferon-producing killer DC (IKDC) [4] because of its NK cell-like properties such as cytotoxic activity and capacity to produce high amounts of interferon (IFN)-γ [4–6]. Although NKDCs were capable of antigen processing and presentation, it soon became apparent that this term was actually a misnomer because NKDCs belong to the NK cell lineage and not to the DC lineage [7–9]. This apparently erroneous terminology has led to confusion and even skepticism over the actual existence of killer DCs.

Recent studies, however, have provided substantial evidence for direct cytotoxic effector function in DCs. These killer DCs, which have been identified in both rodents and humans, appear to constitute a heterogeneous population of cells that have the following characteristics in common: (i) they are endowed with direct cytolytic potential; (ii) they fulfill the phenotypic and functional criteria to be classified as *bona fide* DCs; and (iii) they cannot be defined as NK cells despite their cytotoxic activity (e.g., absence of classical NK cell surface markers, and target cell profile different from that of NK cells). Here, we summarize the findings accumulated in recent years on killer DCs and discuss the potential relevance of these cells to future immunotherapy

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strategies. No major differences in mode of action have been identified between rodent and human killer DCs, and because the existence and function of rodent killer DCs has been excellently reviewed elsewhere [10,11], we focus this discussion on killer DCs in humans.

Killer DCs in humans

Monocytes and monocyte-derived DCs (MoDCs) as killer cells

Immature DCs reside mostly in parts of the body that are in close contact with the outside world, such as skin and mucosal tissue, and are able quickly to sense and take up pathogens that could harm the host. After pathogen recognition, the DCs mature and migrate to lymphoid tissues to present the pathogenic peptides to T cells. MoDCs are by far the most widely used cell type for the study of human DCs *ex vivo* (Table 1). Although a variety of protocols exist to generate MoDCs, the basic procedure consists of two phases: (i) monocytes are differentiated into immature DCs using a combination of cytokines [e.g., granulocyte–macrophage colony-stimulating factor (GM-CSF) and interleukin (IL)-4, IL-15 or IFNα]; and (ii) MoDC maturation is induced with activation stimuli (e.g., proinflammatory cytokines or TLR ligands). Immature DCs exploit a wide variety of pattern recognition receptors to recognize and take up antigens. Several of these differentiating and maturating agents can trigger human MoDCs to acquire a cytotoxic effector function. Different studies have suggested that this cytolytic potential already resides in the monocytic precursor cell compartment (Table 1). Indeed, human $CD14^+$ as well as $CD16^+$ monocytes stimulated with type I or II IFN, R848 a ligand for TLR7 and TLR8, or lipopolysaccharide (LPS) a ligand for TLR4, were shown to exert antitumor activity against a range of cancer cell lines [12–17] (Table 1). In three of these studies, TNF-α-related apoptosis-inducing ligand (TRAIL) was implicated in the direct tumoricidal activity of human monocytes [12,13,15]. TRAIL-dependent apoptosis has also been reported to play a role in the cytotoxic activity of human MoDCs. Viruses, including measles virus [18,19], cytomegalovirus (CMV) [20], and HIV-1 [21–23], TLR ligands (double-stranded RNA), type I IFNs [24–26], IL-15 [27], and the maturating agent CD40L [28], are all capable of inducing TRAIL expression in MoDCs (Table 1). Conversely, another study found that CD40 ligation inhibits TRAIL expression in MoDCs, but the cytotoxic ability of these CD40L-matured MoDCs was preserved, suggesting TRAIL-independent mechanisms for induction of cell death [28]. Indeed, as outlined in Table 1, both cell contact-dependent and -independent mechanisms have been implicated in MoDC-mediated killing and their cytolytic armamentarium includes, in addition to TRAIL, a broad range of cytotoxic effector molecules such as TNFα [21–24,29,30], FAS-L [20–22,29,31,32], caspase-8 [19,33–35], lymphotoxin (LT)-α1β2 [29], TNF-like weak inducer of apoptosis (TWEAK) [21], IFN-γ [28], granzyme B [27,36], and programmed death ligand (PD-L1/2) [32,37].

The majority of studies on killer MoDCs have focused on their tumoricidal potential. MoDCs are capable of exerting cytotoxicity against a broad range of tumor cell lines, while sparing normal cells (Table 1). The reasons for this apparent tumor-selective action remain incompletely understood, although the expression of decoy receptors (e.g., TRAIL decoy receptors DR1 and DR2) and the activation of antiapoptotic mechanisms [e.g., upregulation of cellular FADD-like IL-1β-converting enzyme protease-inhibitory protein (c-FLIP)] may help to explain why normal cells are largely resistant to killing by MoDCs [25].

Despite their seemingly preferential tumor-directed action, under certain circumstances, MoDCs can induce T cell death [21,32,37]. This observation was made in several studies (Table 1); all of which were performed in the context of infectious diseases [21,32,37]. The first study demonstrated that MoDCs infected with measles virus can induce paracrine killing of autologous T cells [19]. Monocytes [38] and MoDCs [21] exposed to HIV-1 were capable of inducing apoptosis of HIV-1-infected as well as noninfected $CD4^+$ T cells from either allogeneic or autologous origin. In another study, it was shown that LPS-matured MoDCs derived from tuberculosis patients had an increased expression of PD-L1, which underlined their antiproliferative and proapoptotic activity towards both $CD4^+$ and $CD8^+$ T cells [37]. Similarly, LPS-matured MoDCs generated from chronic hepatitis C patients were found to lyse both healthy (allogeneic) as well as patient-derived (autologous) $CD4^+$ T cells in a PD-L2- and FAS-L-dependent fashion [32]. Taken together, these findings indicate that human monocytes and MoDCs, when appropriately stimulated, can function as cytotoxic antitumor effectors and, in the context of chronic infection, also as immunoregulatory cells with T cell killing activity.

Blood mDCs as killer cells

Although the observation that *ex vivo* generated MoDCs can act as direct killer cells is interesting, another relevant question is whether this is also applicable to naturally circulating DCs. Although most studies used MoDCs, several studies have delved into the killer function of blood DCs and have shown that the two main blood DC subsets, mDCs and pDCs, can be cytotoxic. The human blood mDC subset is usually defined as lineage $(Lin)^-HLA\text{-}DR^+CD11c^+CD123(IL\text{-}3R\alpha)^{dim}$ cells. Blood mDCs can be further subdivided in nonoverlapping subsets based on the expression of blood dendritic cell antigen (BDCA)-1 (CD1c) and BDCA-3 (CD141) [39]. Classically, mDCs remain in an immature state and migrate from peripheral tissues to lymph nodes after maturation where they can activate T cells. Cytotoxic potential has hitherto been reported for the total $CD11c^+$ mDC population, as well as for the $CD1c^+$ subset (Table 2). The first description of the direct cytotoxic activity of human blood mDCs dates back to the late 1990s, where $CD11c^+$ mDCs, stimulated with IFNα or IFNγ, directly lysed various tumor cell lines in a TRAIL-dependent fashion [40]. TRAIL has also been implicated in blood DC-mediated cytotoxicity in two other studies [41,42] (Table 2). By contrast, TRAIL seems not to be an important mediator of cytotoxicity by TLR-activated mDCs. A recent study showed that neither $BDCA\text{-}1^+$ nor $BDCA\text{-}3^+$ mDCs produce TRAIL after exposure to TLR ligands [43]. In line with this, it was observed that tumor-infiltrating $CD11c^+$ mDCs express and secrete perforin and granzyme B, but not TRAIL, upon TLR7 and TLR8 stimulation [44].

Table 1. Human killer monocytes and MoDCs[c]

Cell type	Stimulation	Target	E:T ratio	Killing mechanism	Refs
Monocytes					
Monocytes	HIV-1	T cells	1:1	Contact dependent	[38]
Monocytes	IFNα, IFNγ	OVCAR3 (ovarian cancer) WM793 (melanoma) MDA231 (breast cancer) Colo205 (colon cancer) PC-3 (prostate cancer) H2126 (lung cancer)	50:1	TRAIL	[12]
Monocytes	IFNγ	HSC3 (oral squamous cell carcinoma)	50:1	TWEAK TRAIL	[15]
Monocytes	LPS	K562 (leukemia)	10:1	No involvement of Fas-L, TNF-α or TGF-β	[14]
Monocytes	IFNα	K562 PC-3 Jurkat (T cell leukemia)	?	TRAIL[a]	[13]
$CD16^+$ slan DCs	Unstimulated	Colo205 SkBr3	40:1	ADCC by 17-1A (colo205) or by herceptin (SkBr3) Effector molecule: TNF-α	[17]
$CD16^+$ slan DCs $M\text{-}DC8^+$	IFN-γ	Capan 1 (pancreatic cancer) MCF-7 Colo205 HT-29 (colon cancer)	40:1	ND	[16]
$CD16^+$ slan DCs (CHC)	IMQ or resiquimod	Capan-1 HT-29	40:1	ND	[77]
MoDCs					
MoDCs (measles)	Measles	T cells (autologous)	1:1	TNF family member (postulated)	[19]
MoDCs	LPS	Jurkat Molt (T cell leukemia) K562 THP-1 (monocytic cancer) U937 (lymphoma)	1:1	Contact dependent	[78]
MoDCs	Measles virus	MDA231	50:1	TRAIL	[18]
MoDCs	Immature	OVA.1 (ovarian cancer) SW626 (ovarian cancer)	40:1	FAS-L	[31]
MoDCs	Immature	SiHA, Caski (HPV+ cervical cancer)	8:1	Contact-dependent no involvement of TRAIL or FAS-L	[79]
MoDCs $CD14^+$, $CD34^+$	IFNβ	HL60 (leukemia)	20:1	TRAIL[a]	[25]
MoDCs	dsRNA → CD40L →	MDA231 MDA231	50:1 50:1	TRAIL[a] TNF-α	[24]
MoDCs	CMV	CMV-reactive T cells	1:53	FAS-L, TRAIL	[20]
MoDCs	Immature	Jurkat Molt MCF-7 (breast cancer) U87 (glioblastoma) HCT-5 (colorectal cancer) A498 (renal cancer) 786.O (renal cancer) Caki.2 (renal cancer)	10:1	Caspase 8 (FADD independent)	[33]
MoDCs	CD40L	PCI-13 SSCHN (head and neck cancer)	1:1	TNF-α, LT-α, LT-β, FAS-L, TRAIL[a]	[29]
MoDCs	CD40L, LPS	MCF-7 MDA-MB-468 (breast cancer) SK-BR-3 (breast cancer)	?	TNF-α[a] Contact independent	[30]
MoDCs	HIV-1 IFNα	MDA231 $CD4^+$ T cell line HIV-H9 $CD4^+$ T cells (HIV-1 viremic patients)	?	TRAIL[a], FAS-L[a], TNF-α[a] TWEAK[a]	[21]
MoDCs	HIV-1 (nef)	$CD8^+$ T cells	?	sTNF-α FAS-L	[22]
MoDCs	Immature	Jurkat	10:1	Caspase 8/Bcl-2 (FADD independent)	[35]
Cordblood MoDCs	IFNγ → LPS →	HL60, Jurkat Daudi, Jurkat	20:1	ND	[80]
MoDCs	IFNα	K562	20:1	ND	[81]
MoDCs	HIV-1 (Vpr) + LPS	Allogeneic $CD8^+$ T cells	1:20	sTNF-α	[23]
MoDCs		U251 (glioma) Jurkat	20:1	Contact dependent FADD and caspase-8 dependent	[34]

Table 1 (*Continued*)

Cell type	Stimulation	Target	E:T ratio	Killing mechanism	Refs
MoDCs	IFNα	K562	50:1	TRAIL[a]	[26]
MoDCs	OK432	T2 K562 EJ 253J	10:1	Contact dependent (CD40–CD40L	[82]
MoDCs	Immature ($CD123^+$)	U937 Jurkat HL-60	40:1	TRAIL	[83]
MoDCs	CD40L	OSC-70 (oral squamous cell carcinoma)	1:8	TRAIL[a] IFN-γ	[28]
MoDCs (PB and CB)	SARS coronavirus	ND	ND	TRAIL	[84]
MoDCs	LPS	SkBr3 (Her2-neu+ breast cancer)	100:1	ADCC by trastuzumab	[85]
MoDCs	LPS	MCF7 (breast) HeLa (cervix) HT29, HCT116, SW480 (colorectal) no killing of T lymphocytes	5:1	peroxynitrites	[86]
MoDCs (TBC)	IFNα, LPS	$CD4^+$ T cells $CD8^+$ T cells	10:1	PD-L1	[37]
MoDCs	IFNγ, LPS	T47D (breast cancer)	ND	ND	[87]
MoDCs	IL-15	K562	50:1	Granzyme B, TRAIL[a]	[27]
MoDCs (CHC patients)[b]	LPS	Allogeneic healthy $CD4^+$ T cells Autologous $CD4^+$ T cells	4:1	FAS-L, PD-L2, Contact dependent	[32]
MoDCs	γ-irradiated HT-29	HT-29 (colon cancer)	20:1	Perforin/granzyme B	[36]

[a]Partially dependent, other mechanisms (shown when possible) may be involved.

[b]Chronic hepatitis C patients.

[c]Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; CB, cord blood; E: T ratio, effector cell to target cell ratio; FADD, FAS-associated protein with death domain; HPV, human papillomavirus; ND, not determined; PB, peripheral blood; TGF, transforming growth factor.

Granzyme B has also been implicated in mDC-mediated apoptosis in IL-15-activated $CD11c^+$ mDCs [45]. Taken together, these data illustrate that killer mDCs, like their *in vitro* MoDC counterparts, can exploit a variety of cytotoxic effector mechanisms to exert killing function (Table 2). Similar to MoDCs, most studies on the killer function of native blood mDCs have been performed using tumor cell lines as target cells. The ability of blood mDCs to kill T cells was examined in one study that showed LPS-activated BDCA-1^+ mDCs from chronic hepatitis C patients induced lysis of autologous patient T cells as well as allogeneic healthy T cells in a FAS-L- and PD-L2-dependent fashion (Table 2) [32]. This study provides evidence for the ability of native blood mDCs to kill T cells during chronic viral infection; a mechanism that may be exploited by viruses to escape antiviral T cells.

pDCs as killer cells

pDCs are defined as $Lin^-D11c^-CD4^+CD45RA^+IL\text{-}3R\alpha$(C-D123)$^+ILT3^+$ cells. Additionally, the markers BDCA-2 (CD303), BDCA-4 (CD304), and immunoglobulin-like transcript (ILT)7 are restricted to pDCs both in peripheral blood and bone marrow [46]. On the functional level, human pDCs differ from other DC subsets by their ability to produce large amounts of type I IFNs upon TLR7 or TLR9 ligation by viral or bacterial components [47]. pDCs are generally found to circulate in the periphery, however they can infiltrate tissue in case of infection, inflammation, or tumor [44,48]. Like their myeloid counterparts, pDCs are also described to exert a direct cytotoxic function (Figure 1 and Table 2). For example, the human pDC cell line GEN2.2 is capable of lysing tumor cells in a partly TRAIL-dependent manner after stimulation with inactivated influenza virus or type I IFNs (Table 2). This pDC cell line expresses the NK cell surface marked CD56, whereas other NK cell markers are absent [49]. pDCs activated by the tick-borne encephalitis vaccine FMSE also upregulate CD56, whereas IL-3 or several TLR agonists do not induce upregulation [50]. The $CD56^+$ pDCs express high amounts of TRAIL and granzyme B but neither the cytotoxic molecules nor CD56 are required for the observed cytotoxicity. Nevertheless, the killing capacity is dependent on cell-to-cell contact, whereby FSME-pDCs specifically lyse MHC-class-I-negative tumor cell lines Daudi and K562, but not MHC class I positive cell lines [50]. By contrast, pDCs stimulated with imiquimod (a TLR7 agonist and to lesser extend TLR8 agonist), CpG, or IFN-α kill MHC-class-I-positive tumor cells in a TRAIL- and contact-dependent manner [44,51]. Although TRAIL appears to be an important mediator of pDC-mediated cytotoxicity, other cytotoxic effector molecules are implicated (Table 2). It has been shown that different cytotoxic effector molecules are expressed by blood pDCs, including TRAIL, granzyme B, and lysozyme. High lysozyme expression by the $CD2^{high}$ pDC subset has been observed, although this is not related to the increased cytotoxic activity of the $CD2^{high}$ pDCs as compared to their $CD2^{low}$ counterparts. It is important to note that the high lysozyme expression in the $CD2^{high}$ pDC subset could not be confirmed in another independently performed study [51], indicating that other mechanisms, such as the superior ability of

Table 2. Human killer DCs divided into major subsets[c]

Subset of DC	Stimulation	Target	E:T ratio	Killing mechanism	Refs
mDCs					
CD11c$^+$ blood mDCs	IFNα, IFNγ	Jurkat OVCAR3 PC-3 WM793	50:1	TRAIL	[40]
CD11c$^+$ blood mDCs	IFNγ, IL-15, LPS	MCF-7 HBL-100 (breast cancer) MDA-MB-231 (breast cancer) MDA-MB-415 (breast cancer)	10:1	ND	[88]
CD11c$^+$ mDCs	IMQ	K562	25:1	Perforin/granzyme B	[44]
CD1c+ mDCs (CHC patients)[b]	Unstimulated	K562 U937 Jurkat	50:1	TRAIL	[42]
CD11c$^+$ blood mDCs	IL-15	Human aortic endothelial cells Porcine aortic endothelial cells	10:1	Granzyme B[a] /caspase 8	[45]
Blood mDCs BDCA-1$^+$	LPS	Allogeneic healthy CD4$^+$ T cells Autologous CD4$^+$ T cells	4:1	FAS-L PD-L2 Contact dependent	[32]
pDCs					
pDC cell line GEN2.2 Blood pDCs →	Influenza virus, Type I IFNs Influenza virus	A549 (epithelial cancer) A549	25:1 15:1	TRAIL[a] TRAIL	[49]
Blood pDCs	IMQ	Jurkat	25:1	TRAIL	[44]
Blood pDCs	HIV-1	SupT1 (CD4$^+$ T cell line)	20:1	TRAIL[a]	[56]
Blood pDCs	HIV-1	CD4$^+$ T cells (HIV-1 viremic patients)	10:1	TRAIL IFNα	[89]
Blood pDCs	IL-3/CD40L → CpG →	K562 K562 1806 (breast cancer) Colo829 (melanoma)	100:1	Contact dependent ND	[52]
Blood pDCs	Flu CpG	Jurkat J32	Culture Sup	TRAIL	[90]
Blood pDCs	HTLV-1	DR5$^+$ T cells	1:2	TRAIL	[55]
Blood pDCs	HIV	HIV-infected Sup-T1 cell line	10:1	TRAIL	[58]
Blood pDCs	IL-3/IL-10	T cells	1:250	Granzyme B	[54]
Blood pDCs	IL-3	K562	10:1	Granzyme B /Caspase	[53]
Blood pDCs	CpG	H9 (CD4$^+$ T cell line)	2:1	TRAIL[a]	[57]
Blood pDCs	IMQ CpG IFNα	Jurkat WM793 SKMel2 (melanoma) Jurkat Jurkat WM793 SKMel2	20:1	TRAIL	[51]
Blood pDCs	IL-3 → R848 → FSME →	K562 K562 K562 Daudi (lymphatic cancer)	20:1	ND ND Contact dependent	[50]

[a]Partially dependent, other mechanisms (shown when possible) may be involved.

[b]Chronic hepatitis C patients.

[c]Abbreviation: IMQ, imiquimod.

CD2^{high} pDCs over CD2^{low} pDCs to bind their targets, might be involved in the cytotoxic action of CD2^{high} pDCs [52]. Expression of granzyme B has been observed in unstimulated pDCs [51,52] as well as in pDCs stimulated with IL-3 and/or IL-10 [50,53,54], but this molecule only seems to contribute to cytotoxicity in the stimulated pDCs. These granzyme-B-producing, IL-3- and IL-10-activated pDCs target T cells in a granzyme-B-dependent, but perforin-independent manner [54]. This confirms the findings by others that killer DCs can mediate cytotoxicity through the granzyme pathway while being completely devoid of perforin [27,51]. Apart from granzyme B, TRAIL has also been implicated as a mediator of T cell lysis by pDCs. pDCs stimulated with purified human T cell leukemia virus (HTLV)-1 or HIV-1 upregulate TRAIL and induced TRAIL-dependent apoptosis in primary CD4$^+$ T cells or CD4$^+$ T cell lines [55,56]. Both the TLR7 pathway and endosomal degradation are involved in the transformation of pDCs into their killer variant by HLTV-1 [55]. In agreement with this, pDCs isolated from viremic HIV patients express TRAIL and induce apoptosis of HIV-infected CD4$^+$ T cells [57]. In another study, TRAIL$^+$ pDCs

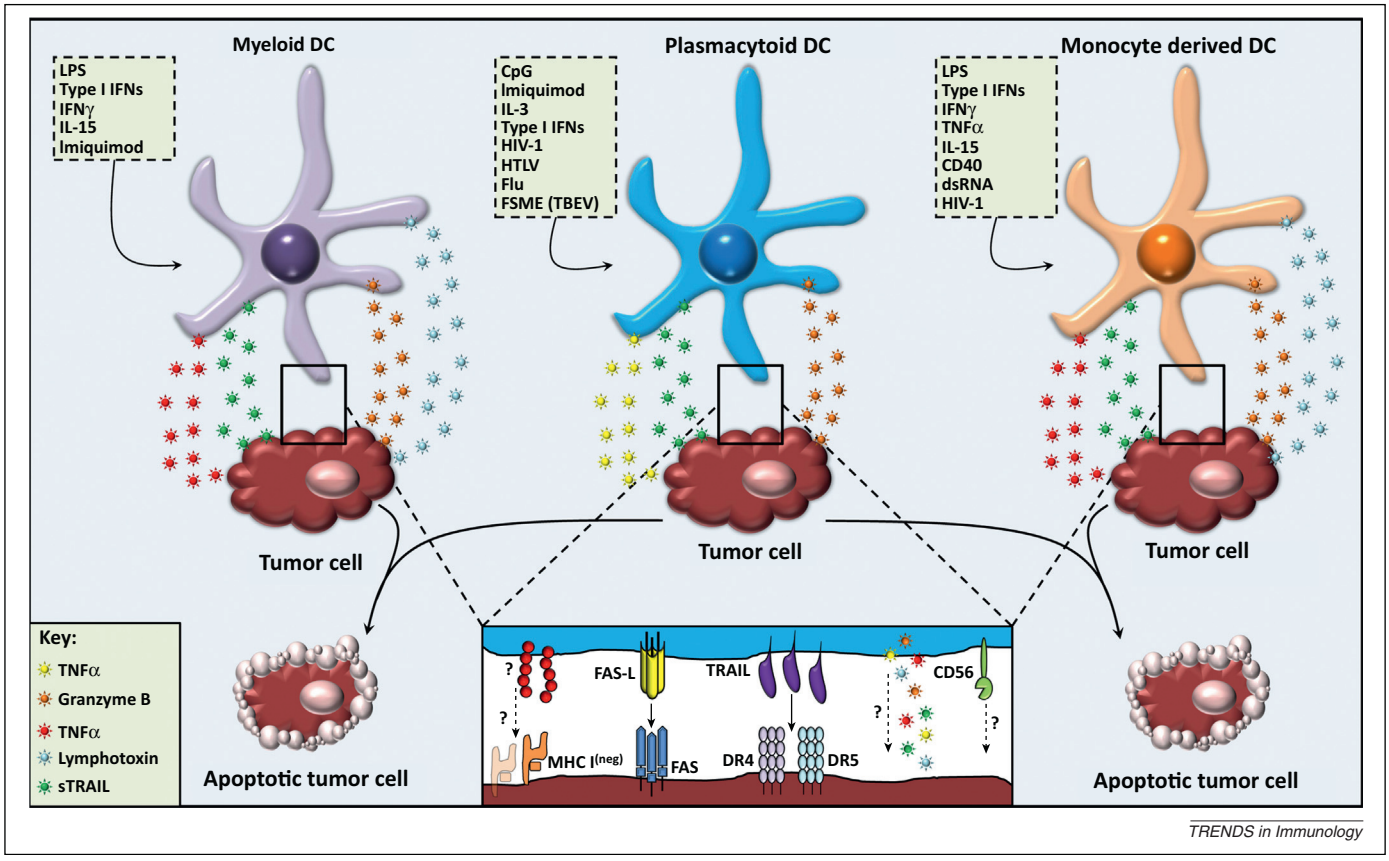

Figure 1. Direct cytotoxicity of human killer DC subsets. Activation of human DCs with various stimuli, for example, viruses, cytokines, TLR ligands, induces a cytotoxic function. DCs can exert their cytotoxic ability either by the secretion of soluble factors or by the expression of apoptosis inducing molecules. It is unclear whether soluble factors play a role at the contact site between target cells and DCs, how killer DCs recognize MHC-class-I-negative target cells, or if there is a role for CD56 in the cytotoxic function of killer DCs. Abbreviations: CpG, CpG oligodeoxynucleotides; DC, dendritic cell; dsRNA, double-stranded RNA; Flu, influenza; FSME, früh sommer meningo-encephalitis; HIV-1, human immunodeficiency virus 1; HTLV, human T lymphotrophic virus; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; sTRAIL, soluble tumor necrosis factor-related apoptosis-inducing ligand; TBEV, tick-borne encephalitis virus; TNF, tumor necrosis factor.

displayed no cytotoxic responsiveness to HIV-infected autologous $CD4^+$ T cells, but were capable of inducing apoptosis of an HIV-infected $CD4^+$ T cell line [58]. The ability of human killer pDCs to induce apoptosis in virus-infected cells may be a protective mechanism by which the host immune system controls virus spread [59].

Killer DCs in the war on cancer

Indirect cytotoxic effects of pDC-derived type I IFNs

pDCs are generally accepted as the major type I IFN-producing cells of the immune system. These type I IFNs can initiate protective immunity through maturation of mDCs and subsequent activation of T cells and NK cells (reviewed in [60]). Thereby, pDCs may play a central role in inducing indirect cytotoxic activity against tumors via various pathways, for example, apoptosis induction and anti-angiogenesis via signaling through a common IFNα receptor. Furthermore, the direct inhibitory effects on tumor cell growth/functions were thought to be the major mechanisms in the antitumor response in IFN-treated patients. In fact, IFNα can directly inhibit the proliferation of tumor cells both *in vitro* and *in vivo*, and can exert other direct effects on tumor cells (Figure 2) [61]. Next to a direct cytotoxic and cytostatic effect, IFNα also has wide stimulatory effects on other immune cells. As discussed above, monocytes can differentiate into killer DCs under the control of IFNα. In addition, recent studies have shown that IFNα also improves mDC survival and the capacity to store and process exogenous antigens, leading to enhanced cross-presentation and cross-priming of antigen-specific $CD8^+$ T cell responses [62,63]. *In vivo* evidence was recently provided by two independent studies showing that, in mice, type I IFNs were critical for the induction of antitumor immune responses [62,64]. Furthermore, type I IFNs can regulate NK cell function, by enhancing the of NK cells to kill target cells and to produce IFNγ [65]. Also, type I IFNs promote the accumulation and/or survival of proliferating NK cells by the type I IFN and signal transducer and activator of transcription (STAT)1-dependent induction of IL-15 [65].

These studies suggest that upon activation, pDCs can exert a wide variety of indirect cytotoxic antitumor effects (Figure 2). This notion is underscored by a study demonstrating that either pDC or IFNα depletion leads to a loss of the TRAIL-mediated tumor cell killing by $CD14^+$ monocytes. This highlights a crucial role for pDC-derived IFNα in antitumor immunity [66]. The expression of TRAIL on a wide variety of immune cells is known to be regulated by type I IFNs [67,68]. Moreover, in some studies there has even been a direct link between pDC-derived type IFN, TRAIL expression, and target killing in the context of HIV [57,69]. Whether or not killer pDCs also acquire TRAIL expression under all other reported conditions in a para-

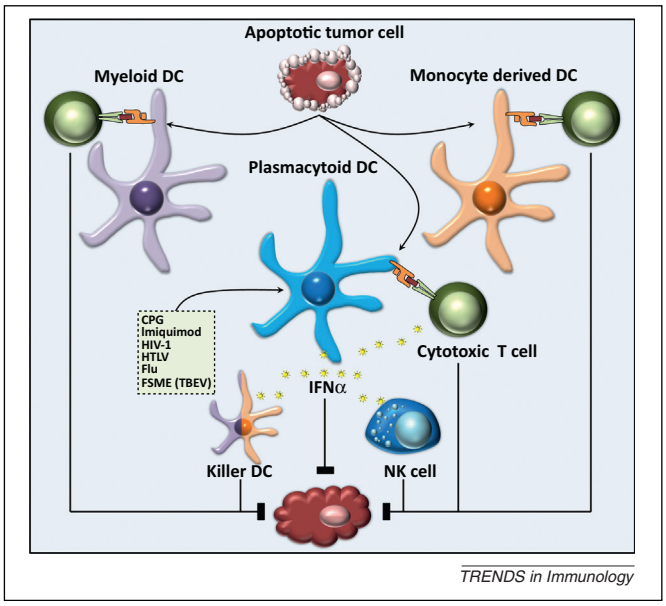

Figure 2. Indirect cytotoxicity of human killer DC subsets. Antigen-loaded killer DCs have the ability to activate antigen-specific cytotoxic T cells that in turn can lyse target cells. Whether killer DCs also have the ability to cross-present antigens obtained from killed target cells and thereafter cross-prime cytotoxic T cells is unclear. Furthermore, human pDCs produce large amounts of type I IFNs upon stimulation and, next to a direct cytotoxic effect, can exert indirect cytotoxic effects by: (i) activating NK cells; (ii) enhancing antigen cross-presentation and cross-priming of T cells; and (iii) generating of IFNα-induced killer MoDCs/mDCs. Abbreviations: CPG, CpG oligodeoxynucleotides; DC, dendritic cell; Flu, influenza; FSME, früh sommer meningo-encephalitis; HIV-1, human immunodeficiency virus 1; HTLV, human T lymphotropic virus; IFN, interferon; NK, natural killer; TBEV, tick-borne encephalitis virus.

crine or autocrine type-I-IFN-dependent manner remains to be determined.

Activation of tumor-infiltrating DCs to boost antitumor immunotherapy

The discovery of the ability of DCs to become tumor cell killers has generated new opportunities for future nonconventional immunotherapeutic strategies. It is generally accepted that macrophages and DCs outnumber NK cells and CTLs in tumor tissues, making these professional APCs ideal candidates to target and induce an antitumor response [10]. Human DCs infiltrate a vast range of tumors including skin cancer, ovarian carcinoma, and lung and colorectal cancer. However, this infiltration does not lead to a conclusive role in prognosis [48]. Infiltration by pDCs in breast cancer and ovarian carcinoma is correlated with an adverse prognostic outcome [70,71], whereas infiltration of pDCs in lung cancer does not correlate with prognosis [72]. In particular, a tolerogenic state seems to be of importance because DCs can remain in an inactivated state due to the immunosuppressive environment of the tumor [48].

Nevertheless, some studies have shown tumor regression upon treatment with several TLR agonists, such as CpG or imiquimod. Stary *et al*. have shown that, upon treatment of basal cell carcinoma patients with imiquimod, mDCs and pDCs are recruited to the tumor site and express cytotoxic effector molecules [44]. In a mouse model of transplantable melanoma, treatment with imiquimod led to tumor clearance in a manner dependent on production of chemokine CC ligand (CCL)2 by mast cells. CCL2 induced the massive recruitment of pDCs into the skin, leading to a pDC-dependent reduced melanoma growth [73]. In another study, treatment of human basal cell carcinoma with imiquimod resulted in tumor regression by recruiting pDCs that specifically lysed the tumor cells expressing TRAIL receptor 1 in a TRAIL-dependent manner, and mDCs that expressed granzyme B [44]. The fact that pDCs only lysed cells expressing TRAILR1 indicates that these cells have the capacity to act as anticancer effector cells, thereby showing potential as targets for tumor clearance. These data suggest that tumor-infiltrating DCs can act as killer cells that are directly involved in tumor clearance. A recent study demonstrated that depletion of unactivated pDCs in an orthotopic mammary tumor model delayed tumor growth; however, in the same model, intratumoral administration of a TLR7 agonist led to pDC- and type-I-IFN-dependent tumor regression [74]. These findings point to a Janus-faced function of tumor infiltrating pDCs, and suggest that their function can be largely determined by context and activation state.

Indirect antitumoral activity of killer DCs via amplification of the adaptive immune response

In the past decade, clinical trials carried out by investigators worldwide have shown that vaccination with DCs loaded *ex vivo* with tumor peptides can induce tumor-specific immune responses in patients with advanced cancer [75]. However, the clinical results obtained so far have been rather disappointing, with only a minority of the treated patients showing long-lasting clinical responses. Many research efforts are currently being undertaken to improve the clinical efficacy of DC-based cancer immunotherapy protocols. Thus far, virtually all clinical trials were based on *ex vivo* generated DCs, either derived from monocytes or $CD34^+$ progenitor cells. Only recently, the possibility has been explored to exploit scarce naturally circulating DCs such as pDCs to vaccinate end-stage melanoma patients, which showed promising results in terms of overall survival [2].

Several research groups have demonstrated that human killer DCs, apart from their direct tumoricidal activity, can present tumor antigen to T cells, providing a strong rationale for the use of killer DCs in DC-based vaccination protocols. Both IL-15 and IFNα differentiated $CD56^+$ MoDCs were found to be efficient stimulators of antigen-specific T cell responses [26,27]. Human pDCs also have the capacity to present antigens and be potent stimulators of both $CD4^+$ and $CD8^+$ T cell responses [2,50,76]. The high effector: target ratios that are required to detect killing activity argue in favor of a more predominant role for DCs in the acquisition and presentation of antigens rather than a role as effector cells capable of killing of tumor or virus-infected cells.

Concluding remarks

We have reviewed recent studies providing evidence for an effector role for DCs in cytolysis. We propose that DCs, and pDCs in particular, present a promising target for immunotherapy because they infiltrate tumor lesions and are, upon activation, capable of specifically kill tumor cells, either directly or via activation of other cytotoxic effector cells. However, many questions remain before killer DCs

can be used in their full capacity in a clinical situation. How exactly do killer DCs recognize tumor/target cells, and in particular MHC-class-I-negative cells? What are the exact mechanisms that these DCs use, for example, exclusively TRAIL or other mechanisms? Furthermore, can human killer DC cross-present antigens derived from their killed target cells? Answering these questions may help to exploit these killer DCs for immunotherapy.

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