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Review Article

Myeloid and Plasmacytoid Dendritic Cells and Cancer – New Insights

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Abstract

Dendritic cells (DCs) use effective mechanisms to combat antigens and to bring about adaptive immune responses through their ability to stimulate näive T cells. At present, four major cell types are categorised as DCs: Classical or conventional (cDCs), Plasmacytoid (pDCs), Langerhans cells (LCs), and monocyte-derived DCs (Mo-DCs). It was suggested that pDCs, CD1c+ DCs and CD141+ DCs in humans are equivalent to mouse pDCs, CD11b+ DCs and CD8α+ DCs, respectively. Human CD141+ DCs compared to mouse CD8α+ DCs have remarkable functional and transcriptomic similarities. Characteristic markers, transcription factors, toll-like receptors, T helpers (Th) polarisation, cytokines, etc. of DCs are discussed in this review. Major histocompatibility complex (MHC) I and II antigen presentation, cross-presentation and Th polarisation are defined, and the dual role of DCs in the tumour is discussed. Human DCs are the main immune cells that orchestrate the immune response in the tumour microenvironment.

Introduction

Since their discovery by Ralph Steinman and Zanvil Cohn in 1973, much information about dendritic cells (DCs) has accumulated in the literature [1]. In 2011 Ralph Steinman was awarded the Nobel Prize in Physiology or Medicine for his contribution in the investigation of dendritic cells and of their importance in initiating the adaptive immune response [2]. The unique function of DCs is their ability to stimulate näive T cells and to be a bridge between innate and adaptive immunity [3]. DCs have highly effective mechanisms to detect and capture antigens and to bring about of adaptive immune responses. Several recent reviews have highlighted similarities and differences in human and mouse DCs [3], [4], [5], [6].

DCs continuously interact with T cells even in the absence of infection. Moreover, DCs presenting self-antigens also interact with T cells in the steady-state [7]. Thus, DCs enforce peripheral T cell tolerance by the continuous presentation of self- or innocuous antigens to T cells in the absence of co-stimulation or activating cytokines. DCs mediate tolerance and silencing, thus preventing unwanted immune reactions to self and environmental antigens. This “tolerogenic” role of DCs is extensively studied in the light of their therapeutic application [2].

In the current review, we present the human DC subsets and some mouse DCs that were thought to be equivalent to human ones and focus on recent advances in human DC development and function.

DC development

In mice, the common myeloid progenitor or macrophage / DC progenitor (MDP) that gives rise to monocytes and macrophages on the one hand and the common DC progenitor (CDP) on the other is localised in bone marrow (BM). The CDPs in BM develop first into pre-DCs (entering blood) that in turn gives rise to classical or conventional DCs (cDCs) and into plasmacytoid DCs (pDCs) [8], [9]. Recent studies showed that cDCs are an independent haematopoietic lineage [9]. The cDC-restricted progenitor is registered in the spleen [10], and Liu et al., defined similar pre-DC populations in the BM and other tissues. In the BM CDPs change to pre-DC, that move using blood flow to peripheral lymph nodes (LN) and to non-lymphoid tissues (NLT), where they differentiate terminally into cDC subsets ($CD11b^+$ DC tissues, $CD4^+CD11b^+$ DCs and $CD8^+$ / $CD103^+$ DCs) [10]. In the periphery, cDCs live briefly and are very plastic, which allows a rapid function in response to antigens [8].

Interferon regulatory factor 8 (IRF8) is a key transcription factor important for the development of $CD8\alpha^+$ cDCs and $CD103^+$ DCs. Basic leucine zipper transcriptional factor ATF-like 3 (BATF3), Id2-GFP and the nuclear factor interleukin 3 (NFIL3) initiate the development of $CD8\alpha^+$ cDCs as well as of $CD103^+$ DCs [11], [12], [13].

In mice, pDCs develop in the BM from multiple progenitor types such as MDP, committed lymphoid (CLP) or myeloid (CMP) progenitors [14]. Pre-PDCs lose their potential to give rise to other cell types (a process called commitment) when maturing [10], [15], [16]. The earliest progenitors suck as CMPs give rise to erythrocytes, granulocytes, megakaryocytes, monocytes, macrophages, myeloid dendritic cells (mDCs) and pDCs [16]. Moreover, pDCs and cDCs developed from CDP or pre-DCs in murine BM, and express FMS-like tyrosine kinase 3-ligand cytokine receptor FLT3 (CD135) triggered by its ligand FLT3L [17], [18] as well as by several transcription factors such as PU.1 and IRF8 [8]. CDP also express macrophage colony-stimulating factor receptor (M-CSFR, CD115) and granulocyte-macrophage colony-stimulating factor receptor (GM-CSFR) [19], [20], and low levels of stem cell factor receptor (c-KIT; CD117) [14], [21], [22]. The development proceeds through immature pDCs in the BM to mature pDCs in blood [22].

In humans, the equivalents of mouse CMPs, CDPs and even pre-DCs are as yet undefined [23]. Human gene expression studies reveal that DCs form a separate cluster from monocytes and macrophages [24], a fact that has also been confirmed in mice [9]. Moreover, in inflammation monocyte-derived dendritic cells (Mo-DCs) were shown to arise from monocytes [25].

Because of their limited availability, human DC subsets have been studied mainly in culture. Commonly, the generation of interstitial DCs and LCs has been achieved in culture with $CD34^+$ hematopoietic progenitor cells (HPCs) with GM-CSF and tumour necrosis factor-alpha (TNFα) [26], [27] with or without IL4 producing Mo-DCs, and that are distinct from DCs developed from CDP [28]. Cells that are developed from whole BM *in vitro* with FTL3L have been used to study cross-presentation [29], [30]. It is established that in $CD34^+$ HPCs GM-CSF / TNF-α-driven culture system, $BDCA3^+$ expression is found on $CD14^+$-derived interstitial DCs. The addition of TGFβ enhances BDCA3 expression on $CD14^+$ DCs (manipulated differentiation towards LCs), whereas IL4 enhances BDCA-3 expression in both $CD14^+$ DCs and $CD1a^+$ DCs (interstitial DC lineage) [26], [31]. Moreover, pDCs, $CD1c^+$ DCs and $CD141^+$ DCs can be derived in vitro by culturing $CD34^+$ HPCs FTL3-L [32]. Identification of early DC precursors in human blood is difficult because all human CD34+ HPC precursors express the DCs activation marker MHC class II antigen. It is reported that human cDCs proliferate in blood or NLT [3], while the pDCs fully develop in BM and then leave it [33].

Human DCs arise from BM precursors such as granulocyte-macrophage DC (progenitors producing granulocytes, macrophages and DCs), and from macrophage-DC progenitors (producing macrophages and DCs), and MDP-derived common DC progenitors restricted to BM (producing cDCs and pDCs). Similarly, to MDPss, CDPs highly express M-CSFR and FTL3R, and low levels of c-KIT, like in mice. CDPs are the precursors of both pre-pDCs and pre-cDCs, cells that are not fully mature. The maturation of pDCs is completed in the BM, and cDCs differentiate in tissues [34], [35].

The common monocyte progenitor through GMP gives rise to blood $CD16^+$ and $CD14^+$ monocytes. The three types of DC, namely cDC1 ($CD141^+$), cDC2 ($CD1c^+$) and pDCs ($CD303^+$) develop therefrom pre-DCs [3], [36], [37]. Differentiated DC subsets and monocytes circulate in peripheral blood and can be found in lymphoid tissue as resident cells. In the skin, $CD14^+$ Mo-DCs, cDC1, cDC2, macrophages and LCs (latter both derived from fetal Yolk sac/liver progenitors) can be detected.

The *genetic control* of DC lineage achieved by distinct transcription factors, particular pattern recognition receptors that lead to the production of specialised secretory products. The development of cDC1 requires BATF3 and IRF8. The development of cDC2 is dependent on IRF4 and Kruppel-like factor 4 (KLF4). The factors ID2 BATF3, and BCL6, associated with cDC development, are expressed at low levels in CDPs. Therefore, the induction of pDC or cDC development deposed on transcription factor expression on CDPs [35].

The origin of pDCs relies on runt-related transcription factor 2 (RUNX2), classic I basic helix

loop helix (bHLH) factors, ZBTB-46, BCL11A, IRF7 and IRF8 [14], [35]. One key transcription factor for the development of pDCs is E2-2 [11]. E2-2 regulates a large pDC gene program, which in turn regulates other key transcription factors for pDC development such as IRF8 and when expressed, it unlocks pDCs differentiation. The loss of E2-2 from mature pDCs converts their phenotype and function into cDC-like phenotype [38].

LCs originate under the control of RUNX3 and ID2 and need IL34 and TGFβ for their development [23], [35].

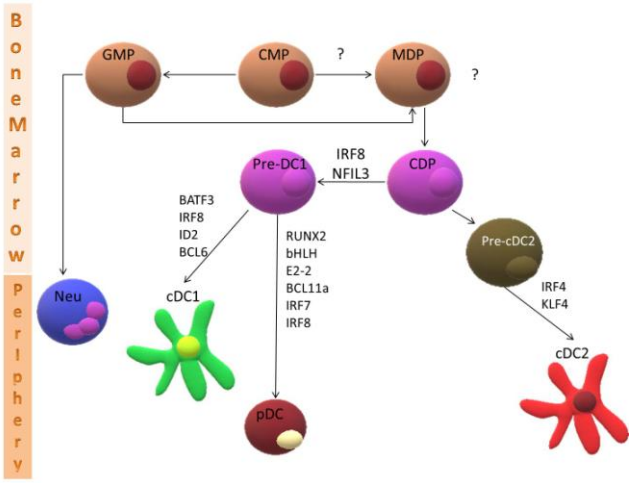

Figure 1: Development of human DCs

DC subsets

There is a great confusion in literature concerning the designation of "myeloid" or 'classical type I DCs (cDC1s)' and type II 'cDC2s'. Some investigators use CD8α$^-$ CD4$^+$ CD205 / DEC205$^-$ CX_3CR1^- CD11b$^+$) for type 1 cDCs and CD8α$^+$ CD4$^-$ CD11b$^-$ CD205 / DEC205$^+$ CX_3CR1^+ and C type lectin domain family 9 member A (CLEC9A)$^+$ for type 2 cDCs in mice [39?], [40], [41]. Moreover, CD1c / BDCA1$^+$CD11c ^{hi}CD123$^-$ are named as mDC1, and CD141/BDCA-3+CD11c^{lo} are named as mDC2 in humans [42], [43]. On the contrary, other investigators use the term of cDC1 for CD8α$^+$ or CD103$^+$ DCs and cDC2 for CD11b$^+$ DCs in mouse [44] and CD1c$^+$ (BDCA1$^+$) for cDC2 and CD141$^+$ / BDCA3$^+$ for cDC1 type in humans [37], [45].

Boltjes and van Wijk use the signature of CD1c$^+$ and CD141$^+$ DCs without determination of DCs type I or II for human DCs (3). Similarly, Collin et al., applied CD1c$^+$ (Clec7A$^+$ Clec6A$^+$) and CD141$^+$ (Clec9A$^+$ XCR_1^+) as major markers for human cDC types, and CD11b$^+$ (tissues) and CD4$^+$CD11b$^+$ endothelial cell-selective adhesion molecule (ESAM)$^+$ (lymphoid) and CD103$^+$ (tissues), CD8α$^+$ (lymphoid) Clec9A$^+$ XCR_1^+ Langerin$^+$ for mouse cDCs [37].

In their excellent review, Reynolds and Haniffa concluded [45] that mouse DCs expressing CD8α in the spleen and CD103 in NLT that are equivalent to human CD141 (thrombomodulin, BDCA-3) DCs [46], [47], [48] are type 1 cDC. The type 2 cDC phenotype in mice are LIN$^-$MHC I ^{hi} CD11c$^+$ CD11b$^+$, and this fraction also includes Mo-DCs and macrophages [25]. Therefore, mouse CD11b$^+$ DCs and human CD1c$^+$ DCs have been regarded as type cDC2 [45]. We also accept their definition of cDC1 and cDC2.

In Mice

All DC subsets in mice have corresponding human counterparts. Murine cDCs or mDCs have been traditionally categorised into two distinct subsets: the 'cDC1s' for CD8α$^+$ and CD103$^+$ (tissues) DCs and cDC2s for CD11b$^+$ DCs and CD172a$^+$ DCs that lack CD8α marker (49). The third type of murine DCs is pDC, which retains their original name [40]. Both subpopulations can be found in LT, including spleen, LNs, BM, and NLT [13], [49].

Table 1: TLR expression in mouse DCs

	cDC1	cDC2	pDC
Phenotype	NLT: CD8α$^+$, CD11c$^+$, MHC II$^+$, CD103$^+$, CLEC9A(DVGR)$^+$, XCR1$^+$, CD11b$^-$ LT: CD8α$^+$, MHC II$^+$, CLEC9A$^+$, XCR1$^+$, CD205$^-$ / DEc205$^+$, SIRPa (CD172a)$^-$, CD11b$^-$, CD4$^-$	NLT: CD11b$^+$, CD103-, MHC II+, XCR1$^+$ LT: CD11b$^+$, CD4$^+$, CD8α$^-$, SIRPa (CD172a)$^+$, CD11c$^+$	LT: CD11c$^+$, MHC II$^+$, CD317 (BST2)$^+$, Siglec H$^+$, CD45R(B220)$^+$, CD11b$^-$, Ly-6C$^+$
TF	TRF8, BATF3, ID2, Bcl6	TRF4, Notch2, Klf4	IRF8, E2-2, RUNX1, Bcl11a
Location	LT, NLT	LT, NLT	LT, NLT, BM
TLRs	TLR3 (TLR6, TLR8, TLR1, TLR2, TLR4) (TLR4 stimulates Th1 immune response of IL12)	TLR8 (TLR (7)9) (TLR2 stimulates Th2 responses)	TLR7 (4,8) (TLR1,2) TLR9
Cytokines	TGFβ (induction of Treg)		
T-cell interactions	CD8$^+$T cell responses cross presentation with MHC class I molecules; Ag and immune complexes	Th2, Th17 (allergies), (fungal) presentation of Ags with MHC class II molecules	CD4$^+$Th2 - ? and CD8$^+$Th1
Biological roles	Cross presentation - CD8$^+$T cell response	CD4$^+$T cells priming	Anti-viral response high production of IFNα / β, antiviral response

CD8α$^+$ and CD103$^+$ cDC1s. The CD8α$^+$ cDCs have been found in murine lymphoid organs. An alogous DC population exists in NLT, and these cells express CD103 integrin marker ($\alpha_\varepsilon\beta7$). CD8α$^+$ and CD103$^+$ cDC1s are the best-characterised cDC subsets, conserved through evolution, and the chemokine receptor XCR1 (important for cross-presentation) was identified first on these DCs [46]. CD8α$^+$ cDCs are highly efficient in cross-presentation of exogenous antigens on MHC-I molecules to CD8$^+$ T cells in CD1d context, a fact that is critical for immunity against viruses and bacteria [46] and in antitumor immunity [23]. Therefore, CD8α$^+$ cDCs can

activate and polarise invariant natural killer T-cells towards the production of T helper 1 (Th1) and Th2 cytokines and CD8α$^+$ cDCs secrete IL12p70 [50], [51]. Skin-derived CD103$^+$ cDCs also have cross-presentation activity using MHC class I molecules to present antigens to CD8$^+$ T lymphocytes [13].

The phenotype of CD8α$^+$ cDCs in LT has been delineated by the expression of CD11c^{hi}, MHC class II^{hi}, XCR1$^+$, CLEC9A$^+$, CD8α$^+$, CD4$^-$, CD205 (DEC205)$^+$ and that of CD103$^+$ DCs in NLT (analogous to CD8α$^+$ in peripheral tissues) – by CD11c^{hi}, MHC class II^{hi}, XCR1$^+$, CLEC9A$^+$, CD8α$^+$, CD4$^-$ CD11b$^-$ and CD103$^+$ [52].

CD11b$^+$ DCs and CD172a$^+$ DCs (cDC2s). A second and largely complementary DC subset can be distinguished in lymphoid organs by the expression of CD4 [12]. CD4$^+$ CD11b$^+$DCs cDC2 are considered to be poor cross-presenters in vivo but are more efficient while endogenous cytosolic antigens are presented on MHC class II to CD4$^+$ T cells [53]. Moreover, CD4 is not expressed on the complementary peripheral subset (in NLT), which can be instead identified by the expression of CD11b. CD11b$^+$ DCs are mostly defined by the absence of activities associated with CD8α$^+$ DCs [41]. They are inefficient at cross-presenting antigens and do not produce IL12. In contrast to CD8α$^+$ DCs, CD11b$^+$ DCs are superior in the induction of CD4$^+$ T cell immune response because of their prominent expression of MHC class II machinery [13], [53], [54].

CD11b$^+$ DCs prevail in lymphoid organs except for the thymus. They can also be detected in NLT. In the spleen DCs can be classified into three populations of resident cDCs: CD8α$^+$ DCs, endothelial cell-selective adhesion molecule (ESAM)^{hi} CD11b$^+$ cDCs and ESAM^{lo} CD11b$^+$ cDCs [23], [54]. Both CD11b+ cDCs in NLT and LT-resident DCs are occupied in the antigen presentation in MHC II-restricted manner [52], [53].

Table 2: TLR expression in human DCs

	cDC1	cDC2	pDC
Phenotype	Blood: CD141$^+$(BDCA-3)$^+$; LT: HLA-DR$^+$, CLEC9a$^+$, αCR1+, CD11c$^+$, CD11b$^-$, CD123$^-$	Blood – LT: CD1c(BDCA-1)$^+$, HLA-DR$^+$, CD11b$^+$, CD11c$^+$, SIRPa(CD172a)$^+$	Blood: HLA-DR$^+$, CD303 (BDCA-2)$^+$, CD304 (BDCA-4)$^+$, CD123 (IL-3R)$^{++}$, CD85g (IαT7)$^+$, CD11c$^-$
TF	IRF8, BATF3, ID2, Bcl6	TRF4, Klf4	IRF8, E2-2, RUNX2, Bcl11a, IRF7, bHLH
Location	Blood, LT, NLT	Blood, LT, NLT	Blood, LT
TLRs	TLR3 (TLR1, TLR2, TLR4), TLR5,6,8,10	TLR8 (TLR7,9) TLR4	TLR7, 9 (endosomes) (TLR1,6,10 low) facilitated IFN type I expression
Cytokines			IFN α (TLR7/9) IFN III
T-cell interactions	CD8$^+$T cell responses cross presentation with cellular Ags and immune complexes Th1	Th2(allergies), (Th17 fungal)	CD4$^+$Th2 CD8$^+$Th1 Granzime B secretion
Biological roles	Anti-tumor, Anti-viral	CD8$^+$Th1 (IL-12) Regulation of immune responses; Anti-parasites, anti-bacterial	Anti-viral, Anti-fungal, Anti-tumor

Conceivably, CD11b$^+$ESAM^{hi} cells are also CD11c^{hi}MHC class II^{hi}, CX$_3$CR1^{low}, CD11b$^+$ and ESAM^{hi} and are associated with CD4$^+$ DC responses, while CD11b$^+$ESAM^{lo} cDCs are CD11c^{hi}MHC class II^{hi}, CD103$^-$, CD11b$^+$ and CD24$^-$ and produce inflammatory cytokines such as IL6 [55] and IL23 [3] upon toll-like receptor (TLR) triggering [40], [54]. CD11b$^+$ DCs secrete also pro-inflammatory chemokines CCL3, CCL4 and CCL5 after TLR stimulation [56]. The two DCs types are NOTCH2-dependent [54], and the latter type is also IRF4-dependent [31].

In Humans

Historically, human DC subsets have been defined concerning some phenotypic markers and anatomic location. Human DCs express high levels of MHC class II (HLA-DR) and CD45$^+$ and lack typical lineage markers CD3 (T-cell), CD19 / 20 (B-cell) and CD56 (natural killer cell). The classical description of human DCs is HLA-DR$^+$ lineage$^-$ including myeloid and plasmacytoid subsets [37], [57].

Human DCs consist of heterogeneous with distinct functional specializations categorized into, blood and lymphoid organ-resident DCs comprising CD11c$^-$ CD123^{hi} CD303 (BDCA2)$^+$ CD304 (BDCA4)$^+$ or pDCs secreting type I IFN. The other subset in this category is mDC that has been further delineated into a CD141 (BDCA3)^{hi} CLEC9A$^+$ or the major cross-presenters to CD8 T cells [47] and CD1c (BDCA1)$^+$ population [57]. Secondly, migratory DCs also exist that reside in NLT and response to danger signals migrate to lymphoid organs. Three migratory DC subsets belonging to myeloid lineage and expressing CD11c have been described in NLT including the skin. These are epidermal LCs (langerin$^+$ CD1a^{hi} DC-SIGN$^+$), interstitial (CD1a$^+$ DC-SIGN$^-$) and CD14$^+$ (CD1a$^-$ DC-SIGN$^+$) DCs [27]. The latter subset is linked to human monocyte / macrophage populations [27], [48], [58]. Additionally, BDCA3+ CLEC9A+ DCs, capable of cross-presentation and IFNλ production have been identified in the human dermis [48]. Finally, inflammatory DCs differentiate from peripheral blood monocytes [59].

Concerning anatomic location human DCs are blood DCs (pDCs and mDCs), and mDCs have been separated into two subsets, namely BDCA3 / CD141$^+$ DCs and BDCA1 / CD1c$^+$ DCs [17]. These three DC populations are found in all lymphoid organs and are considered as resident DCs [47], [58], [60]. Conceivably, immature cDCs leave the BM, disseminate via blood to lymphoid organs and peripheral tissues, where they achieve resident and migratory phenotype [61]. The resident cDCs in lymphoid tissue stay in an immature state unless they get activation signals and become mature [62]. The migratory (mature) cDCs travel from the tissues to the LNs via afferent lymph and mature upon reaching regional LNs [63]. Migratory cDCs transport and also present peripheral self-antigens to induce T-cell tolerance [64].

In skin, liver, lung and intestine two main populations of cDCs exist, namely CD1c$^+$CD1a$^+$ and

CD141$^+$ CLEC9A$^+$ DCs [48]. These DCs migrate to draining lymph nodes and are called migratory DCs with mature phenotype [58]. In human mucosa tissues, additional DC subsets: LCs and CD14$^+$ DCs in the skin and vaginal mucosa and CD103$^-$ CD172a$^+$ DCs in the intestine [65].

Some of the used phenotypic markers for DC definition can be expressed on several cell types or can be changed upon activation [17]. For example, CD141 is also upregulated after activation on pDCs and on CD1c$^+$ DCs (except on traditional cDC1s) [42]. Intermediate levels of CD141 / BDCA-3 (thrombomodulin) are expressed on tissue CD14$^+$ DCs [66], [67]. BDCA3 is a cell surface transmembrane glycoprotein that is predominantly expressed on vascular endothelial cells and has anti-coagulant activity and anti-inflammatory function [68].

Another example is the rapid down-regulation of the classical cDC1s marker CLEC9A (restricted to CD141$^+$ DCs) during maturation [69]. Moreover, using the classical hallmark of DCs (dendritic morphology, migratory capacity and the ability to stimulate naïve T-cells) one can distinguish DCs from macrophages and monocytes [17].

Finally, transcriptomic studies are useful to confirm DC identity. Homology between human (XCR1$^+$ CD141$^+$) cDC1s and mouse (CD8α$^+$ / CD103$^+$) cDC1s is demonstrated by comparative transcriptomic, phenotype and functional analyses [45], [47], [48], [60]. It has been suggested that pDCs, CD1c$^+$ DCs and CD141$^+$ DCs represent distinct lineages and are equivalent to mouse DC subsets pDCs, CD11b$^+$ DCs and CD8α$^+$ DCs, respectively [48], [65]. The origin of CD141+ DCs is maintained by BATF3 transcription factor [70].

CD141$^+$ BDCA3$^+$

The essential role of DCs in the induction and regulation of immune responses to pathogens, self-antigens, and cancer has been well established [71]. The characterisation of human DC subsets is difficult because of their rarity, the lack of distinctive markers, and limited access to human tissues [47]. Human blood DCs comprise ~ 1% of circulating peripheral blood mononuclear cells defined as antigen-presenting leukocytes that lack other leukocyte markers such as CD3, CD14, CD15, CD19, CD20 and CD56, and express high levels of MHC class II (HLA-DR) molecules [17].

Gene -expression profiling and hierarchical clustering data have indicated that CD1c+ DCs and CD141+ DCs have a common origin and represent two different stages of a similar subset [72]. However, CD1c+ DCs and CD141+ DCs have unique gene -expression profiles differentiating them from monocytes and mo-DCs [42], [72].

Human CD141+ (thrombomodulin+) DCs comprise only ~ 0.03% of human peripheral blood mononuclear cells and 10% of human blood mDCs [42]. Moreover, CD141+ DCs are present at small numbers in tissues, and other cells also express this marker although at a low level (CD14+ DCs, CD1c+ DCs and monocytes) therefore, they are difficult to identify [47]. Their differentiation from CD1c+ DCs by flow cytometry has been made possible by the fact that CD141+ DCs express less CD11b and CD11c [37].

An efficient protocol for the isolation of highly pure CD141+ and CD1c+ mDCs from leukapheresis products from normal and healthy volunteers has been reported [73]. In an extensive and excellent study [48] isolate human DC subsets from human blood and skin (from mammoplasty), lung and liver (from peritumoral tissue), tonsil and dermatopathic LNs (from tonsillectomy and LN diagnostic excision). DCs can be isolated by fluorescence-activated cell sorting (FACS) analysis and are studied by flow cytometry. FACS-purified dermal DCs are cultured with TLR ligands, and cytokine secretion of DCs has been studied. Cross-presentation and ELISpot assay have been done. By quantitative real-time polymerase chain reaction, the following genes have been examined: *GAPDH*, *XCR1*, *TLR3*, and *CADM1*, and the results suggest that CD141^{hi} DCs are functional homologs of mouse CD103$^+$ DCs and that these are distinct from the major population of human CD1c$^+$ DCs and mouse CD11b$^+$ DCs.

The main characteristics of the human CD141$^+$ DC subset have been a high expression of TLR3 (but not of TLR4, 5, or 7) and the production of IFNβ, CXCL10 and IL12p70. Another characteristic of this subset is the induction of superior Th1 response after activation with polyinosinic–polycytidylic acid (poly I:C) and the induction of Th2 response to a lower degree, therefore, CD141$^+$ DCs are the major subset involved in the induction of CTL responses against tumours and viruses [31]. Detailed functional analyses of human CD141$^+$ DCs with impact of their role in the induction of Th1 and Th2 immune responses, TLR stimulation, TNFλ production, MHC class I and class II antigen and MHC class I cross-presentation, cytokine production and their origin in culture by CD34$^+$ HPCs has been reported [17], [23], [31], [74], [75], [75], [76], [77], [78].

It has been shown that HLA-DR$^+$ lineage$^-$ cells in human blood and tissues comprised two fractions CD14$^-$ and CD14$^+$. The CD14$^-$ fraction is further separated by CD141 and CD11c expression by flow cytometry. CD141$^+$ cells in the blood have low CD11c expression, and in tissues, they are CD141^{hi} CD11c^{lo} [48]. CD14$^+$ cells in tissues express CD141, but they correspond to CD14$^+$ “interstitial type DCs” that do not have very potent allo-stimulatory or cross-presenting capacity [27], [79]. Tissue CD141^{hi} (isolated from human skin, liver and lung) and also blood CD141$^+$ show higher expression of the cross-presentation signature *CLEC9A*, *TLR3*, *CADM1*, and *XCR1*

(whereas CD14$^+$ and CD1c$^+$ express these at much lower levels) and consequently migrate in response to XCL1. CD141^{hi} DCs migrate in response to XCL1 and show the highest expression of Flt3 and CLEC9A in blood, skin and lung whereas CD14+ DCs intensely express M-CSFR and CX3CR1, markers associated with monocyte and macrophage lineages.

CD1c$^+$ DCs show lower expression of FLT3 and CLEC9A and intermediate levels of M-CSFR and CX3CR1 than CD141^{hi} DCs [48]. Reynolds and Haniffa suppose that blood CD141$^+$ DCs are the precursors of immature CD141^{hi} DCs, before to acquire CD1a, CD1c, activation antigens, and CCR7. Moreover, migrating CD141^{hi} DCs represent the CD1a and CD1c mature fraction [45], [48].

Human CD141$^+$ DCs have been compared to mouse CD8α$^+$ DCs, and remarkable functional or transcriptomic similarities have been established [24].

Both subsets share the expression of CLEC9A [80], [81], NECL2 [71], [82] and of the chemokine receptor XCR-1 [46], and are extremely rare in blood but are present in the T cell areas of LT [82].

The recognition of pathogen-associated molecular patterns by DCs involves pattern recognition receptors and TLRs [73]. To date, 10 TLRs (TLR1-10) have been identified [83]. Human CD141$^+$ DCs have strong expression of TLR3 and do not express TLR4, -5, and -7 [47], [84]. Mouse CD8α$^+$ DCs also have high expression of TLR3 and lacked TLR7 and TLR10 [47]. However, unlike human CD141$^+$ DCs, mouse CD8α$^+$ DCs express TLR4 and 9 [85]. Human CD141$^+$ DCs express TLR10 (absent in mice) at higher levels than CD1c+ mDCs [84]. TLR10 belongs to the TLR1 subfamily like TLR1, -2, and -6 [73] and its function remains to be determined.

The effect of pathogen-TLR recognition is the induction of cytokine and chemokine production [86]. Like human CD141$^+$ DCs, mouse CD8α$^+$ DCs trough high TLR expression produce IFN-β in response to poly I:C [87].

Mouse CD8α$^+$ DCs produce IL12p70, and induce Th1 cytokines IL2 and IFNγ [47], [88]. Most importantly, human CD141$^+$ DC and mouse CD8α$^+$ DCs have the cross-presenting capacity [45]. Both subtypes express high levels of MHC class I [53] that together with TLR3 and CLEC9A (sensors of necrotic cells) regulate cross-priming [89].

Despite their similarities, there are notable differences between human CD141$^+$ DCs and mouse CD8α$^+$ DCs. Murine cDC1 differentiation requires the expression of *BATF3* and *IRF8* [47], [60] that are not selectively expressed by CD141$^+$ DC. Human DCs are isolated mainly from blood, while mouse DCs are generally isolated from spleen [45].

CD1c$^+$ mDCs

Human CD1c$^+$ DCs are the major population of mDCs in blood, peripheral tissues (NLT) and LT [37]. CD1c$^+$ DCs comprise about 1% of all mononuclear cells in blood [37]. In kidney tissue there are about four times more BDCA1$^+$ (CD1c$^+$) DCs than BDCA2$^+$ (pDCs) [90]. Human CD1c$^+$ DCs classified by 45, as cDC2 phenotype are defined as lineage$^-$ MHC class II$^+$ (HLA-DR$^+$) CD14$^-$ CD16$^-$ CD11c$^+$ CD1c$^+$, a definition, they share with *in vitro* Mo-DCs [45]. Human peripheral blood and murine cDC2 additionally express CD11b, CX3CR1 and SIRPα (CD172) [91] similarly to Mo-DCs [45].

Human CD1c$^+$ DCs are identified by the commercial antibody BDCA1 [42]. Human blood CD1a$^+$CD11c$^+$ cells express high CD1c (BDCA1) levels and can rapidly acquire an LC phenotype [92], [93]. It has been shown that blood BDCA1$^+$ DCs treated with thymic stromal lymphopoietin (TSLP) and TGFβ induce expression of high numbers of LCs (CD1a$^+$ CD207$^+$) [94].

Human tissue CD1c$^+$ DCs appeared to be more activated than blood CD1c$^+$ DCs and express co-stimulatory molecules such as CD80, CD83, CD86, and CD40, they lose homing receptors CLA and CD62L, while preserving CCR7 responsible for tissue homing [37], [93]. CD1c$^+$ DCs are also detected in T-cell areas of LNs, tonsils and spleen [47], human kidneys [57], [90], skin [94], and lung [95].

The pathogenic role of CD1c$^+$ DCs in human disease is not clear, but they have been found to accumulate in chronic kidney disease [57], atopic airway asthma and are reduced in number in non-small cell lung cancer [95] and atopic disease [96]. CD1c$^+$ DCs express a wide range of lectin receptors, TLRs (TLR2, TLR3, TLR4, TLR5, TLR7, TLR8) and other pattern recognition receptors [73], [97] that are necessary for antigen uptake, transport and presentation.

Human and mouse cDC2 share a similar cytokine production profile, which includes

IL6, IL23 and IL1β, TNFα, IL8 and IL10 [73], [79]. This cytokine profile implies a dual role of CD1c$^+$ DCs in Th1, Th2 and Th17 sensitisation.

Using a new isolation protocol Hemont et al., studied human CD141$^+$ and CD1c$^+$ mDCs concerning their TLR expression pattern and TLR ligands that determine DCs cytokine and chemokine expression. The average value is 1084 ± 580 CD1c$^+$ mDCs and 169 ± 81 CD141$^+$ mDCs / 1x10^6 peripheral blood mononuclear cells [73]. CD1c$^+$ mDCs from human peripheral blood, BM and tonsils, and LT cross-present soluble antigens and prime CTLs, and are most potent human IL12 producing DCs as compared to CD141$^+$ mDCs. CD1c$^+$ mDCs perform best upon TLR4 and TLR8 stimulation, whereas CD141$^+$ mDCs

require agonists of TLR3 and TLR8 [98]. It has been shown that the immune reaction against *Escherichia coli* and Gram-negative bacteria in humans is most efficient by Mo-DCs that phagocytised it and are the main producers of TNFα, IL8 and IL6. $CD1c^+$ DCs phagocytise *Escherichia coli* to a lesser extent than Mo-DCs and are weaker producers of cytokines in response to TLR4 ligand whereas $CD141^+$ DCs are not responsible for processing and presentation of bacterial antigens [99]. Moreover, $CD1c^+$ DCs exhibit a tolerogenic phenotype by secreting a high level IL10 and expressing CD25 and IDO molecules on their surface [99], [100], [101].

pDCs

pDCs were described first in human LNs by Frederick Siegal et al., [102] and later in mice by Asselin-Paturel et al., [111]. Recently, pDCs have been regarded as a part of the DC family [100], but cells with pDC features have been known as T-cell associated plasma cells or as plasmacytoid T cells, or as natural interferon-producing cells for several decades [101]. These cells produce 200 to 1,000 times more IFNα and IFNβ than other blood cells in response to viruses [102]. pDCs produce IFN type I after engagement of their TLRs, namely TLR7 and TLR9 of viruses or self-nucleic acids [103].

The markers usually used to identify pDCs in mice are $CD11c^+$, $B220^+$, $Ly6C^+$, bone marrow stromal antigen 2 (BST2) and sialic acid-binding immunoglobulin-like lectin H $(SIGLEC\text{-}H)^+$ [52]. Mouse pDCs also express CD8α and like human pDCs express CD4 and MHC class II. Mouse pDCs also express the chemokine receptor 9 (CCR9), Ly49Q SCA1 [18].

Human pDCs

In contrast to mouse pDCs that show intermediate levels of $CD11c^+$ expression, human pDCs are $CD11c^-$ [18]. BST2 is fairly expressed on pDCs and plasma cells in steady-state and upon activation has been found on many cell types [104]. The SIGLEC-H expression is mainly confined to pDCs [105]. In humans, the origin of pDCs is not well understood because of the lack of reliable markers, paucity of DCs in blood, and the limited access to human tissues [60]. The typical phenotype of human pDCs is LIN^- $CD11c^-$ $CD123$ $(IL\text{-}3R\alpha)^+$ [22]. It has been shown that $CD141^+$ cDCs develop after culturing $CD34^+$ HPCs with c-KIT, FLT3L, GM-CSF, and IL4 [60], and after stromal cell addition to the former cocktail, pDCs develop [106]. Importantly, DCs that arise from stromal cell cultures resembled $CD1c^+$ cDCs, $CD141^+$ cDCs and pDCs obtained from peripheral blood as determined by gene expression, surface phenotype, and cytokine production [14]. Stromal cell culture has been used to support the development of HPCs into three major human DC subsets, and into monocytes, granulocytes, NK and B cells [107].

Genome-wide analysis reveals that the gene expression profile of pDCs is closer to that of cDCs than to lymphocytes or myeloid cells [24]. After stimulation human pDCs can differentiate into cDCs [108]. PDCs are distinct from cDCs and possess features of lymphocytes [14]. The morphology of pDCs in the steady-state is that of a secretory lymphocyte [108], and their circulation/localisation is different from that cDCs resembling that of lymphocytes – pDCs matured in BM and then circulate in the blood and are seeded in the secondary lymphoid organs and thymus [33], [61]. Concerning viability pDCs are long-lived, as compared to cDCs and finally, pDCs share some molecular features of B lymphocytes (expression of CD45RA, MHC class-II molecule and BDCA-2) [109], [110].

Immature or resting pDCs are round in shape and are named pre-pDCs [108] with low expression of MHC class II and low T cell co-stimulation [63]. In peripheral tissues, pDCs are very low in number [111]. By secreting IFN I, pDCs can influence innate (e.g.NK cells) or acquired (e.g. cDCs and B cells) immunity [101]. At the site of inflammation, pDCs achieve DC morphology, proliferate and reach draining LNs (100). Mature pDCs secrete IFN, acquire a dendritic morphology and show up-regulation of MHC and T-cell co-stimulatory molecules [111]. Mature pDCs can present antigen via MHC I and MHC II to $CD8^+$ T cells and $CD4^+$ T cells, respectively [112]. It has been supposed that pDCs participated mainly in antigen presentation and immunomodulation at sites of inflammation rather than in antigen transport to draining LNs for T-cell priming [63].

DC MHC Class I and MHC Class II Antigen Presentation. Cross-presentation

Endogenous MHC I antigen presentation

MHC class I molecules are expressed on the plasma membrane of all nucleated cells and until recently were considered to present endogenous peptide-derived antigens from dead and dying cells and to preserve cognate T-cell epitopes [113]. The MHC class I molecule consist of two chains – a heavy chain and a light chain called β2-microglobulin. The genetic nucleotide polymorphisms of the heavy chain ensure plenty of peptide-binding regions for antigenic proteins [114].

Antigen presentation consists in two

processes: Firstly, capturing and processing of precursor polypeptides from the extracellular compartment, and second the resulting T-cell priming, proliferation and consequent cytokine secretion after the recognition of MHC-peptide complexes by T-cells [64].

The classical MHC I presentation pathway consist of three steps. Endogenous peptides (with errors appearing during protein synthesis) are attached with ubiquitin to be degraded in the cytosol by the proteasome, a process called antigen processing [115]. Some of these degradation products are required for MHC I attachment and are therefore delivered to the endoplasmic reticulum by the transporter associated with antigen processing, and are loaded onto newly formed MHC class I molecules [116]. In the endoplasmic reticulum longer, peptides are additionally degraded (trimmed by ERAP – endoplasmic reticulum aminopeptidases) – via endoplasmic reticulum-associated degradation and loaded onto MHC I molecules [117]. This process is called antigen loading. MHC I-peptide complexes are then exported to the cell surface through the Golgi complex (along the secretory pathway) [113]: antigen transport. T-cells use their TCR to recognise antigenic peptides presented on MHC molecules on the surface of antigen-presenting cells. MHC class I molecules are recognised by CD8 T cells [118].

MHC I cross-presentation

Cross-presentation is considered to be the presentation of acquired exogenous antigens on MHC class I molecules that prime CD8+ T cell responses [119]. Therefore, DCs have to be infected with a virus or take other exogenous antigens, to break foreign peptides through its mechanism of "endogenous antigen processing" and to present the exogenous antigens via MHC I pathway [119]. This mechanism of presentation of exogenous antigens by the machinery of endogenous antigen presentation via MHC I is termed cross-presentation [113]. Exogenous antigens are internalised through micro- or macropinocytosis, receptor-mediated endocytosis or phagocytosis. To be cross-presented, these antigens go through the same three steps that comprised the endogenous pathway i. e. processing, loading and transport [113].

Cross-presentation represents an important pathway for the initiation of immune responses against tumours and viruses. Efficient presentation of exogenous antigens is realised by some other cells such as macrophages, B lymphocytes, liver sinusoidal endothelial cells, neutrophils and DCs [120]. B lymphocytes load antigens on MHC I and MHC II molecules but are less efficient presenters than DCs [121]. Neutrophils can cross-prime CD8+ T cells by MHC I-peptide complexes and use the vacuolar pathway but die within hours [122]. Liver sinusoidal endothelial cells express low levels of MHC II molecules but are unable to activate T lymphocytes [123]. Macrophages can engulf pathogens, form phagolysosomes can initiate proliferation and differentiation of CD8+T cells, but their effectiveness is restricted because of poor migratory properties [124]. Immature DCs phagocytose antigens and upon maturation present them complexed on MHC I molecules [120]. Mature DCs have the low endocytic capacity and express high levels of co-stimulatory molecules [120]. DCs suppress lysosomal proteases and inhibit lysosomal acidification via NADPH oxidase 2-mediated alkalization of phagosomes and endosomes and thus maintain exogenous antigens for a long time ready for cross-presentation (delayed antigen degradation) [125]. Delayed antigen degradation allows antigens to move into the cytosol through channels such as SEC61 [126].

During the first step (antigen processing), two main tracks are – "available cytosolic" and "endocytic", through which the exogenous peptides are degraded and loaded [113]. In the "cytosolic" track antigens are transported from endosomes to the cytosol for processing, loading in the ER, and transport of MHC I-peptide complexes to the plasma membrane following the secretory pathway [30]. In the "endocytic" track processing (TAP-independent) and loading occur in the endosome, and MHC I molecules are recycled from the plasma membrane. The MHC I complex transported back to the plasma membrane from the endosome. TLRs induce MHC I molecules from the intracellular pool to phagosomes [30], [127].

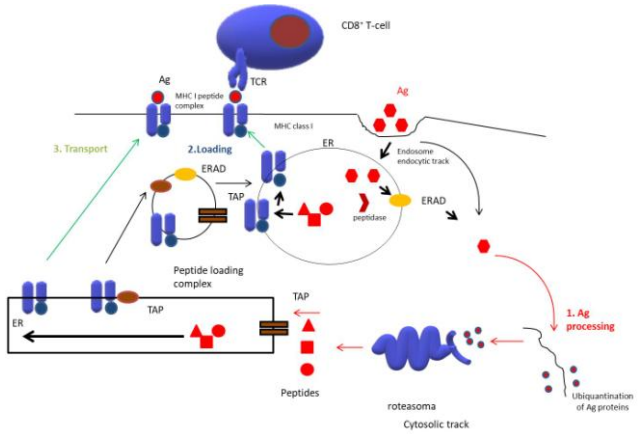

Figure 2: MHC class II antigen presentation

The new understanding of cross-presentation has been built from data obtained from experiments in culture with Mo-DCs, GM-CSF cultures (GMDCs) and FTL3L-derived DC cultures [30]. The FTL3L-derived DCs in culture express *RAB43*, a molecule necessary for cross-presentation in *in vivo* cDC1s [128] and therefore are more suitable for studying cross-presentation than GMDCs or Mo-DCs.

In mice, the CD8α$^+$ DCs (in lymphoid organs) are considered to be the dominant cross-presenting APC [129], but CD103+ DCs and inflammatory DCs are cross-presenters in certain conditions [130]. In

humans, one study shows superior cross-presentation of unstimulated CD141$^+$ cDCs compared to CD1c$^+$ cDC and pDC [46]. Others report that unstimulated CD141$^+$ cDCs are unable to cross-present [47]. Recent studies have revealed that, with the proper stimuli, all human DC subsets can cross-present in vitro [127]. However, CD141$^+$ DCs are shown to be the most efficient cross-presenting subset following poly (I: C) stimulation, when using necrotic cell-associated antigens [47], antigens delivered by Fc$_\gamma$ receptor targeting [3], or antigens delivered to endosomes / lysosomes [131]. The ability to cross-present necrotic cell-derived antigens depends on the selective expression of ClEC9A on CD141$^+$ DCs, a dead cell receptor that acts through delivery to both MHC class I and II [16], [47].

Haniffa et al., 2012 [48] tested the cross-presentation ability of human skin (tissue) CD141^{hi} DC, CD1c$^+$ DC, CD14$^+$ cells and epidermal LCs in comparison to CD141$^+$ DCs, CD1c$^+$ DCs, CD14$^+$ monocytes, and of (in vitro-derived) Mo-DCs and Mo-LCs obtained from human blood. It has been established that in blood, only CD141$^+$ DCs were able to cross-present efficiently, and require TLR3 stimulation with poly (I: C) or exposure to a maturation cocktail (containing poly (I: C), LPS, IFNγ, IL1β, TNFα and IFNα). Mature Mo-DCs and Mo-LCs are also able to cross-present upon exposure to maturation cocktail but are refractory to TLR3 stimulus. In the skin, superior cross-presenting capacity has been found in CD141^{hi} DCs in the absence of stimulation, compared to all other DC subsets, including LCs. CD1c$^+$ DCs show a little ability to cross-present [48].

In general, “resident” DCs are those in LN and other lymphoid organs and reside there during their entire life span. Moreover, the migratory DCs are that in peripheral tissues (NLT), they can capture antigen, mature, and migrate to draining LNs [33], [47]. In human axillary LNs there have been defined three subsets of blood-derived “resident” DCs namely, BDCA1$^+$ DCs, Clec9A$^+$ cDCs and BDCA4$^+$ pDCs, and three subsets of skin-derived migratory DCs, namely LCs, CD1a$^+$ DCs and CD14$^+$ CD1a$^-$ DCs [58]. It has been shown that resident DC subsets induce Th1 and Th2 polarisation and are powerful in cross-presentation [58].

In vivo cross-presentation occurs in secondary lymphoid organs, where resident CD1c$^+$ cDCs, CD141$^+$ cDCs, and pDCs display equal cross-presenting capacity [59]. Usually, antigens are captured by migratory cDC1s (CD8α+ DCs; CD141$^+$ cDC) or cDC2s (CD11b+; CD1c$^+$ cDC) at the site of infection (NLT). Migratory cDCs migrate to regional LNs, where they can prime naïve CD4$^+$ and CD8$^+$ T cells through MHC: TCR contact. Migratory cDCs transfer antigen to resident cDC1s through cross-dressing (see below). Resident cDC1s are helped through CD40 / CD40L from CD4+ T cells and can prime naïve CD8+ T cells via MHC I: TCR interaction [132].

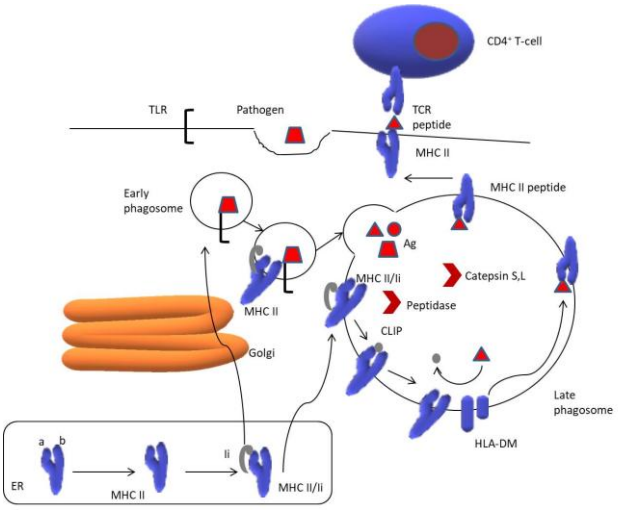

Figure 3: Encountering of antigen at the site of infection; cross-presentation occurring in secondary lymphoid organs; priming of naïve CD4+T-cells and CD8+ T-cells

MHC Class II Antigen Presentation

Professional APCs (mainly DCs and to a lesser extent, macrophages and B lymphocytes) express high levels of MHC class II molecules [16]. As opposed to macrophages, cDCs degrade the engulfed material slowly and in that way, preserve antigens for T cell recognition [50].

MHC class II molecules on DCs sample the extracellular matrix milieu and present exogenous antigens to CD4+ T-helper cells. For effective T-helper cell polarization already mature DCs express high levels of costimulatory molecules (CD80 / 86, CD40 / 40L) and secrete cytokines such as IL12p70 and IL2 (for Th1 immune responses), IL4 (for Th2 immune responses), IL23, IL6 and TGFβ (for Th17 immune responses) and TGFβ1, IL2 (for Treg responses) [125].

Similarly, to MHC class I molecules α and β chain of MHC class II molecules are synthesised in the endoplasmic reticulum and attached to the invariant chain (Ii or CD74) – (MHCII / Ii) [118]. Newly formed MHC class II molecules are delivered to the phagolysosome (late endosome) called MHCII compartment (MHCIIC). Bacterial or viral peptides, attached to TLRs are transported from the cellular surface to the late endosome via early endosome. TLR4 signalling by bacterial LPS triggers the efficient loading of MHC class II molecules with peptides [118]. In the late endosome-MHCIIC, the Ii is cleaved by the proteases (cathepsin S and L) and is replaced by the class II-associated peptide (CLIP). MHC class II molecules need a specific protein HLA-DM in humans to substitute CLIP for the antigenic peptide. Later CLIP is exchanged by the antigen, followed by vacuolar pathway transport of MHC II/antigen peptides to the plasma membrane to connect with TCR of CD4+ T cells [16], [118].

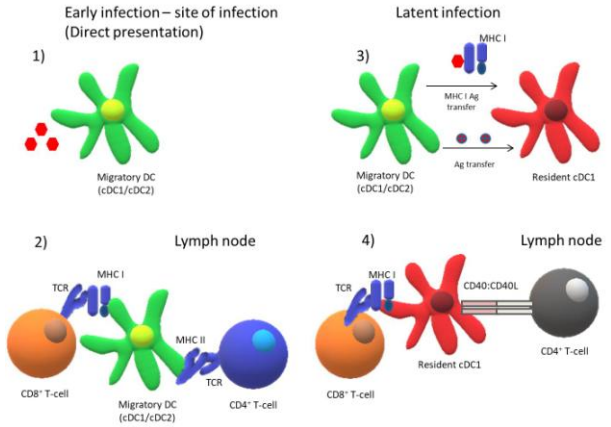

Figure 4: Th-cell polarisation

Antigen Presentation by pDCs

The antigen-presentation by pDCs is similar but with a modulated efficiency and complementary to that of cDCs. The expression of MHC class I and class II and that of T cell co-stimulatory molecules on activated pDCs is lower as compared to cDCs, and therefore pDCs are less efficient at T-cell priming than cDCs [112]. It has also been shown that pDCs like cDCs can provoke T-cell tolerance via inducing Tregs [133].

Concerning MHC class II synthesis and viability, mature cDCs lose their ability to present via MHC II (because of inactivation of the promoter III – pIII) newly encountered antigens due to silencing of MHC presentation machinery. The master transcription factor responsible for MHC synthesis CIITA is down-regulated in mature cDCs [112]. Meanwhile, pIII, responsible for MHC II activation is activated in pDCs (non-silenced upon pDC activation) [110]. Therefore, pDCs are more efficient than cDCs in the presentation of endogenous antigens via MHC II [110], but the roles of both cDCs and pDCs in that process are complementary [110].

The differences in antigen presentation between cDCs and pDCs cannot be explained only by variability in MHC expression [112]. Several studies report that pDCs efficiently present endogenous antigens, constitutively expressed, degraded and attached to MHC I or II in the cytosolic or endosomal route similarly to cDCs [110], [134]. It is known that peptides degraded in the cytosol are presented on MHC I molecules (direct presentation), while peptides processed in the endocytic route (endogenous or exogenous) are presented on MHC II molecules [134].

Nevertheless, pDCs can phagocytise exogenous antigens using specific receptors [110]. Such receptors are BDCA2, SIGLEC-H and DCIR [135] that mediate endocytosis, processing and presentation of exogenous antigens. These receptors induce a signalling cascade in pDCs inhibiting IFN I secretion [136]. Other receptors on pDCs are BST2 (CD317 or HM1.24), PDCA1 [137] and FcRII (CD32) that mediate internalisation of immunoglobulins bound to integrin [112] and the tumour antigen NY-ESO-1 [138].

Cross-presentation by pDCs

Conceivably, the most efficient cross-presenters are cDCs [119]. The cross-presenting capability of pDCs is controversial; for example, mouse pDCs do not possess cross-presenting capacity [137]. Some studies report that human pDCs can cross-present lipoproteins, cell-associated antigens or viral particles [16], [139]. The cross-presenting capacity of human pDCs may be supported by still unknown receptors that capture exogenous antigens [112].

Recently, it was shown that there is another pathway of cross-presentation of tumour-associated antigen (TAA) – peptides complexed with MHC class I molecules to $CD8^+$ CTLs, the process is called “cross-dressing” [140]. The term cross-dressing means that peptide-MHC I complexes including TAAs belonging to neighbouring tumour cells, are transferred on the membrane of DCs [140], [141]. This process has been well documented for cDCs, but only recently was it shown that pDCs are very efficient in acquiring cell membrane patches from neighbouring cancer cells, and pDCs dressed with TAA-MHC I complexes are called drag cells. Tumor-specific CTLs efficiently recognize TAA-MHC I molecule complexes on pDCs [141].

Moreover, pDCs also secrete other pro-inflammatory cytokines and chemokines, such as IL6, IL12, CXCL8, CXCL10, CCL3 and CCL4. pDCS can promote several processes: via IFNs and IL12 promote $CD8^+$ T-cells and Th1 immune responses; via TGFβ, IL6 idoleamine 2, 3-dioxygenase (IDO) and inducible co-stimulatory ligand (ICOSL) they drive Treg cell and Th17 immune responses; via IFNs, IL12 and IL18 they promote the activation of NK cells. Expressed chemokines such as CCL3, CCL4, CXCL8 and CXCL10 ensure immune cell recruitment, while the expression of MHC class I and II and of the co-stimulatory molecules CD80, CD86 and CD40 enable pDCs to cross-prime $CD8^+$ T cells as well as presenting antigen to $CD4^+$ T-cells [18]. When pDCs are either unstimulated or activated by IDO, ICOSL, OX40L, programmed death-ligand (PD-L1) or granzyme B, they promote tolerance to tumour cells, alloantigens and harmless antigens [18], [142].

Human and mouse pDCs express cell surface receptors (TLR7 or TLR9) that control the production of IFN type I in response to the appropriate ligands (nucleic acids derived from viruses, bacteria and dead cells) [143].

T-Cell Polarization

DCs have different phenotypes which alert their ability to polarise different Th subsets. Mature DCs produce cytokines, which induce differentiation of definite Th cell subsets that modify the immune response in the direction of effective or tolerogenic and immunosuppressive [144].

DC1 phenotype (secreting IL12, IL15 and IFN type I) is named so because it induces the Th1 helper subset, which is responsible for immunity to intracellular pathogens [145], autoimmunity [145] and antitumor immunity. Th1 helpers secrete IFNγ and IL2 by themselves and IL12 released by DC1s enhance antitumor immunity and activated NK cells [146].

DC2 phenotype during maturation leads to the secretion of IL1 which and they together with anti-IFNγ, favours the production of Th2 cells. IL4 (not released by DCs, but by basophils and T-cells) [147] and IL10 also induced Th2 specialisation [148]. Th2 immunity is directed against parasites and promotes allergic reactions [148]. Th2 cells secrete IL4, IL5, IL10, IL13 [125]. Two surface markers define DCs specialised in promoting Th2 cell responses. One marker is macrophage galactose-type C-type lectin 2 (MGL2 / CD301b) and the second marker is PD-L2 [149]. Th2 DCs express a specific transcription factors, IRF4 and STAT5, which regulate Th2 differentiation [150], [151].

DC17s phenotype leads in the course of their maturation secretion IL6, TGFβ (released by stromal cells, macrophages etc.), IL21 and IL23 (inhibited by IL4 or IFNγ) and drive the generation of Th17 cells via IL-6, TGF-β and STAT3 pathway [150], [152]. Th17 helper cells secrete high levels of IL-17, IL-21 and IL-22 [125]. Their role in cancer is mainly maintenance of immunosuppression [153].

DC_0 phenotype secreting IL10 and TGFβ (inhibited by IL6 and IL21) direct naïve T-cells into Treg differentiation [125].

$CD141^{hi}$ DCs are also the most active allo-stimulators of $CD4^+$ and $CD8^+$ T-cells, as compared to $CD1c^+$ and $CD14^+$ DCs. Only $CD141^{hi}$ DCs produce CXCL10 and TNFα after TLR3 stimulation but secrete little IL12 and IL23. No stimuli induce the secretion CXCL10 and TNF-α in $CD1c^+$ and $CD14^+$ DCs [48].

It has been reported that DCs activate $CD4^+$ T cells via three signals: i) stimulation of TCR through MHC class II attached to an antigen-specific peptide complex; ii) co-stimulation meaning an interaction between co-stimulatory molecules on DCs (CD80 and CD86) with their ligands on T cells (CD28) and initiation of clonal expansion of TCR-stimulated T-cells; iii) cytokines mainly provided by activated DCs that trigger polarization of naïve T-cells into effector T helper cells [148]. Upon stimulation by exogenous pathogens, allergens, or endogenous inflammatory signals, DCs produce various types of cytokines such as IL1, IL6, IL12, IL21, IL23, IL27, and TNFα functioning as signal 3 [154]. Cytokines trigger the type of STAT activation in T cells that is crucial in determining the effector lineages of T helper cells via inducing distinct transcription factors. In other words, distinct cytokines are required for the commitment of T cells to each T helper lineage.

Dendritic Cells and Cancer

DCs play a key role in the regulation of tumour-specific immune responses [155]. Different DC subsets in cancer can exert an effective anti-tumor immune response, since immature DCs capture tumor-specific antigens, while immunogenic or mature DCs up-regulate MHC and co-stimulatory molecules (CD80, CD83, CD86, CD40), secrete high levels of bioactive IL12p70, skewing and prime $CD8^+$ T cell responses (CTLs), skewing the response to Th1 and induce optimal anti-tumor immunity [156], [157].

Tolerogenic DCs have a role in maintaining immunosuppression in tumour [155]. Tumor-infiltrating DCs are immature with down-regulation of co-stimulatory molecules, secretion of IL-10 and induction of Th2 immune responses and Treg expansion in the tumour milieu [156], [158]. Tumour cells impair DCs function through the secretion of immunosuppressive molecules such as IL10, TGFβ and PGE2 [158], or VEGF, which inhibit DCs maturation and their ability to activate T cells [157]. Tumours produce elevated levels of CCL22 chemokine and ICOSL, molecules that attract DCs [159] and increase the expression of CTLA4 and PD1 / PD-L1, co-stimulatory molecules that can suppress T cell proliferation and activity in cancer [159], [160].

In human tumor tissue four DC subsets are found namely pDCs and mDCs including $CD16^+$ DCs, $BDCA1^+$ DCs, and $BDCA3^+$ DCs [155]. The tumour microenvironment inhibits immunogenic Mo-DCs through secretion of IL-10 and IL6 cytokines, and parallelly promote monocyte maturation into macrophages [161], [162]. Tumor-infiltrating DCs are shown to be immunogenic at early stages of cancer development and convert to immunosuppressive types (MHC II^{low}, $CD40^{low}$ and $PD\text{-}L1^{high}$) at advanced tumour stages. Moreover, immunostimulatory cDCs can transform into regulatory macrophage-like cells that suppress T-cell responses through nitric oxide, arginase activity and IL10 [163].

pDCs and tumour microenvironment

Immature myeloid DCs and pDCs [164] accumulate in human tumors and in peripheral blood [159] and predict poor prognosis for specific cancer types. In the tumour microenvironment, pDCs are non-activated (immature) that don't produce IFN type I

and lack the expression of co-stimulatory molecules [165], [166]. Tumor-infiltrating pDCs produce IDO that promotes Treg activation and immunosuppression in tumours [167]. Tumour pDCs express high levels of ICOS-L and in that way stimulate ICOS+ Tregs (ICOS+ FoxP3+ Tregs) [168].

Also, pDCs after activation can undergo important phenotypic changes towards mDC phenotype and induce IFN I production that amplifies the release of IL12p70 from mDCs and NK cells [169]. Interestingly, pDCs can promote Th2-like immune responses, since increased IFNα stimulate the change of pDCs into Th1-inducing pDCs, while the absence of IFNα leads to Th2-inducing pDCs [169]. It was shown that pDCs expressed on their surface CD56, PD-L1, granzyme B and the TNF-related apoptosis-inducing ligand (TRAIL) [170]. The pDCs tumour cell killing is dependent strictly on TRAIL-associated apoptosis.

DCs have the capacity of the direct cytotoxic killing of tumour cells together with $CD8^+$ CTLs, NK cells, and γ/δ T-cells) [170]. TpDC cytotoxicity was granzyme dependent [167], [171].

In conclusion, we may state that human DCs are the main immune cells that orchestrate the immune response in the tumour microenvironment and represent the most hopeful tool for future DC vaccines that are an alternative of check-point inhibitors for tumour immunotherapy.

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