Review article

CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

Distinct features of dendritic cell-based immunotherapy as cancer vaccines

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Dendritic cells (DCs) are the most professional antigen presenting cells that play important roles in connection between innate and adaptive immune responses. Numerous studies revealed that the functions of DCs are related with the capture and processing of antigen as well as the migration to lymphoid tissues for the presenting antigens to T cells. These unique features of DCs allow them to be considered as therapeutic vaccines that can induce immune responses and anti-tumor activity. Here, we discuss and understand the immunological basis of DCs and presume the possibilities of DC-based vaccines for the promising cancer therapy.

Keywords: Dendritic cells, Vaccines, Immunotherapy, Neoplasms

Introduction

After Paul Langerhans firstly described dendritic cells (DCs) as nerve cells in 1868, Steinman and Cohn firstly discovered DCs in 1973 as a large stellate or tree-like cell with dendritic morphology of prominent cytoplasmic veils and protrusions [1]. DCs are distinguished from other cells by their unique features, so called dendrites delivering the original name [2]. DCs are broadly expressed in the body but sparsely [3]. They are extremely proficient antigen presenting cells (APCs) that are fundamental to the adaptive immune responses [3-5]. DCs are not only critical for the induction of primary immune responses, but also important for the induction of immunological tolerance, as well as for the regulation of the type of T cell-mediated immune response [3,6-8].

DCs are derived from hematopoietic bone marrow progenitors and initially transform into immature DCs [9,10]. These cells are characterized by high endocytic activity and low T-cell activation potential [7]. After DCs contact with an antigen, they become mature DCs and migrate to the adjacent lymph node (LN) [7]. Immature DCs can capture foreign antigens and degrade them into peptide level, and undergo the process which presents the antigen to cell surface by MHC molecules [11]. After antigen capture during inflammation or infection, immature DCs undergo a complex maturation process through Toll-like receptors (TLRs) or members of tumor necrosis factor receptor family. DCs upregulate cell surface costimulatory molecules in T-cell activation such as CD80, CD86, and CD40 highly enhancing their ability to activate T cells [12]. DCs also upregulate a chemotactic receptor such as C-C chemokine receptor type 7 (CCR7) that induces the DCs into the blood stream to the peripheral lymphoid organ or via the lymphatic vessel to lymph node. Finally, DCs activate T helper (Th)

cells and natural killer (NK) cells as well as B cells by presenting the antigens together with costimulatory signals [13].

The tumor microenvironment promotes immune tolerance and innovative approaches are required to stimulate immunological antitumor activity or modulate favorable immune system. DCs are the most authoritative candidates which can be helpful to promote immune responses in tumor microenvironment. DCs promote tumor tolerance and modulate the imbalance of Th cells responses. Mature DCs enable to activate T helper 1 (Th1) cells and antigen specific $CD8^+$ cytotoxic T lymphocytes (CTL) under the tumor microenvironment. In this review, we will discuss fundamental features of DCs and the roles of DC-based vaccine as promising cancer therapy.

The Features of DCs

Migration of DCs is an indispensable process before DCs initiate their immune responses (Fig. 1) [14]. Most DCs circulate in the body as an "immature" state. Even though immature DCs lack important functions to induce a strong T-cell response, they are ideally controlled and well equipped to capture antigens and microbes [3,15]. Once they have acquired and processed the foreign antigens, DCs move to the T-cell areas in peripheral lymphoid organs such as LNs and the spleen, and undergo maturation and stimulate immune responses [16].

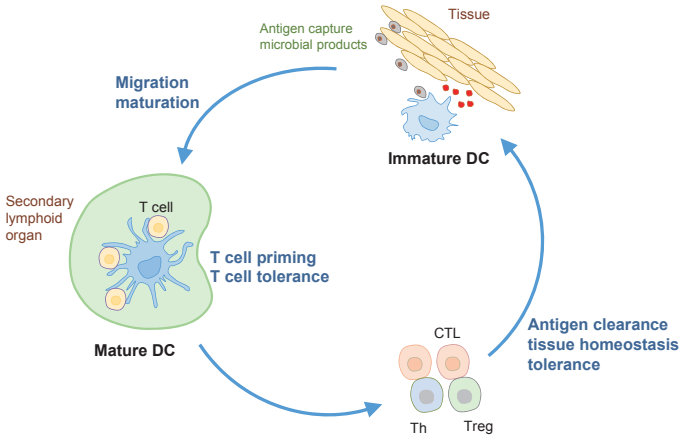

Fig. 1. Role of dendritic cells (DCs) in antigen capture, processing and presentation. Immature dendritic cells capture exogenous particles, proteins, and pathogens in peripheral tissues. Upon maturation in response to inflammatory stimuli, antigen-loaded dendritic cells then migrate to secondary lymphoid organs. In these sites, mature dendritic cells present antigen to T cells and induce T-cell priming, leading to generation of helper T cells (Th), regulatory T cells (Tregs) and cytotoxic T lymphocytes (CTLs). Under certain conditions, antigen-loaded dendritic cells can induce T-cell tolerance.

Circulating DCs and their precursors exit the blood via tissue-specific recruitment signals such as chemokines that derive from sites of inflammation [17]. DCs are located at surfaces where antigens gain access to the body. DCs are also positioned in distinct incoming channels, called lymphatic vessels, which allow cells to move from peripheral tissues to lymphoid organs [16,18,19]. DCs can encounter immune lymphocytes, selecting those cells that specifically recognize the antigens being carried by the DCs [20]. The lymphocytes begin to grow vigorously and they start to produce materials that will serve to eliminate infections and other sources of antigens [20].

Conventional/Classical DCs

Conventional or classical dendritic cells (cDCs) function as efficient APCs and can induce immune activation or promote tolerance. cDCs have a characteristic morphology defined by long dendrite extensions, and high levels of CD11c and MHC class II expression [21,22]. Human cDCs are found in both lymphoid and peripheral tissues [21]. Although there appears to be functional homology between human and mouse cDCs, these cells express their own unique markers, respectively. Two subsets of human cDCs have been characterized that are Lin^- ($CD3^-$, $CD14^-$, $CD19^-$, $CD20^-$, and $CD56^-$) and either CD1c/BDCA-1^+ or CD141/BDCA-3^+ [23,24]. CD1c/BDCA-1^+ DCs promote a Th1 immune response and act in a tolerogenic manner in response to *Escherichia coli* [23]. CD141/BDCA-3^+ DCs also cross-present extracellular antigens to $CD8^+$ T cells, promote CTL lymphocytes activation, and induce a Th1 immune response [23].

Mouse resident cDCs are found in the central and peripheral lymphoid organs including thymus, spleen, LNs, and Payer's patches. Mouse cDCs comprise two subsets as $CD8^-$ cDCs and $CD8^+$ cDCs [25,26]. $CD8^-$ cDCs can increase MHC class II-mediated presentation of exogenous antigen. Like human CD141/BDCA-3^+ cDCs, $CD8^+$ cDCs are able to induce antigen cross-presentation to CTL lymphocytes [25]. Mouse $CD8\alpha^+$ cDCs show their ability to cross-present extracellular antigens to CTLs [27]. They act to maintain tolerance in the steady state and produce IL-12 and interferon (IFN)-γ upon activation [28]. $CD8\alpha^-$ cDCs are efficient activators of $CD4^+$ T cells. $CD4^+CD8\alpha^-$ cDCs comprise a significant proportion of cDCs localized to the spleen, while $CD4^-CD8\alpha^-$ cDCs account for a significant proportion of cDCs present in mucosal-associated lymphoid tissues [29]. In addition to the lymphoid-resident cDCs, two subsets of mouse migratory cDCs have also been identified that are either Integrin α_E/$CD103^+$ or Integrin α_M/$CD11b^+$ [30].

Integrin α_E/CD103$^+$ cDCs enable to cross-present antigens to CTL cells [31]. They mediate immune tolerance or induce Th2 immune responses. Integrin α_M/CD11b$^+$s are found in most tissues including the lung, intestine, and skin [30].

Plasmacytoid DCs

Plasmacytoid DCs (pDCs) are rare subset of DCs that is specialized in type I interferon production [32-35]. pDCs have round lymphocytic morphology and express low level of MHC class II and costimulatory molecules [36,37]. pDCs develop in the bone marrow from Flt3$^+$ c-Kit^{low} progenitors including lymphoid progenitors and common DC progenitors [38]. pDCs are low or negative for CD11c in mouse or human, respectively, but positive for the B-cell marker B220/CD45RA. Particularly, steady-state pDCs are similar to the features of lymphocytes but are different from those of cDCs. Human pDCs express the surface markers blood dendritic cell antigen-2 (BDCA-2; CD303) and immunoglobulin-like transcription-7 [39]. Mouse pDCs express Siglec-H and BST-2/Tetherin [40]. Human IL-3Rα (CD123), BDCA-4 and murine Ly6C, Ly49Q are also useful markers [36]. As components of the innate immune system, pDCs express intracellular TLR7 and TLR9 that detect ssRNA and CpG DNA motifs, respectively [41,42]. Upon stimulation and subsequent activation, pDCs produce large amounts of type I interferon (mainly IFN-α and IFN-β), which are pleiotropic anti-viral compounds facilitating various effects [34].

Inflammatory DCs/Monocyte-derived DCs

Monocyte-derived DCs (moDCs) are newly discovered a subset of DCs, which shows common features with classical DCs [43]. moDCs have essential roles in defense mechanisms that induce of both adaptive and innate immune responses [44]. In contrary to cDCs, moDCs are differentiated from Ly6C^{high} monocyte progenitors only during inflammatory reactions [45]. However, they share their common features with cDCs; morphology, migration property, priming of T cells, and expression surface markers such as CD11c, MHC II, CD40, CD80, and CD86 [43].

General Properties of DCs

Antigen uptake

DCs are professional antigen processing cells [5,46]. Immature DCs have several features that allow them to capture antigen. They have a variety of receptors to perform the uptake of antigens, and they are specialized to convert these antigens into MHC-peptide complexes that can be recognized by lymphocytes [46,47]. Immature DCs firstly take up antigens by phagocytosis [48]. Next, they form large pinocytic vesicles via a process called macropinocytosis or interaction with a variety of cell surface receptors [49]. Finally, they express receptors that mediate adsorptive endocytosis [48,50]. DCs express a variety of receptors that include members of pattern recognition receptors family (such as TLRs, C-type lectin receptors, intracytoplasmic nucleotide oligomerization domain-like receptors), Fc receptors (FcR), complement receptors, mannose receptors and receptors involved in uptake of apoptotic bodies such as phosphatidylserine receptor [51-53]. The most prevalent antigen receptors expressed by DCs include members of the C-type lectin family [54,55]. For example, DEC-205, a type I C-type lectin containing multiple calcium-dependent binding domains and a unique cytoplasmic tail, may function in directing captured antigens to specialized antigen-processing compartments within DCs [56].

Antigen processing and presentation

Antigen processing by DCs is primarily through two major pathways such as exogenous or endogenous pathway [5]. For exogenous pathway, the captured antigens undergo the endocytic pathway and proteases initiate the degradation of antigens. DCs degrade antigens within a MHC class II-rich endosomal compartment (MIIC) and preserve sufficient peptide structure to be expressed on their cell surface bound to MHC class II, which are produced in endoplasmic reticulum (ER) [57,58]. During this process, MIICs change to non-lysosomal vesicles and release the peptide bound MHC complexes on the surface of cells. For endogenous pathway, the phagocytosis and receptor-mediated endocytosis enable antigen uptake, the restricted proteolysis, and the active transport into the cytosol [59]. The cytosolic antigens are additionally degraded via the proteasome. Antigens enter the ER utilizing transporter associated with antigen presenting, and are bound to newly generated MHC class I molecules. MHC class I-peptide is consequently transported by vesicular transport to the surface of cells.

In addition to two antigen-processing pathways, DCs have a specialized antigen-processing process called cross-presentation [60-63]. Antigen cross-presentation describes the process through which DCs obtain exogenous antigens on MHC class I. The antigen is hydrolyzed into oligopeptides after transferring into the cytosol. Then, the antigens are transported to

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MHC class I molecules in phagosomes or ER [63]. Alternatively, the cleaved antigens by endosomal proteases such as cathepsin S are processed by MHC class I in the endocytic compartment.

Linking of Innate and adaptive immunity

DCs link innate and adaptive immunity by receiving danger signals that render them capable of maturing and inducing productive immunity [7,64]. DCs also respond to danger signals deriving from foreign substances mentioned to as pathogen-associated molecular patterns that let DCs undergo maturation. TLRs are the most important receptors that recognize microbial products and communicate the information to initiate adaptive immunity. Once primed, the DCs migrate to secondary lymphoid organs, and then present antigens to naïve $CD4^+$ T cells and CTLs. Moreover, DCs release cytokines that further modulate the immune response.

Activation of immune cells

Antigen presentation by DCs is of crucial for the initiation of primary immune responses, due to their unique role in capturing, processing, and transporting antigens [3]. Following activation by antigen encounter, DCs migrate from tissues into LNs. During this process, DC upregulates MHC class I and II as well as costimulatory molecules such as B7.1 and B7.2. This is important for the activation of naïve T cells because they require both signaling the antigen-specific T-cell receptor (TCR) interaction and the costimulatory B7/CD28 mediated second signal. In addition, adhesion molecules such as intercellular adhesion molecule-1 and lymphocyte function-associated antigen 1 are also highly expressed by DCs and induce prolonged cell to cell interaction. They allow naïve T cells differentiate into effector cells. Productive activation of naïve T cells by DCs results in clonal expansion and the effector and memory T cells differentiation [65].

Besides T cell stimulation, DCs are able to stimulate of B cells where happens in LN and germinal centers. Antigens are captured by FcRγIIB can be reserved in intracellular vesicles and presented to B cells [66]. DCs also modulate the functions of NK cells and CTL cells and influence the immune response [67].

Immune tolerance

DCs also induce immune tolerance in both central and peripheral lymphoid organs. They are involved in the important regulatory mechanisms that are clonal selection in thymus, TCR/B-cell receptor editing and regulatory T cells (Tregs) generation [7,68,69]. DCs allow the immune system to tolerate harmless antigens that are originated from own body's tissues, cells and proteins [70]. This is essential to inhibit the body from self-immune response. During the T-cell development in the thymus, DCs contribute in eliminating those cells bearing self-reactive antigens via a mechanism known as central tolerance. DCs also regulate the mechanisms of peripheral tolerance that represent T-cell death, T-cell anergy, and active suppression by Treg [68,69]. Proficient immune responses occur when DCs present optimal levels of MHC-peptide complexes with costimulatory molecules. In the event, T cells recognize only low levels of MHC-peptide and have a low affinity for their cognate ligand, or receive no costimulation from DCs, they become anergic or undergo apoptosis [71,72].

DC-Based Vaccines as Cancer Therapy

DCs are considered as a leading light of the immune system that connects between innate immunity and adaptive immunity. As mentioned previously, once DC meet the antigen, the antigen is processed and degraded into small peptide to express on the cell surface. These unique functions allow DC-based vaccines to introduce the potent immunotherapeutics for the patients suffering from serious disease such as cancer

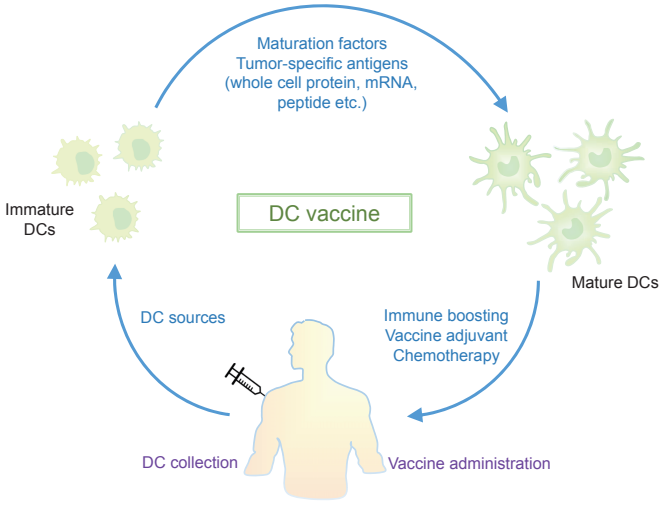

Fig. 2. The generation of dendritic cell (DC) vaccine. The multiple steps of process are inevitable for the generation of DC-based vaccine. The syngeneic source of DCs are collected and undergo the maturation of immature DCs to mature DCs by the exposure to the tumor specific antigens, mRNA, or peptides, etc. Finally, DC-based vaccines are administered with contemporary immune modulators or adjuvants.

(Fig. 2) [73,74]. DC-based vaccines can be generally categorized by the matured autologous monocytes *in vitro* or *ex vivo*, and an antigen-stimulated DCs just before injection [75-77]. DC-based immunotherapy is theoretically safe and can promote antitumor immune responses and prolonged survival of patients [78]. DC-based vaccines aims to initiate the immune responses by the stimulation of T cells that can destroy cancer cells and the induction of the memory cells to prevent cancer recurrence [77]. Currently, there exist two types of DC-based vaccines. The one is *ex vivo* antigen-loaded DC-based vaccines and the other is *in vivo* DC-targeted vaccines [79]. For *in vivo* DC-targeted vaccine, it can be divided again according to the types of reactive targets. The first target is ligand such as TLR agonists, and the other is antibody such as DEC205, DC-SIGN, CD11c, and FcγR [80]. In addition, new target is being focused on the delivery system using nanoparticles even though this system is still need to be improved [81,82].

DCs for vaccine therapy can be generated from monocytes or $CD34^+$ progenitor cells by the stimulation of cytokines and granulocyte-colony stimulating factor culture medium *ex vivo* [83]. moDCs are more advantageous than $CD34^+$ progenitor derived DCs because they are possible to be fully differentiated and homogeneous [84]. moDCs are frequently applied for clinical application or trial, and they induce efficient immune responses by tumor-derived antigens.

In tumor microenvironment, DCs can take up damaged tumor cells and then can respond tumor-specific immune responses according to the inflammatory signals. The population of myeloid-derived suppressor cells and Treg keeps high levels at the steady state which means that tumor cells are suppressive [85]. However, the maturation of DCs is inhibited by the specific factors such as vascular endothelial growth factor, interleukin 10 resulting in T-cell anergy and tumor progression [86]. Under tumor microenvironment, the maturation of DCs and the production of mature DCs are decreased and impair tumor suppressive immune response [87]. Also, cancerous cells prevent the efficient antigen presentation and recognition of cytotoxic effects by the conversion of monocytes into macrophages instead of DCs [88].

Recently, DC-based immunotherapy has been focused as a therapeutic approach for cancer treatment. The ability of DCs against tumor has been proven and DCs are produced from monocytes with granulocyte-macrophage colony-stimulating factor/interleukin 4 *in vitro*, and tumor-derived antigens or tumor mRNA-loaded DCs were directly injected into patients as cancer vaccine resulting the antitumor immune response or tumor killing ability of DCs [87,89]. DC-based immunotherapy can be useful for the treatment of unique diseases such as cancer basically depends on functional and immunobiology of DCs.

Conclusion

During more than four decades, the impor¬tance of DCs finally has been accepted as indispensable immune cells that connect between innate and adaptive immunity. The prospective roles of DCs as an immunotherapeutic tool are having been effectively resumed by verifying the limitation of cellular and molecular mechanisms of DCs. DC based therapy is supposed to influence to the leader of cancer immunotherapy.

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References

1. Steinman RM, Cohn ZA. Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution. J Exp Med 1973;137:1142-62.
2. Steinman RM, Nussenzweig MC. Dendritic cells: features and functions. Immunol Rev 1980;53:127-47.
3. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature 1998;392:245-52.
4. Banchereau J, Briere F, Caux C, et al. Immunobiology of dendritic cells. Annu Rev Immunol 2000;18:767-811.
5. Mellman I, Steinman RM. Dendritic cells: specialized and regulated antigen processing machines. Cell 2001;106:255-8.
6. Steinman RM. The dendritic cell system and its role in immunogenicity. Annu Rev Immunol 1991;9:271-96.
7. Munz C, Steinman RM, Fujii S. Dendritic cell maturation by innate lymphocytes: coordinated stimulation of innate and adaptive immunity. J Exp Med 2005;202:203-7.
8. Steinman RM. Decisions about dendritic cells: past, present, and future. Annu Rev Immunol 2012;30:1-22.
9. Steinman RM, Pack M, Inaba K. Dendritic cell development and maturation. Adv Exp Med Biol 1997;417:1-6.

10. Steinman RM, Idoyaga J. Features of the dendritic cell lineage. Immunol Rev 2010;234:5-17.
11. Steinman RM, Inaba K, Turley S, Pierre P, Mellman I. Antigen capture, processing, and presentation by dendritic cells: recent cell biological studies. Hum Immunol 1999; 60:562-7.
12. Cella M, Engering A, Pinet V, Pieters J, Lanzavecchia A. Inflammatory stimuli induce accumulation of MHC class II complexes on dendritic cells. Nature 1997;388:782-7.
13. Guermonprez P, Valladeau J, Zitvogel L, Thery C, Amigorena S. Antigen presentation and T cell stimulation by dendritic cells. Annu Rev Immunol 2002;20:621-67.
14. Alvarez D, Vollmann EH, von Andrian UH. Mechanisms and consequences of dendritic cell migration. Immunity 2008;29:325-42.
15. Thery C, Amigorena S. The cell biology of antigen presentation in dendritic cells. Curr Opin Immunol 2001;13:45-51.
16. Bonasio R, von Andrian UH. Generation, migration and function of circulating dendritic cells. Curr Opin Immunol 2006;18:503-11.
17. MartIn-Fontecha A, Sebastiani S, Hopken UE, et al. Regulation of dendritic cell migration to the draining lymph node: impact on T lymphocyte traffic and priming. J Exp Med 2003;198:615-21.
18. Dieu MC, Vanbervliet B, Vicari A, et al. Selective recruitment of immature and mature dendritic cells by distinct chemokines expressed in different anatomic sites. J Exp Med 1998;188:373-86.
19. Randolph GJ, Sanchez-Schmitz G, Angeli V. Factors and signals that govern the migration of dendritic cells via lymphatics: recent advances. Springer Semin Immunopathol 2005;26:273-87.
20. Cavanagh LL, Bonasio R, Mazo IB, et al. Activation of bone marrow-resident memory T cells by circulating, antigen-bearing dendritic cells. Nat Immunol 2005;6:1029-37.
21. Shortman K, Liu YJ. Mouse and human dendritic cell subtypes. Nat Rev Immunol 2002;2:151-61.
22. Shortman K, Naik SH. Steady-state and inflammatory dendritic-cell development. Nat Rev Immunol 2007;7:19-30.
23. MacDonald KP, Munster DJ, Clark GJ, Dzionek A, Schmitz J, Hart DN. Characterization of human blood dendritic cell subsets. Blood 2002;100:4512-20.
24. Dzionek A, Fuchs A, Schmidt P, et al. BDCA-2, BDCA-3, and BDCA-4: three markers for distinct subsets of dendritic cells in human peripheral blood. J Immunol 2000;165: 6037-46.
25. Shortman K, Heath WR. The CD8+ dendritic cell subset. Immunol Rev 2010;234:18-31.
26. Villadangos JA, Schnorrer P. Intrinsic and cooperative antigen-presenting functions of dendritic-cell subsets in vivo. Nat Rev Immunol 2007;7:543-55.
27. den Haan JM, Lehar SM, Bevan MJ. CD8(+) but not CD8(-) dendritic cells cross-prime cytotoxic T cells in vivo. J Exp Med 2000;192:1685-96.
28. Hochrein H, Shortman K, Vremec D, Scott B, Hertzog P, O'Keeffe M. Differential production of IL-12, IFN-alpha, and IFN-gamma by mouse dendritic cell subsets. J Immunol 2001;166:5448-55.
29. Vremec D, Pooley J, Hochrein H, Wu L, Shortman K. CD4 and CD8 expression by dendritic cell subtypes in mouse thymus and spleen. J Immunol 2000;164:2978-86.
30. del Rio ML, Bernhardt G, Rodriguez-Barbosa JI, Forster R. Development and functional specialization of CD103+ dendritic cells. Immunol Rev 2010;234:268-81.
31. Bedoui S, Whitney PG, Waithman J, et al. Cross-presentation of viral and self antigens by skin-derived CD103+ dendritic cells. Nat Immunol 2009;10:488-95.
32. Liu YJ. IPC: professional type 1 interferon-producing cells and plasmacytoid dendritic cell precursors. Annu Rev Immunol 2005;23:275-306.
33. Gilliet M, Cao W, Liu YJ. Plasmacytoid dendritic cells: sensing nucleic acids in viral infection and autoimmune diseases. Nat Rev Immunol 2008;8:594-606.
34. Villadangos JA, Young L. Antigen-presentation properties of plasmacytoid dendritic cells. Immunity 2008;29:352-61.
35. Swiecki M, Colonna M. Unraveling the functions of plasmacytoid dendritic cells during viral infections, autoimmunity, and tolerance. Immunol Rev 2010;234:142-62.
36. O'Keeffe M, Hochrein H, Vremec D, et al. Mouse plasmacytoid cells: long-lived cells, heterogeneous in surface phenotype and function, that differentiate into CD8(+) dendritic cells only after microbial stimulus. J Exp Med 2002; 196:1307-19.
37. Liu K, Waskow C, Liu X, Yao K, Hoh J, Nussenzweig M. Origin of dendritic cells in peripheral lymphoid organs of mice. Nat Immunol 2007;8:578-83.
38. Naik SH, Sathe P, Park HY, et al. Development of plasmacytoid and conventional dendritic cell subtypes from single precursor cells derived in vitro and in vivo. Nat Immunol 2007;8:1217-26.
39. Blasius AL, Giurisato E, Cella M, Schreiber RD, Shaw AS,

Colonna M. Bone marrow stromal cell antigen 2 is a specific marker of type I IFN-producing cells in the naive mouse, but a promiscuous cell surface antigen following IFN stimulation. J Immunol 2006;177:3260-5.
40. Blasius A, Vermi W, Krug A, Facchetti F, Cella M, Colonna M. A cell-surface molecule selectively expressed on murine natural interferon-producing cells that blocks secretion of interferon-alpha. Blood 2004;103:4201-6.
41. Honda K, Ohba Y, Yanai H, et al. Spatiotemporal regulation of MyD88-IRF-7 signalling for robust type-I interferon induction. Nature 2005;434:1035-40.
42. Sasai M, Linehan MM, Iwasaki A. Bifurcation of Toll-like receptor 9 signaling by adaptor protein 3. Science 2010; 329:1530-4.
43. Leon B, Lopez-Bravo M, Ardavin C. Monocyte-derived dendritic cells formed at the infection site control the induction of protective T helper 1 responses against Leishmania. Immunity 2007;26:519-31.
44. Rotta G, Edwards EW, Sangaletti S, et al. Lipopolysaccharide or whole bacteria block the conversion of inflammatory monocytes into dendritic cells in vivo. J Exp Med 2003; 198:1253-63.
45. Ginhoux F, Tacke F, Angeli V, et al. Langerhans cells arise from monocytes in vivo. Nat Immunol 2006;7:265-73.
46. Trombetta ES, Mellman I. Cell biology of antigen processing in vitro and in vivo. Annu Rev Immunol 2005;23:975-1028.
47. Watts C. Capture and processing of exogenous antigens for presentation on MHC molecules. Annu Rev Immunol 1997;15:821-50.
48. Watts C, Amigorena S. Antigen traffic pathways in dendritic cells. Traffic 2000;1:312-7.
49. Sallusto F, Cella M, Danieli C, Lanzavecchia A. Dendritic cells use macropinocytosis and the mannose receptor to concentrate macromolecules in the major histocompatibility complex class II compartment: downregulation by cytokines and bacterial products. J Exp Med 1995;182:389-400.
50. Garrett WS, Chen LM, Kroschewski R, et al. Developmental control of endocytosis in dendritic cells by Cdc42. Cell 2000;102:325-34.
51. Palm NW, Medzhitov R. Pattern recognition receptors and control of adaptive immunity. Immunol Rev 2009;227:221-33.
52. Amigorena S, Bonnerot C. Fc receptor signaling and trafficking: a connection for antigen processing. Immunol Rev 1999;172:279-84.
53. East L, Isacke CM. The mannose receptor family. Biochim Biophys Acta 2002;1572:364-86.
54. Weis WI, Taylor ME, Drickamer K. The C-type lectin superfamily in the immune system. Immunol Rev 1998;163: 19-34.
55. Geijtenbeek TB, van Vliet SJ, Engering A, t Hart BA, van Kooyk Y. Self- and nonself-recognition by C-type lectins on dendritic cells. Annu Rev Immunol 2004;22:33-54.
56. Mahnke K, Guo M, Lee S, et al. The dendritic cell receptor for endocytosis, DEC-205, can recycle and enhance antigen presentation via major histocompatibility complex class II-positive lysosomal compartments. J Cell Biol 2000; 151:673-84.
57. Castellino F, Germain RN. Extensive trafficking of MHC class II-invariant chain complexes in the endocytic pathway and appearance of peptide-loaded class II in multiple compartments. Immunity 1995;2:73-88.
58. Turley SJ, Inaba K, Garrett WS, et al. Transport of peptide-MHC class II complexes in developing dendritic cells. Science 2000;288:522-7.
59. Pamer E, Cresswell P. Mechanisms of MHC class I--restricted antigen processing. Annu Rev Immunol 1998;16:323-58.
60. Heath WR, Carbone FR. Cross-presentation, dendritic cells, tolerance and immunity. Annu Rev Immunol 2001;19:47-64.
61. Heath WR, Belz GT, Behrens GM, et al. Cross-presentation, dendritic cell subsets, and the generation of immunity to cellular antigens. Immunol Rev 2004;199:9-26.
62. Monu N, Trombetta ES. Cross-talk between the endocytic pathway and the endoplasmic reticulum in cross-presentation by MHC class I molecules. Curr Opin Immunol 2007; 19:66-72.
63. Joffre OP, Segura E, Savina A, Amigorena S. Cross-presentation by dendritic cells. Nat Rev Immunol 2012;12:557-69.
64. Inaba K, Turley S, Iyoda T, et al. The formation of immunogenic major histocompatibility complex class II-peptide ligands in lysosomal compartments of dendritic cells is regulated by inflammatory stimuli. J Exp Med 2000;191: 927-36.
65. Lanzavecchia A, Sallusto F. Dynamics of T lymphocyte responses: intermediates, effectors, and memory cells. Science 2000;290:92-7.
66. Bergtold A, Desai DD, Gavhane A, Clynes R. Cell surface

recycling of internalized antigen permits dendritic cell priming of B cells. Immunity 2005;23:503-14.
67. Kitamura H, Iwakabe K, Yahata T, et al. The natural killer T (NKT) cell ligand alpha-galactosylceramide demonstrates its immunopotentiating effect by inducing interleukin (IL)-12 production by dendritic cells and IL-12 receptor expression on NKT cells. J Exp Med 1999;189:1121-8.
68. Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. Cell 2008;133:775-87.
69. Wing K, Sakaguchi S. Regulatory T cells exert checks and balances on self tolerance and autoimmunity. Nat Immunol 2010;11:7-13.
70. Brocker T. The role of dendritic cells in T cell selection and survival. J Leukoc Biol 1999;66:331-5.
71. Thompson AG, Thomas R. Induction of immune tolerance by dendritic cells: implications for preventative and therapeutic immunotherapy of autoimmune disease. Immunol Cell Biol 2002;80:509-19.
72. Chen M, Wang YH, Wang Y, et al. Dendritic cell apoptosis in the maintenance of immune tolerance. Science 2006;311:1160-4.
73. Palucka K, Banchereau J. Dendritic-cell-based therapeutic cancer vaccines. Immunity 2013;39:38-48.
74. Mullard A. New cancer vaccines show clinical promise. Nat Rev Drug Discov 2017;16:519.
75. Palucka K, Banchereau J. Human dendritic cell subsets in vaccination. Curr Opin Immunol 2013;25:396-402.
76. Baek S, Lee SJ, Kim MJ, Lee H. Dendritic cell (DC) vaccine in mouse lung cancer minimal residual model: comparison of monocyte-derived DC vs. hematopoietic stem cell derived-DC. Immune Netw 2012;12:269-76.
77. Palucka K, Banchereau J. Cancer immunotherapy via dendritic cells. Nat Rev Cancer 2012;12:265-77.
78. Carreno BM, Magrini V, Becker-Hapak M, et al. Cancer immunotherapy: a dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. Science 2015;348:803-8.
79. Palucka K, Ueno H, Fay J, Banchereau J. Harnessing dendritic cells to generate cancer vaccines. Ann N Y Acad Sci 2009;1174:88-98.
80. Tacken PJ, Torensma R, Figdor CG. Targeting antigens to dendritic cells in vivo. Immunobiology 2006;211:599-608.
81. Thomann JS, Heurtault B, Weidner S, et al. Antitumor activity of liposomal ErbB2/HER2 epitope peptide-based vaccine constructs incorporating TLR agonists and mannose receptor targeting. Biomaterials 2011;32:4574-83.
82. Gregory AE, Titball R, Williamson D. Vaccine delivery using nanoparticles. Front Cell Infect Microbiol 2013;3:13.
83. Chinnasamy N, Treisman JS, Oaks MK, Hanson JP, Chinnasamy D. Ex vivo generation of genetically modified dendritic cells for immunotherapy: implications of lymphocyte contamination. Gene Ther 2005;12:259-71.
84. Banchereau J, Palucka AK, Dhodapkar M, et al. Immune and clinical responses in patients with metastatic melanoma to CD34(+) progenitor-derived dendritic cell vaccine. Cancer Res 2001;61:6451-8.
85. Gabrilovich DI, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours. Nat Rev Immunol 2012;12:253-68.
86. De Monte L, Reni M, Tassi E, et al. Intratumor T helper type 2 cell infiltrate correlates with cancer-associated fibroblast thymic stromal lymphopoietin production and reduced survival in pancreatic cancer. J Exp Med 2011;208:469-78.
87. Palucka K, Banchereau J, Mellman I. Designing vaccines based on biology of human dendritic cell subsets. Immunity 2010;33:464-78.
88. Bonaccorsi I, Pezzino G, Morandi B, Ferlazzo G. Novel perspectives on dendritic cell-based immunotherapy of cancer. Immunol Lett 2013;155:6-10.
89. Cavallo F, Offringa R, van der Burg SH, Forni G, Melief CJ. Vaccination for treatment and prevention of cancer in animal models. Adv Immunol 2006;90:175-213.