Review Article

Dendritic Cells and Their Role in Cancer Immunotherapy

Ahmad Jalili

Division of Immunology, Allergy and Infectious Diseases (DIAID), Department of Dermatology, Medical University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria, Tel: (+) 43 1 404007658, Fax: (+) 43 1 404007790, e-mail: ahmad.jalili@meduniwien.ac.at

ABSTRACT

Dendritic cells (DCs) are antigen presenting cells with unique capability to take up and process antigens in the peripheral blood and tissues. They subsequently migrate to draining lymph nodes where they present these antigens and stimulate naive T lymphocytes. During their life cycle, DCs go through two maturation stages and are referred to as immature and mature cells, respectively. While immature DCs are very good at capturing antigens, mature DCs are suitably equipped to present antigens to T cells and to initiate an immune response. DCs with different phenotypes serve as sentinels in nearly all tissues including the peripheral blood, where they are continuously exposed to antigens. Very small numbers of activated DCs are extremely efficient at generating immune response against viruses, other pathogens and in experimental models of tumors. Protection against infectious microorganisms and probably against tumors is provided by complex interactions of the innate and adaptive immune systems. For the initiation to occur, pathogens must first be recognized as a “danger”. DC possesses specific receptors to detect such danger signals. The unique immune-stimulating properties of DC and the feasibility of manipulating their function arouse much enthusiasm and hold great promise for the treatment of cancer. Early clinical trials showed that DC can induce immune responses in cancer patients. Nonetheless, cancer treatments based on DC administration require further studies that will optimize this promising treatment modality.

Keywords: Dendritic cells, Cancer, Immunotherapy

1. HISTORICAL OUTLINE OF DENDRITIC CELLS DISCOVERY

In 1868 a medical student, Paul Langerhans, applied gold salts to human skin samples and observed a strikingly organized network of cells. Because of their dendritic morphology, he suggested they might be a new type of nerve cells. Although we now know much more about Langerhans cell (LC, a member of the DC family which resides in the epidermis of the skin) functions, their origins have long remained controversial. In the late 19th century, it was suggested that LC might be leukocytes, but it was not until the early 1970s, when DCs were identified and characterized as specialized bone marrow-derived antigen-presenting cells, that some understanding of the functions of LC developed.
Ralph Steinman and Zanvil Cohn identified murine splenic DCs in 1973 (1) and initiated a series of experiments that established lymphoid-tissue derived DCs as potent stimulators of primary immune responses (2-5). The identification of similar cells in non-lymphoid organs gave the start for intense investigations that led not only to better understanding of the immune response but also to performing first clinical trials using DCs in the treatment of human diseases (6-10).

2. CLASSIFICATION OF DENDRITIC CELLS

Dendritic cells represent a heterogeneous cell population, residing in most peripheral tissues, particularly at sites of interface with environment such as skin and mucosa where they represent 1-2% of the total cell population (11, 12). DCs were originally thought to be derived from myeloid precursors due to their functional, phenotypic and morphological similarities with macrophages (13), and the fact that macrophages, granulocytes and DCs can develop from a common precursor in the presence of granulocyte-macrophage colony stimulating factor (GM-CSF) (14). Although the issue of the origin of DCs precursor has not yet been unequivocally resolved, it was found that both the common lymphoid and the common myeloid precursors (CLP and CMP, respectively) had the potential to produce DCs. All the different DC populations identified in mouse thymus and spleen could be produced by all these precursor populations (15).
DCs can be classified either according to their anatomical localization (circulating DCs, LC, mucosal surface-associated DCs, interstitial DCs, veiled cells, interdigitating DCs and thymic DCs), or their differential expression of specific cell surface markers (e.g: CD8, CD4, CD11b, CD11c, DEC-205) and their function. To simplify, the classification of mice and human DCs subtypes are discussed separately.
2.1. Mouse DCs. Murine DCs can be divided into lymphoid, myeloid, plasmacytoid DCs and LC. Lymphoid DCs are characterized by expression of CD8, in contrast to myeloid DCs which lack this marker. The main biological difference of these two main DC groups (lymphoid and myeloid) is the ability of $CD8^+$ to induce a Th1-biased cytokine response in reactive $CD4^+$ T cells, whereas $CD8^-$ DCs tend to induce a Th2-biased response (16). $CD8^+$ DCs have the greatest capability to produce IL-12, the fact that may explain their capacity to induce Th1-biased immune response. Uninfected LN tissue of mice contains five different subtypes of DCs. $CD4^-$ $CD8^{hi}$ $CD205^{hi}$ $CD11b^-$ lymphoid DCs, $CD4^+$ $CD8^-$ $CD205^-$ $CD11b^+$ myeloid DCs, $CD4^-$ $CD8^-$ $CD205^-$ $CD11b^+$ myeloid DCs, $CD4^-$ $CD8^-CD205^+$ $CD11b^+$ myeloid DCs and $CD4^-$ $CD8^{low}$ $CD205^{hi}$ $CD11b^+$ LC. Plasmacytoid dendritic cells (pDC) are $CD11c^+$ $CD45RA^{low}$ $MHCII^{hi}$ $CD4^{low}$ $CD8^+$. Mouse pDC are found in all lymphoid organs and as with the human

pDC, it is a potent producer of type I interferons when stimulated by CpG or in viral infections (see below for details) (17).

2.2. Human DCs. In contrast to mouse DCs, there are relatively few studies on the human DCs freshly isolated from tissues. Human DCs do not express CD8, so making it difficult to compare them directly with mouse DCs. Most of our understandings of human DCs are by studying blood derived DCs. Human DCs can be classified as myeloid, pDC and LC. Myeloid DC or DC1 ($CD11c^{+}$ $CD123^{lo}$ $CD45RO^{high}$) have a myeloid progenitor whereas pDC or DC2 ($CD11c^{-}$ $CD123^{high}$ $CD45RO^{low}$) are derived from lymphoid precursors, both precursors arising from hematopoietic stem cells.

Currently there are two theories regarding the origin of DCs subtypes in both mouse and humans: a) the functional plasticity model in which DC subtypes might represent different activation states of a single lineage, the functional difference depending completely on local environmental signals or, b) the specialized lineage model in which DCs could be the product of entirely separate developmental lineages (18).

In both mouse and humans, pDC are found in lymphoid tissues (LN, tonsil, spleen, thymus, bone marrow and Peyer's patches) (17), blood (19) and peripheral tissues (during inflammation) including skin (lymphoid hyperplasia of the skin (20), cutaneous SLE (21), psoriasis vulgaris (21) and contact dermatitis (21)), mucosa (allergic mucosa (22)) and tumor infiltrates (melanoma (23), head and neck carcinoma (24) and ovarian carcinoma associated ascites (25)). They play a central role in immunity, not restricted to their ability to produce type I interferons and antiviral immune responses. Blood-borne pathogens can stimulate maturation of pDC which can lead to the bystander maturation of surrounding pDC and myeloid dendritic cells (mDC). Mature pDC can migrate to LN (26), where they activate antigen specific B cells (differentiation into antibody secreting cell (27)), $CD4^{+}$ T cells (priming and restimulation of memory response (28)), $CD8^{+}$ T cells (priming and restimulation of memory response (29)), regulatory T cells (anergy and IL-10 production (30)), mDC (bystander maturation (31)), NK cells (recruitment and activation (32)) and monocytes (DC differentiation (33)).

pDC express CD123 (IL-3 receptor α-chain), respond to IL-3 and express TLR9 that binds to bacterial DNA and unmethylated CpG deoxynucleotides (34, 35). The term plasmacytoid makes these cells distinct from the mDC, but it has not been so far proven that these cells do not have myeloid origin. There is still a lot to be learned and discovered about the DC subsets before we will be able to come up with a clear-cut classification of these cells. Table 1 summarizes some of the surface markers of mDC and pDC in human.

Table 1. Human mDC and pDC surface markers

mDC			pDC		
Markers	**TLRs**	**CLRs**	**Markers**	**TLRs**	**CLRs**
CD11c	TLR2	DC-SIGN (CD209)	CD123	TLR7	BDCA-2
CD11b	TLR3	DC-LAMP (CD208)	CD62L	TLR9	Dectin-1
CD13	TLR4	Macrophage Mannose Receptor (CD206)	CD45RA		DEC-205 (CD205)
CD45RO	TLR5	DEC-205 (CD205)	CD36		DC-LAMP (CD208)
CD33	TLR6		MHC class II		
MHC class II	TLR7		CD40		
CD40	TLR8		CD54		
CD54			CD80		
CD80			CD86		
CD86					

CLRs: C-type lectin receptors

3. MATURATION OF DENDRITIC CELLS

During their life cycle, DCs are present either as immature or mature cells. Immature DCs specialize in antigen capture. They express characteristic chemokine receptors for inflammatory chemokines (e.g. MIP-3α) released at sites of antigen challenge within peripheral tissues (36). Immature DCs capture antigens by phagocytosis, macropinocytosis or endocytosis via interaction with a variety of cell surface receptors (37). These receptors include lectins, immunoglobulin superfamily molecules, Fc receptors, heat shock protein (HSP) receptors, and Toll-like receptors (TLR) (38). A number of these cell surface receptors are down-regulated upon DC maturation, emphasizing their specific roles in antigen uptake (38). Both exogenous and endogenous antigens can be processed by DCs and presented in the context of either MHC class I or II molecules (37, 38).

Endogenous antigens are processed and loaded into the MHC class I exclusively (37, 39). Exogenous antigens are proteolytically processed and loaded into the grooves of MHC class II molecules for the presentation to T cells. In DC only, exogenous antigens may also undergo processing and presentation in association with class I MHC molecules by the classical proteasome and TAP-dependent pathway, a phenomenon referred to as "cross presentation" (40-43). This function is particularly important for *in vivo* priming of CTL responses to antigens that are not synthesized by DC (44).

Maturation of DCs is accompanied by morphological and functional changes in these cells. Table 2 shows differential expression of some important molecules and receptors as well as several properties of immature and mature DC.

Table 2. Differences between immmature and mature dendritic cells

Immature DC	Mature DC
Low capacity of antigen presentation	High capacity of antigen presentation
Short dendritic projections	Long dendritic projections
High intracellular MHC class II	High surface MHC class II
High capacity of endocytosis, phagaocytosis and macropinocytosis	Low capacity of endocytosis, phagaocytosis and macropinocytosis
High expression of CCR1, CCR2, CCR5, CCR6, CXCR1, CXCR2 and CXCR4	High expression of CCR7
Expression of low levels of CD54, 58, 80 (B7-1), 86 (B7-2), PD-L1 (CD274) and PD-L2 (CD273)	Expression of high levels of CD54, 58, 80 (B7-1), 86 (B7-2), PD-L1 (CD274) and PD-L2 (CD273)
Expression of low levels of CD40, CD83 (human but not murine DC), DC-LAMP and p55 TNF receptor subunit	Expression of high levels of CD40, CD83 (human but not murine DC), DC-LAMP and p55 TNF receptor subunit
Induce expansion of regulatory T cells	Induce expansion of helper/cytotoxic T cells

Morphological changes include decreased adhesiveness to extracellular matrix, cytoskeleton reorganization, formation of dendritic projections and acquisition of high cellular motility (45). Abundant dendritic projections on mature DCs increase their surface area and help them in having better contact with T cells. Maturation is also linked with upregulation of MHC class II (46), with co-stimulatory and adhesion molecules needed for the stimulation of T cells and down-regulation of receptors and with molecules used by immature DCs for the uptake of antigens (47). All these morphological and functional changes are to facilitate effective priming of naïve T lymphocytes. Table 3 shows a list of some of the known stimulants that induce DC maturation.

Table 3. Some of the endogenous and exogenous stimulants and their receptors inducing maturation of DCs

Endogenous stimulants	Receptors
ATP and UTP	P2X7 purinergic receptor (48)
Reactive oxygen intermediates	--- (49)
Hyaluronan	CD44 (50, 51)
HSP70, HSP90, and HSP96	CD91 (52)
HSP60	TLR4 (53)
CD40L	CD40 (54)
TNF	TNFR (55)
IL-1β	IL-1βR (56)
Type 1 IFNs	IFN-R (57)
Vasoactive intestinal polypeptide	VIP-R (58)
Fas	FasL (59, 60)
CCL19 (MIP-3β) & CCL21 (SLC) *	CCR7 (61)
Exogenous stimulants	**Receptors**
Bacterial peptidoglycans, lipoteichoic acids and lipopeptides	TLR 1, TLR 2 and TLR 6 (62)
LPS	TLR 4 (63, 64)
DNA containing unmethylated CpG dinucleotides	TLR 9 (65)
Bacterial and mitochondrial unmethylated RNA	TLR3, 7, 8 (66)
dsRNA	TLR 3 (67, 68)
Viral and bacterial ssRNA	TLR 7/8 (69, 70)
Flagellin	TLR 5 (71)
Mannoproteins	Mannose Receptor (72)
Candida albicans	Mannose Receptor (73) (74)
Toxoplasma gondii-derived cyclophilin	CCR5 (75)
Uropathogenic E.coli & Toxoplasma gondii	TLR11 (76, 77)

*****In our work CCL19 (MIP-3β) & CCL21 (SLC) induce surface expression of CD40 on DC but not maturation as manifested by upregulation of co-stimulatory molecules or characteristic morphological changes (author's unpublished observation).

4. MIGRATION OF DENDRITIC CELLS

With the exception of thymic DCs that are located exclusively within thymus and do not seem to traffic (78), all DC types continuously migrate from blood into tissues and consequently into lymphoid organs. They traffic from one site to the next, performing specific functions at each location (79, 80). An important question for the understanding of DC biology is how DCs populate the periphery in homeostasis, and how they are recruited in inflammation. Myeloid DCs enter the blood stream from bone marrow and circulate as precursor/immature DCs capable of slow constitutive migration required for the maintenance of resident tissue populations (81). In inflammatory circumstances endothelial adhesion molecules and chemokines are up-regulated, facilitating efficient recruitment of circulating DCs to the affected site (82). Upon maturation, DCs reprogram their repertoire of chemokine receptors (83, 84) and after a time necessary for antigen loading they migrate to lymph nodes where they obtain access to the naïve T cell population (85, 86). Plasmacytoid DCs circulate in peripheral blood in precursor form, and comprise a significant leukocyte population in most secondary lymphoid organs (17). They migrate directly from blood to secondary lymphoid organs.

The extravasation of DCs from the blood to peripheral tissues and the movement from peripheral tissues into lymphoid organs requires chemoattractants, including chemokines and non-chemokine chemotactic factors (Table 4-6) (87-89). The anatomic location of inflammatory chemokines within peripheral tissues and constitutive chemokines within lymphoid organs regulate the migration of DCs initially to sites of antigen delivery and ultimately to lymphoid tissues to initiate an immune response.

Rapid recruitment of DCs from blood into inflamed tissues is thought to be a response to the increased requirement for surveillance at the local site (90). At such inflammatory sites, endothelial cell adhesion molecule expression including E- and P-selectin, VCAM-1 and L-selectin ligands is upregulated, mediating DCs tethering and rolling (91, 92). Using radioactive tracing techniques and confocal microscopy *in vivo*, immature, but not mature bone marrow derived DCs accumulated in inflamed ear skin as early as 6 h after intravenous injection (93). Immature and mature DCs differentially express chemokines and their receptors (Table 4 and 6). Similar phenomenon is true for myeloid and plasmacytoid DCs (94). Table 4 shows chemokine receptors expressed by immature and mature DCs and their respective ligands.

Table 4. Chemokine receptors expressed by immature and mature DCs

Immature DC		Mature DC	
Chemokine receptor	**Ligand**	**Chemokine receptor**	**Ligand**
CCR1 (84)	CCL3 (MIP-1α), CCL4 (MIP-1 β), CCL5 (RANTES)	CCR7 (95)	CCL19 (MIP-3β), CCL21 (SLC)
CCR2 (84)	CCL2 (MCP-1), CCL7 (MCP-3), CCL8 (MCP-2), CCL13 (MCP-4)	CCR8 (96)	CCL1 (I-309)
CCR3 (97)	CCL5 (RANTES), CCL8 (MCP-2), CCL11 (Eotaxin)	CXCR4 (84)	CXCL12 (SDF-1α/β)
CCR4 (98)	CCL17 (TARC), CCL22 (MDC)		
CCR5 (84)	CCL3 (MIP-1α), CCL4 (MIP-1β), CCL5 (RANTES)		
CCR6 (99)	CCL20 (MIP-3α)		
CXCR1 (84)	CXCL8 (IL-8)		
CXCR2 (100)	CXCL1 (GRO-α), CXCL5 (ENA-78), CXCL7 (NAP-2), CXCL8 (IL-8)		
CXCR3 (101)	CXCL9 (Mig), CXCL10 (IP-10), CXCL11 (I-TAC)		
CXCR4 (84)	CXCL12 (SDF-1 α/β)		

DCs express a variety of receptors for chemotactic stimuli which are different from chemokines. These encompass receptors for bacterial components, bioactive lipids and for signals of "tissue danger". At the site of inflammation these chemotactic stimuli are rapidly produced within minutes, therefore they represent an early signal for the recruitment of DCs and their precursors before chemokines start their action. Table 5 summarizes some of these chemotactic receptors expressed by DCs and their respective ligands.

Table 5. Non-chemokine chemotactic receptors expressed mainly by immature DCs

Receptor	Ligand
ChemR23 (102)	Chemerin
FPR (103)	FMLP
FPRL1 (104)	LL37
FPRL2 (105)	F2L
C5aR (106)	C5a
PAFR (107)	PAF
CCR6 (107)	α and β -defensins
CXCR3 and CXCR5 (108)	S-antigen, IRBP

In order to attract different cell types to their site and also to facilitate their own migration, DCs depending on their maturation status, produce different types of chemokines. Table 6 summarizes some of these chemokines produced by immature and mature DCs.

Table 6. Differential secretion of chemokines by immature and mature DCs

Immature DC	Mature DC
CCL17 (TARC) (109)	CCL2 (MCP-1) (110)
CCL18 (DC-CK-1, MIP-4) (111)	CCL3 (MIP-1α (110)
CCL20 (MIP-3α.Exodus-1) (98)	CCL4 (MIP-1β) (109)
CCL22 (MDC) (111)	CCL5 (RANTES) (84)
CXCL8 (IL-8) (110)	CCL17 (TARC) (109)
CXCL16 (112)	CCL18 (DC-CK-1, MIP-4) (111)
	CCL20 (MIP-3α Exodus-1) (111)
	CCL22 (MDC) (113)
	CXCL8 (IL-8) (110)
	CXCL10 (IP-10) (109)
	CXCL13 (BLC) (114)
	CXCL16 (112, 115)
	CXCL17 (101)
	CX3CL1 (Fractalkine) (116)

Upon maturation, parallel to down-regulation of inflammatory chemokine receptors is the up-regulation of CCR7, which confers lymph node homing capability on maturing DCs (117). The critical role for CCR7 ligands in DC homing is demonstrated in mice that lack CCR7, and also in *plt/plt* (paucity of lymph node T cells) mice that are deficient in both of the CCR7 ligands i.e. CCL19 and CCL21 in their secondary lymphoid tissues (118, 119).

Inside the lymph node, CCL19 and CCL21 are expressed within the T cell area by stromal cells where they are thought to be important for appropriate DC localization (120). Gene gun-mediated administration of plasmid DNA expressing CCL21 in the skin leads to drainage/accumulation of transgenic CCL21 into/in the draining peripheral lymph nodes (PLN) and attraction of CCR7 expressing cells including DCs (author's unpublished observations).

5. DENDRITIC CELLS, ANTIGEN PRESENTATION AND T CELL STIMULATION

Several conditions have to be fulfilled in order to switch on an immune response. These include: a) the capture of the antigen and its processing, b) the presentation of antigenic peptide in the context of self MHC, c) the physical interaction of antigen-bearing APC with T cells specific for the same antigen, and d) the presence of T cell costimulatory signals. An inadequate immune response may even be deleterious and result in tissue damage, allergic reactions, or autoimmune diseases, thus requiring the action of the most professional antigen presenting cells, the dendritic cells. When compared directly to other cells, DCs showed to be far superior in *in vitro* assays for the priming of alloreactive, naïve TCR transgenic T cells or the expansion and activation of antigen-specific naïve precursors from polyclonal populations (11). *In vivo*, injection of antigen loaded DCs induce potent $CD4^+$ and $CD8^+$ T cell primary responses (121). Interaction between antigen-specific transgenic T cells and antigen-loaded DCs has been visualized by immunofluorescence on lymph node sections (122).

$CD4^+$ and $CD8^+$ cells respond to peptide antigens displayed on MHC class II and MHC class I molecules, respectively (referred to as Signal 1). Accessory molecules on DCs are required to ensure that T cells will divide and differentiate into effector cells (Signal 2). In the absence of sufficient costimulation, T cells exhibit anergy or undergo apoptosis. Secretion or lack of secretion of additional factors by DCs, particularly IL-12, is instrumental in the final differentiation of T cells into type 1 or type 2 effector T helper cells, respectively (Signal 3). As mentioned earlier two distinct populations of DCs can be observed based on CD8 expression in mice: $CD8^+$ and $CD8^-$ DC (123). Splenic $CD8^+$ and $CD8^-$ DCs do not exhibit significant differences in their ability to stimulate naïve $CD8^+$ T cells *in vitro* and after *in vivo* intravenous injection (124). Subcutaneous injection of antigen-loaded $CD8^+$ DCs primed Th1 responses, whereas $CD8^-$ DCs primed Th2 responses (125). The selective induction of Th1 responses by $CD8^+$ DC is in direct causal relationship with their ability to produce Th1 promoting cytokines such as IL-12 and IFN-γ (125, 126). On the other hand IL-10 production and lack of IL-12 production capability of $CD8^-$ DC leads to their capacity to induce Th2 immune response (126).
Expression of MHC products and MHC-peptide complexes are 10- to 100-fold higher on DCs than on other APC like B cells and monocytes (127). Besides MHC-TCR, DC-T cell clustering is mediated by several adhesion molecules, like integrins β1 and β2 and members of the immunoglobulin superfamily (CD2, CD50, CD54, and CD58) (12, 128). The crucial factor that constitutes Signal 2 (as mentioned earlier) requirement to sustain T cell activation is the interaction between co-stimulatory molecules expressed by DCs and their ligands expressed by T cells. Molecules belonging to B7 family (B7-1 (CD80), B7-2 (CD86) in particular and ICOS ligand, PD-L1 (B7-H1), PD-L2 (B7-DC), B7-H3, and B7-H4 (B7x/B7-S1)) are so far the most critical molecules for amplification of T cell responses (129). Although, B7-CD28 interaction leads to stimulation of T lymphocytes, B7-CTLA4 plays the opposite role and dampens the T lymphocyte activation, therefore controlling the magnitude of the immune response (129). Table 7 lists some of the known co-stimulatory molecules and their ligands involved in DC-T cell interaction.

Table 7. Surface molecules engaged in the interaction between dendritic cells and T cells.

Dendritic cells	T cells
B7-1 (CD80)	CD28, CTLA-4 (CD152)
B7-2 (CD86)	CD28, CTLA-4 (CD152)
ICOSL (B7h, B7-H2; B7RP-1)	ICOS
PD-L1 (B7-H1)	PD-1
PD-L2 (B7-DC)	PD-1
B7-H3	?
B7-H4 (B7x; B7S1)	?
CD40	CD40L (CD154)
OX40L	OX40 (CD134)
TRANCE-R	TRANCE
ICAM-1 (CD54)	LFA-1 (CD11a/CD18)
DC-SIGN (CD209)	ICAM-3 (CD50), ICAM-2 (CD102)
CD58	CD2

Reciprocally, T cells can activate DCs via CD40 ligand (CD40L)-CD40 signalling leading to increased expression of CD80/CD86, cytokine release (IL-1, TNF-α, chemokines and IL-12) and DC survival (130-133).

6. TOLEROGENIC/REGULATORY DENDRITIC CELLS

So far, it has been accepted that immature DCs are capable of inducing T-cell anergy and Treg cells, whereas mature DCs are potent stimulants of T effector cell responses. This bimodal concept of immature and mature DCs has been recently challenged by studies demonstrating that antigen-bearing mature DCs can expand Treg cells that have suppressive properties (134). Immature DCs are disseminated through peripheral tissues and capture antigens from apoptotic cells during normal tissue turn over. Necrotic cells promote maturation of DCs and induce strong $CD4^+$ and $CD8^+$ T-cell stimulation, whereas apoptotic cells fail to activate DCs. Recent evidences suggest that semi-mature DCs can also be tolerogenic (135). These semi-mature tolerogenic DCs can be defined based on high expression levels of co-stimulatory and MHC class II molecules but produce low levels of proinflammatory cytokines such as IL-1β, IL-6, TNF-α and IL-12, therefore they are referred to as 'semi-mature DCs' (135, 136). Interestingly, respiratory exposure to ovalbumin induces migration of IL-10-producing pulmonary DCs with mature phenotype into the draining lymphoid tissue where they stimulate antigen-specific Treg cells (137). Rutella et al. have recently summarized current strategies used to promote the tolerogenicity of DCs *in vitro* (138).

7. DENDRITIC CELLS AND TUMOR IMMUNITY

Tumor immunotherapy aims at activation of the body's own immune system to fight an existing tumor. At the time of diagnosis, the tumor has successfully adapted to the various immune effector mechanisms via exhaustion (139), ignorance (140), tolerization (141), inhibition of antigen specific lymphocytes (142) or by the generation of antigen loss variants (143). In addition, tumor antigens are relatively weak and are often masked or sequestered inside of the tumor cell, or are expressed in barely detectable amounts. Growing tumor is generally capable of creating a local micro-milieu, which hampers antigen presentation as well as induction of immune effector functions. Effector mechanisms against endogenous tumors include both cellular and humoral immunity. The majority of experimental systems clearly demonstrate that tumor immunity is largely provided by $CD4^+$ (144-146), $CD8^+$ T lymphocytes (147-149) and NK cells (150). T cells require activation by antigen-presenting cells. Although activation of NK cells is less well understood, their direct interaction with DCs has been demonstrated (150). Apart from generating a powerful anti-tumor immune response, DCs may also play an active role in the elimination of tumor cells themselves, since DCs have been shown to kill tumor cells via expression of death receptor ligands (151) and recent data suggest that DCs activated by pro-inflammatory cytokines, LPS or TLR-7 ligand imiquimod, can directly inhibit the growth of tumor cell lines (152-155). Even a single intra-tumoral injection of DCs is able to reduce tumor growth in mice (156). Thus, DCs are at the very center of developing tumor-specific immune response, and are involved both in the initiation of tumor-specific immunity and in the generation of immune effector mechanisms. The rapid increase in the understanding of DC physiology and their importance in the generation of immune responses has raised many hopes that the antigen presenting capacity of DCs might be exploited for tumor therapy (157). With the techniques for the *in vivo* modification of DCs or their large scale *ex vivo* production from precursors (11,

128, 158), this dream has come into reality and is now intensively being studied in numerous clinical trials.

8. THE USE OF DENDRITIC CELLS FOR CANCER THERAPY

Currently, there are numerous attempts to induce cancer immunity, both by activation of DCs *in vivo* as well as by manipulation and reinfusion of *ex vivo* generated DCs.

***In vivo* Approaches.** Direct enhancement of tumor antigen presentation by DCs has been a strategy for tumor therapy. *In vivo* modifications of DCs generally aim at either expanding the DCs pool within the tumor-bearing host, at attracting and activating DCs locally, or both. Systemic administration of DC-specific growth factors, such as GM-CSF, Flt3-L, G-CSF or DC activation signals like CD40-L (159-166) are intended to positively influence DC function by increasing DC numbers and stimulating DCs to present tumor-derived antigens more effectively. It could indeed be demonstrated convincingly that the DCs can be expanded significantly by administration of these factors, and that this can be associated with augmented tumor immunity (159-161). Different subsets of DCs appear to expand after administration of GM-CSF versus Flt3-L, opening the potential for selective augmentation of certain DC subsets (162). Bacteria transduced with tumor antigen-encoding genes and administered orally have been used to provide a DC activation signal (CpG, LPS) and the relevant antigen. Material derived from such bacteria is taken up by intestinal DC, which afterwards become activated and induce a productive immune response (167, 168).

Enhancing tumor antigen presentation *in vivo* can also be done by engineering of tumor cells to express functions of APC. Transfection of tumor cells with co-stimulatory molecules of the B-7 or the TNF/TNF-R family alone or together with MHC II has been successful in generating protective immunity both against the transfected as well as the unmodified wild-type tumor (169-171). However, it appears unlikely that tumor cells can acquire the full functional properties of professional APC by simple transfection of individual co-stimulatory molecules. It seems that induction of tumor immunity is likely to be due to indirect antigen presentation via locally recruited and/or activated endogenous host-derived APC rather than due to direct presentation of tumor antigen by the gene-modified tumor cells (172, 173). To achieve local activation of DCs in the vicinity of the autologous tumor, tumor cells were obtained from patients, transfected with DC-activating genes (such as GM-CSF or CD40-L), and re-administered (174-176).

In summary, several strategies are being evaluated that aim at the enhancement of tumor antigen presentation within the tumor-bearing host. These approaches are attractive and appear to be rather easily adaptable for clinical use, and have proven to be effective in preclinical models. Initial trials are in progress that will evaluate the clinical effect of some of these approaches in cancer patients. A critical consideration in attempts to activate or expand DCs *in vivo* is that neither tumor antigen loading nor the exact state of DC activation can be controlled directly. This might be deleterious, as the presentation of antigen on immature DCs can lead to the induction of antigen-specific tolerance (177). Moreover, effective DC activation greatly depends on the local cytokine microenvironment (178), which is almost impossible to control. Therefore, resident DCs in a patient may often be functionally suppressed (141), and their use as inducers of tumor immunity is not likely to be successful.

***Ex vivo* Approaches.** A promising approach to reach effective vaccination has been the isolation of DCs from the patient, their propagation and activation in the absence of a putatively suppressive tumor milieu, and their re-infusion after tumor antigen exposure and/or suitable manipulation (reviewed in detail in (179)). While methods to generate DCs were being developed, it has become clear that DCs are diverse both by origin and function. The DC system has become even more complicated due to the discovery that ontogenetically diverse subtypes of DCs exist which may stimulate different types of immune responses, such as preferential priming of Th1 versus Th2 responses (18, 28, 180, 181). The recent observation that activated DCs produce Th1 inducing cytokines only for a limited period after activation (182) might pose a problem for using terminally mature DCs for tumor vaccination. Following this concept, it might be expected that after the usual period of 24–48 h in the presence of an activating stimulus the transferred DCs, although mature, might be 'exhausted' and thus induce a Th2 rather than Th1 response (182). These considerations have to be taken into account when searching for the 'right' DCs for use in tumor vaccination.

Due to the recent availability of defined tumor antigens, clinical trials with these reagents are currently underway or have already been completed successfully (183-186). Antigens of the MAGE family have been employed to induce melanoma specific immunity, first by using immature DCs (183) and later by using terminally mature DCs (184-186). Indeed, the use of defined antigens for tumor immunotherapy has the clear advantage of being able to control the amount of antigen administered, and to monitor the emerging immune response. For vaccination against B-lymphoma, DCs were loaded with lymphoma specific whole idiotype proteins with success (187). Alternatively, the direct transfection of DCs with whole tumor RNA (188) or RNA that was specific for a given tumor antigen (189) was effectively used to generate tumor immunity (190). Indeed, preclinical models show that tumors expressing a model antigen can be rejected when DCs were transfected with the relevant gene (191, 192). In line with this, DCs transfected with a melanoma-associated antigen were able to induce melanoma antigen-specific CTL from PBMC *in vitro* (193). *In vivo* transfection of DCs with DNA led to induction of an immune response against a model antigen (194). Whole cell protein extracts represent a broad source of tumor antigens, and have been used for vaccination against melanoma by loading *ex vivo* generated DCs with tumor lysate (author's unpublished observation and (186)). Since DCs are very effective at taking up and processing apoptotic material which might lead to the presentation of previously unrecognized antigens (195, 196), loading DCs with apoptotic tumor cells has been used in melanoma (149) and leukemia vaccination models (196). Injection of immature DCs locally to the solid tumor that has been treated with agents inducing apoptosis/necrosis (e.g photodynamic therapy, PDT) seems to be also a good strategy while it provides DCs with tumor antigen and danger signals needed for their maturation (197, 198).

In a recent study conducted by Schadendorf et al, DCs (MHC class I- and II-restricted tumor-peptides-pulsed) showed similar efficacy as conventional chemotherapy with dacarbazine (DTIC) in melanoma patients, however DC immunotherapy was accompanied with slightly lower side effects (199). Unscheduled subset analyses revealed that only in the DC-arm, did those patients with (i) an initial unimpaired general health status (Karnofsky = 100) or (ii) an HLA-$A2^{+}$/HLA-$B44^{-}$ haplotype survive significantly longer than patients with a Karnofsky index < 100 or other HLA haplotypes (199).

DCs are being also fused with tumor cells and is shown to be able to induce tumor specific immune response (200). Fused DC-tumor cell hybrids are thought to combine the

whole antigenic spectrum of the tumor with the powerful antigen presentation capabilities of DCs. An intriguing approach is suggested by studies showing that DCs can be generated in cell culture from leukemic blasts of AML (201, 202), ALL (203, 204), and CML patients (205). Since such *ex vivo* generated DCs maintain their characteristic chromosomal disorders, at the same time developing the powerful antigen presentation capacities of DCs, they are considered as a promising way to generate APC for vaccination against leukemias (206).

Besides different DC generation protocols, types of tumor antigen, and modes of tumor antigen delivery as well as other variables such as the use of syngeneic MHC-matched or fully allogenic DCs, the dose of DCs, DCs injection site and intervals, and concomitant treatment with substances that stimulate the proliferation of DC-precursors, activate them, or recruit them to either the tumor site or the regional lymph node or concomitant removal of Tregs need to be taken into consideration for planning the optimal DC vaccination protocol (157, 207-213).

ACKNOWLEDGEMENT

I acknowledge the support of the Center for Molecular Medicine (CeMM) of the Austrian Academy of Sciences. I would like to thank Dr. Mikhail Pashenkov for critically reading the manuscript and his valuable comments.

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, Lustig DS, Cohn ZA. Identification of a novel cell type in peripheral lymphoid organs of mice. 3. Functional properties in vivo. J. Exp. Med. 1974; 139:1431-45.
3 Steinman RM, Adams JC, Cohn ZA. Identification of a novel cell type in peripheral lymphoid organs of mice. IV. Identification and distribution in mouse spleen. J. Exp. Med. 1975; 141:804-20.
4 Inaba K, Witmer MD, Steinman RM. Clustering of dendritic cells, helper T lymphocytes, and histocompatible B cells during primary antibody responses in vitro. J. Exp. Med. 1984; 160:858-76.
5 Witmer MD, Steinman RM. The anatomy of peripheral lymphoid organs with emphasis on accessory cells: light-microscopic immunocytochemical studies of mouse spleen, lymph node, and Peyer's patch. Am. J. Anat. 1984; 170:465-81.
6 Anderson AO, Warren JT, Gasser DL. Presence of lymphoid dendritic cells in thoracic duct lymph from Lewis rats. Transplant. Proc. 1981; 13:1460-8.
7 Cohen DA, Kaplan AM. Adherent Ia+ murine tumor lines with characteristics of dendritic cells. I. Morphology, surface phenotype, and induction of syngeneic mixed lymphocyte reactions. J. Exp. Med. 1981; 154:1881-98.
8 Hart DN, Fabre JW. Demonstration and characterization of Ia-positive dendritic cells in the interstitial connective tissues of rat heart and other tissues, but not brain. Exp Med. 1981; 154:347-61.
9 Hart DN, Fabre JW. Major histocompatibility complex antigens in rat kidney, ureter, and bladder. Localization with monoclonal antibodies and demonstration of Ia-positive dendritic cells. Transplantation. 1981; 31:318-25.
10 Winchester RJ, Burmester GR. Demonstration of Ia antigens on certain dendritic cells and on a novel elongate cell found in human synovial tissue. Scand J Immunol. 1981; 14:439-44.
11 Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature 1998; 392:245-52.
12 Bell D, Young JW, Banchereau J. Dendritic cells. Adv.Immunol. 1999; 72:255-324.
13 Van FR, Cohn ZA. The origin and kinetics of mononuclear phagocytes. J.Exp.Med. 1968; 128:415-35.
14 Inaba K, Inaba M, Deguchi M, Hagi K, Yasumizu R, Ikehara S et al. Granulocytes, macrophages, and dendritic cells arise from a common major histocompatibility complex class II-negative progenitor in mouse bone marrow. Proc.Natl.Acad.Sci.U.S.A. 2007; 90:3038-42.
15 Wu L DAHHOMSKLK. Development of thymic and splenic dendritic cell populations from different hemopoietic precursors. Blood 2007; 98:3376-82.
16 Shortman K, Liu YJ. Mouse and human dendritic cell subtypes. Nat. Rev. Immunol. 2002; 2:151-61.
17 McKenna K, Beignon AS, Bhardwaj N.Plasmacytoid dendritic cells: linking innate and adaptive immunity. J. Virol. 2005; 79:17-27.
18 Kalinski P, Moser M. Consensual immunity: success-driven development of T-helper-1 and T-helper-2 responses. Nat. Rev. Immunol. 2005; 5:251-60.
19 O'Doherty U, Peng M, Gezelter S, Swiggard WJ, Betjes M, Bhardwaj N et al. Human blood contains two subsets of dendritic cells, one immunologically mature and the other immature. Immunology. 1994; 82:487-93.

20 Eckert, F., and U. Schmid. 1989. Identification of plasmacytoid T cells in lymphoid hyperplasia of the skin. Arch Dermatol. 1989; 125:1518-24.
21 Wollenberg A, Wagner M, G[illegible]nther S, Towarowski A, Tuma E, Moderer M et al. Plasmacytoid dendritic cells: a new cutaneous dendritic cell subset with distinct role in inflammatory skin diseases. J. Invest. Dermatol. 2002; 119:1096-102.
22 Jahnsen FL, Lund-Johansen F, Dunne JF, Farkas L, Haye R, Brandtzaeg P. Experimentally induced recruitment of plasmacytoid (CD123high) dendritic cells in human nasal allergy. J. Immunol. 2000; 165:4062-8.
23 Palamara F, Meindl S, Holcmann M, Luhrs P, Stingl G, Sibilia M. Identification and characterization of pDC-like cells in normal mouse skin and melanomas treated with imiquimod. J. Immunol. 2004; 173:3051-61.
24 Hartmann E, Wollenberg B, Rothenfusser S, Wagner M, Wellisch D, Mack B et al. Identification and functional analysis of tumor-infiltrating plasmacytoid dendritic cells in head and neck cancer. Cancer Res. 2003; 63:6478-87.
25 Curiel TJ, Cheng P, Mottram P, Alvarez X, Moons L, Evdemon-Hogan M et al. Dendritic cell subsets differentially regulate angiogenesis in human ovarian cancer. Cancer Res. 2004; 64:5535-8.
26 Cella M, Jarrossay D, Facchetti F, Alebardi O, Nakajima H, Lanzavecchia A et al. Plasmacytoid monocytes migrate to inflamed lymph nodes and produce large amounts of type I interferon. Nat. Med. 1999; 5:919-23.
27 Jego G, Palucka AK, Blanck JP, Chalouni C, Pascual V, Banchereau J. Plasmacytoid dendritic cells induce plasma cell differentiation through type I interferon and interleukin 6. Immunity. 2003; 19:225-34.
28 Cella M, Facchetti F, Lanzavecchia A, Colonna M. Plasmacytoid dendritic cells activated by influenza virus and CD40L drive a potent TH1 polarization. Nat. Immunol. 2000; 1:305-10.
29 Fonteneau JF, Gilliet M, Larsson M, Dasilva I, M[illegible]nz C, Liu YJ et al. Activation of influenza virus-specific CD4+ and CD8+ T cells: a new role for plasmacytoid dendritic cells in adaptive immunity. Blood. 2003; 101:3520-6.
30 Wei S, Kryczek I, Zou L, Daniel B, Cheng P, Mottram P et al. Plasmacytoid dendritic cells induce CD8+ regulatory T cells in human ovarian carcinoma. Cancer Res. 2005; 65:5020-6.
31 Fonteneau JF, Larsson M, Beignon AS, McKenna K, Dasilva I, Amara A et al. Human immunodeficiency virus type 1 activates plasmacytoid dendritic cells and concomitantly induces the bystander maturation of myeloid dendritic cells. J. Virol. 2004; 78:5223-32.
32 Megjugorac NJ, Young HA, Amrute SB, Olshalsky SL, Fitzgerald-Bocarsly P. Virally stimulated plasmacytoid dendritic cells produce chemokines and induce migration of T and NK cells. J. Leukoc. Biol. 2004; 75:504-14.
33 Gursel M, Verthelyi D, Klinman DM. CpG oligodeoxynucleotides induce human monocytes to mature into functional dendritic cells. Eur. J. Immunol. 2002; 32:2617-22.
34 Krug A , Towarowski A, Britsch S, Rothenfusser S, Hornung V, Bals R et al. Toll-like receptor expression reveals CpG DNA as a unique microbial stimulus for plasmacytoid dendritic cells which synergizes with CD40 ligand to induce high amounts of IL-12. Eur J Immunol .2001; 31:3026-37.
35 Bauer M, Redecke V, Ellwart JW, Scherer B, Kremer JP, Wagner H et al. Bacterial CpG-DNA triggers activation and maturation of human CD11c-, CD123+ dendritic cells. J. Immunol. 2001; 166:5000-7.
36 Schutyser E, Struyf S, Van Damme J. The CC chemokine CCL20 and its receptor CCR6. Cytokine Growth Factor Rev. 2003; 14:409-26.
37 Mellman I. Antigen processing and presentation by dendritic cells: cell biological mechanisms. Adv. Exp. Med. Biol. 2005; 560:63-7.
38 Trombetta ES, Mellman I. Cell biology of antigen processing in vitro and in vivo. Annu Rev Immunol. 2005; 23: 975-1028.
39 Rock KL. A new foreign policy: MHC class I molecules monitor the outside world. Immunol. Today. 1996; 17:131-7.
40 Belz GT, Carbone FR, Heath WR. Cross-presentation of antigens by dendritic cells. Crit Rev Immunol. 2002; 22:439-49.
41 Larsson M, Fonteneau JF, Bhardwaj N. Cross-presentation of cell-associated antigens by dendritic cells. Curr. Top. Microbiol. Immunol. 2003; 276:261-75.
42 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.
43 Bevan MJ. Cross-priming for a secondary cytotoxic response to minor H antigens with H-2 congenic cells which do not cross-react in the cytotoxic assay. J Exp Med. 1976; 143:1283-88.
44 Bevan MJ.Antigen presentation to cytotoxic T lymphocytes in vivo. J Exp Med. 1995; 182:639-41.
45 Winzler C, Rovere P, Rescigno M, Granucci F, Penna G, Adorini L et al. Maturation stages of mouse dendritic cells in growth factor-dependent long-term cultures. J. Exp. Med.1997; 185:317-28.
46 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.
47 Banchereau J, Briere F, Caux C, Davoust J, Lebecque S, Liu YJ et al. Immunobiology of dendritic cells. Annu. Rev. Immunol. 2000; 18:767-811.
48 Berchtold S, Ogilvie AL, Bogdan C, Muhl-Zurbes P, Ogilvie A, Schuler G et al. Human monocyte derived dendritic cells express functional P2X and P2Y receptors as well as ecto-nucleotidases. FEBS Lett. 1999; 458:424-8.
49 Rutault K, Alderman C, Chain BM, Katz DR. Reactive oxygen species activate human peripheral blood dendritic cells. Free Radic. Biol. Med. 1999; 26:232-8.
50 Termeer CC, Hennies J, Voith U, Ahrens T, Weiss JM, Prehm P et al. Oligosaccharides of hyaluronan are potent activators of dendritic cells. J Immunol. 2000; 165:1863-70.
51 Termeer C, Johannsen H, Braun T, Renkl A, Ahrens T, Denfeld RW et al. The role of CD44 during CD40 ligand-induced dendritic cell clustering and maturation. J. Leukoc. Biol. 2001; 70:715-22.
52 Basu S, Binder RJ, Ramalingam T, Srivastava PK. CD91 is a common receptor for heat shock proteins gp96, hsp90, hsp70, and calreticulin. Immunity. 2001; 14:303-13.
53 Ohashi K, Burkart V, Flohe S, Kolb H. Cutting edge: heat shock protein 60 is a putative endogenous ligand of the toll-like receptor-4 complex. J. Immunol. 2000; 164:558-61.
54 Quezada SA, Jarvinen LZ, Lind EF, Noelle RJ. CD40/CD154 interactions at the interface of tolerance and immunity. Annu. nol. 2005; 174:3273-80.
55 Tough DF. Type I interferon as a link between innate and adaptive immunity through dendritic cell stimulation. Leuk Lymphoma . 2004; 45:257-64.
56 Delneste Y, Herbault N, Galea B, Magistrelli G, Bazin I, Bonnefoy JY et al. Rev. Immunol. 2004; 22:307-28.
57 McIlroy D, Tanguy-Royer S, Le Meur N, Guisle I, Royer PJ, Leger J et al. Profiling dendritic cell maturation with dedicated microarrays. J. Leukoc. Biol. 2005; 78:794-803.

58 Iizasa H, Yoneyama H, Mukaida N, Katakoka Y, Naito M, Yoshida N et al. Exacerbation of granuloma formation in IL-1 receptor antagonist-deficient mice with impaired dendritic cell maturation associated with Th2 cytokine production. J. Immu-Vasoactive intestinal peptide synergizes with TNF-alpha in inducing human dendritic cell maturation. J. Immunol. 1999; 163:3071-5.
59 Guo Z, Zhang M, An H, Chen W, Liu S, Guo J et al. Fas ligation induces IL-1beta-dependent maturation and IL-1beta-independent survival of dendritic cells: different roles of ERK and NF-kappaB signaling pathways. Blood. 2003; 102:4441-7.
60 Guo Z, Zhang M, Tang H, Cao X. Fas signal links innate and adaptive immunity by promoting dendritic cell secretion of CC and CXC chemokines. Blood. 2005; 106:2033-41.
61 Marsland BJ, B¦¤ttig P, Bauer M, Ruedl C, L¦¤ssing U, Beerli RR et al. CCL19 and CCL21 induce a potent proinflammatory differentiation program in licensed dendritic cells. Immunity. 2005; 22:493-505.
62 Takeuchi O, Hoshino K, Kawai T, Sanjo H, Takada H, Ogawa T et al. Differential roles of TLR2 and TLR4 in recognition of gram-negative and gram-positive bacterial cell wall components. Immunity. 1999; 11:443-51.
63 Poltorak A, He X, Smirnova I, Liu MY, Van Huffel C, Du X et al. Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene. Science. 1998; 282:2085-8.
64 Hoshino K, Takeuchi O, Kawai T, Sanjo H, Ogawa T, Takeda Y et al. Cutting edge: Toll-like receptor 4 (TLR4)-deficient mice are hyporesponsive to lipopolysaccharide: evidence for TLR4 as the Lps gene product. J. Immunol. 1999; 162:3749-52.
65 Hemmi H, Takeuchi O, Kawai T, Kaisho T, Sato S, Sanjo H, et al. A Toll-like receptor recognizes bacterial DNA. Nature. 2000; 408:740-5.
66 Kariko K, Buckstein M, Ni H, Weissman D. Suppression of RNA Recognition by Toll-like Receptors: The Impact of Nucleoside Modification and the Evolutionary Origin of RNA. Immunity. 2005; 23:165-75.
67 Alexopoulou L, Holt AC, Medzhitov R, Flavell RA. Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. Nature. 2001; 413:732-8.
68 Guillot L, Le Goffic R, Bloch S, Escriou N, Akira S, Chignard M et al. Involvement of toll-like receptor 3 in the immune response of lung epithelial cells to double-stranded RNA and influenza A virus. J. Biol. Chem. 2005; 280:5571-80.
69 Diebold SS, Kaisho T, Hemmi H, Akira S, Reis e Sousa C. Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA. Science. 2004; 303:1529-31.
70 Heil F, Hemmi H, Hochrein H, Ampenberger F, Kirschning C, Akira S et al. Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. Science. 2004; 303:1526-9.
71 Hayashi F, Smith KD, Ozinsky A, Hawn TR, Yi EC, Goodlett DR et al. The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5. Nature. 2001; 410:1099-103.
72 Pietrella D, Corbucci C, Perito S, Bistoni G, Vecchiarelli A. Mannoproteins from Cryptococcus neoformans promote dendritic cell maturation and activation. Infect. Immun. 2005; 73:820-7.
73 Newman SL, Holly A. Candida albicans is phagocytosed, killed, and processed for antigen presentation by human dendritic cells. Infect. Immun. 2001; 69:6813-22.
74 Romagnoli G, Nisini R, Chiani P, Mariotti S, Teloni R, Cassone A et al.The interaction of human dendritic cells with yeast and germ-tube forms of Candida albicans leads to efficient fungal processing, dendritic cell maturation, and acquisition of a Th1 response-promoting function. J. Leukoc. Biol. 2004; 75:117-26.
75 Aliberti J, Valenzuela JG, Carruthers VB, Hieny S, Andersen J, Charest H et al. Molecular mimicry of a CCR5 binding-domain in the microbial activation of dendritic cells. Nat. Immunol. 2003; 4:485-90.
76 Yarovinsky F, Zhang D, Andersen JF, Bannenberg GL, Serhan CN, Hayden MS et al. TLR11 activation of dendritic cells by a protozoan profilin-like protein. Science.2005; 308:1626-29.
77 Zhang D, Zhang G, Hayden MS, Greenblatt MB, Bussey C, Flavell RA et al. A toll-like receptor that prevents infection by uropathogenic bacteria. Science. 2004; 303:1522-6.
78 Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature. 1998; 392:245-52.
79 Rescigno M, Granucci F, Ricciardi-Castagnoli P. Dendritic cells at the end of the millennium. Immunol. Cell Biol. 1999; 77:404-10.
80 Sallusto F, Mackay CR, Lanzavecchia A. The role of chemokine receptors in primary, effector, and memory immune responses. Annu. Rev. Immunol. 2000;18:593-620
81 Steinman RM, Nussenzweig MC. Avoiding horror autotoxicus: the importance of dendritic cells in peripheral T cell tolerance. Proc. Natl. Acad. Sci. U.S.A. 2002; 99:351-8.
82 Robert C, Fuhlbrigge RC, Kieffer JD, Ayehunie S, Hynes RO, Cheng G et al. Interaction of dendritic cells with skin endothelium: A new perspective on immunosurveillance. J. Exp. Med. 1999; 189:627-36.
83 Sozzani S, Allavena P, Vecchi A, Mantovani A. The role of chemokines in the regulation of dendritic cell trafficking. J Leukoc Biol. 1999; 66:1-9.
84 Sallusto F, Schaerli P, Loetscher P, Schaniel C, Lenig D, Mackay CR et al. Rapid and coordinated switch in chemokine receptor expression during dendritic cell maturation. Eur J Immunol. 1998; 28:2760-9.
85 Steinman RM.The dendritic cell system and its role in immunogenicity. Annu Rev Immunol. 1991; 9:271-96.
86 Von Andrian UH, Mackay CR. T-cell function and migration. Two sides of the same coin. N Engl J Med. 2000; 343:1020-34.
87 Kunkel SL. Through the looking glass: the diverse in vivo activities of chemokines. Clin Invest. 1999; 104:1333-4.
88 Baggiolini M. Chemokines and leukocyte traffic. Nature. 1998; 392:565-8.
89 Cyster JG. Chemokines and cell migration in secondary lymphoid organs. Science. 1999; 286:2098-102.
90 Sallusto F, Lanzavecchia A. Mobilizing dendritic cells for tolerance, priming, and chronic inflammation. J Exp Med. 1999; 189:611-4.
91 Carlos TM, Harlan JM. Leukocyte-endothelial adhesion molecules. Blood. 1994; 84:2068-101.
92 Kansas GS. Selectins and their ligands: current concepts and controversies. Blood. 1996; 88:3259-87.
93 Pendl GG, Robert C, Steinert M, Thanos R, Eytner R, Borges E et al. Immature mouse dendritic cells enter inflamed tissue, a process that requires E- and P-selectin, but not P-selectin glycoprotein ligand 1. Blood.2002; 99:946-56.
94 Penna G, Vulcano M, Sozzani S, Adorini L. Differential migration behavior and chemokine production by myeloid and plasmacytoid dendritic cells. Hum Immunol. 2002; 63:1164-71.
95 Saeki H, Moore AM, Brown MJ, Hwang ST. Cutting edge: secondary lymphoid-tissue chemokine (SLC) and CC chemokine receptor 7 (CCR7) participate in the emigration pathway of mature dendritic cells from the skin to regional lymph nodes. J Immunol. 1999; 162:2472-5.

96 Qu C, Edwards EW, Tacke F, Angeli V, Llodra J, Sanchez-Schmitz G et al. Role of CCR8 and other chemokine pathways in the migration of monocyte-derived dendritic cells to lymph nodes. J Exp Med. 2004; 200:1231-41.
97 Delgado E, Finkel V, Baggiolini M, Mackay CR, Steinman RM, Granelli-Piperno A.Mature dendritic cells respond to SDF-1, but not to several beta-chemokines. *Immunobiology* .1998; 198: 490–500.
98 Godiska R, Chantry D, Raport CJ, Sozzani S, Allavena P, Leviten D et al. Human macrophage-derived chemokine (MDC), a novel chemoattractant for monocytes, monocyte-derived dendritic cells, and natural killer cells. J Exp Med. 1997; 185:1595-604.
99 Kucharzik T, Hudson JT 3rd, Waikel RL, Martin WD, Williams IR. CCR6 expression distinguishes mouse myeloid and lymphoid dendritic cell subsets: demonstration using a CCR6 EGFP knock-in mouse. Eur J Immunol. 2002; 32:104-12.
100 Sozzani S, Luini W, Borsatti A, Polentarutti N, Zhou D, Piemonti L et al.Receptor expression and responsiveness of human dendritic cells to a defined set of CC and CXC chemokines. J Immunol.1997; 159: 1993-2000.
101 Sozzani S. Dendritic cell trafficking: More than just chemokines. Cytokine Growth Factor Rev. 2005; 16:581-92.
102 Vermi W, Riboldi E, Wittamer V, Gentili F, Luini W, Marrelli S et al. Role of ChemR23 in directing the migration of myeloid and plasmacytoid dendritic cells to lymphoid organs and inflamed skin. J Exp Med. 2005; 201:509-15.
103 Yang D, Chen Q, Gertz B, He R, Phulsuksombati M, Ye RD et al.Human dendritic cells express functional formyl peptide receptor-like-2 (FPRL2) throughout maturation. J Leukoc Biol. 2002; 72:598-607.
104 Le Y, Wetzel MA, Shen W, Gong W, Rogers TJ, Henderson EE et al. Desensitization of chemokine receptor CCR5 in dendritic cells at the early stage of differentiation by activation of formyl peptide receptors. Clin Immunol. 2001; 99:365-72.
105 Migeotte I, Riboldi E, Franssen JD, Gregoire F, Loison C, Wittamer V et al. Identification and characterization of an endogenous chemotactic ligand specific for FPRL2. J Exp Med. 2005; 201:83-93.
106 Morelli A, Larregina A, Chuluyan I, Kolkowski E, Fainboim L. Expression and modulation of C5a receptor (CD88) on skin dendritic cells. Chemotactic effect of C5a on skin migratory dendritic cells. Immunology. 1996; 89:126-34.
107 Sozzani S, Longoni D, Bonecchi R, Luini W, Bersani L, D'Amico G et al. Human monocyte-derived and CD34+ cell-derived dendritic cells express functional receptors for platelet activating factor. FEBS Lett. 1997; 418:98-100.
108 Howard OM, Dong HF, Su SB, Caspi RR, Chen X, Plotz P et al. Autoantigens signal through chemokine receptors: uveitis antigens induce CXCR3- and CXCR5-expressing lymphocytes and immature dendritic cells to migrate. Blood. 2005; 105:4207-14.
109 Penna G, Vulcano M, Roncari A, Facchetti F, Sozzani S, Adorini L. Cutting edge: differential chemokine production by myeloid and plasmacytoid dendritic cells. J Immunol. 2002; 169:6673-6.
110 Allavena P, Sica A, Vecchi A, Locati M, Sozzani S, Mantovani A. The chemokine receptor switch paradigm and dendritic cell migration: its significance in tumor tissues. Immunol Rev. 2000; 177:141-9.
111 Vulcano M, Albanesi C, Stoppacciaro A, Bagnati R, Amico GD, Struyf S et al. Dendritic cells as a major source of macrophage-derived chemokine/CCL22 in vitro and in vivo. Eur J Immunol.2001; 31:812-22.
112 Papadopoulos EJ, Sassetti C, Saeki H, Yamada N, Kawamura T, Fitzhugh DJ et al. Fractalkine, a CX3C chemokine, is expressed by dendritic cells and is up-regulated upon dendritic cell maturation. Eur J Immunol. 1999; 29:2551-9.
113 Tang HL, Cyster JG. Chemokine Up-regulation and activated T cell attraction by maturing dendritic cells. Science. 1999; 284:819-22.
114 Perrier P, Martinez FO, Locati M, Bianchi G, Nebuloni M, Vago G et al.Distinct transcriptional programs activated by interleukin-10 with or without lipopolysaccharide in dendritic cells: induction of the B cell-activating chemokine, CXC chemokine ligand 13. J Immunol. 2004; 172:7031-42.
115 Kanazawa N, Nakamura T, Tashiro K, Muramatsu M, Morita K, Yoneda K et al.Fractalkine and macrophage-derived chemokine: T cell-attracting chemokines expressed in T cell area dendritic cells. Eur J Immunol. 1999; 29:1925-32.
116 Foussat A, Bouchet-Delbos L, Berrebi D, Durand-Gasselin I, Coulomb-L'Hermine A, Krzysiek R et al. Deregulation of the expression of the fractalkine/fractalkine receptor complex in HIV-1-infected patients. Blood. 2001; 98:1678-86.
117 Dieu MC, Vanbervliet B, Vicari A, Bridon JM, Oldham E, Ait-Yahia S 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.
118 Forster R, Schubel A, Breitfeld D, Kremmer E, Renner-Muller I, Wolf E et al. CCR7 coordinates the primary immune response by establishing functional microenvironments in secondary lymphoid organs. Cell. 1999; 99:23-33.
119 Gunn MD, Kyuwa S, Tam C, Kakiuchi T, Matsuzawa A, Williams LT et al. Mice lacking expression of secondary lymphoid organ chemokine have defects in lymphocyte homing and dendritic cell localization. J Exp Med. 1999; 189:451-60.
120 Luther SA, Tang HL, Hyman PL, Farr AG, Cyster JG. Coexpression of the chemokines ELC and SLC by T zone stromal cells and deletion of the ELC gene in the plt/plt mouse. Proc Natl Acad Sci U S A. 2000; 97:12694-99.
121 Mayordomo JI, Zorina T, Storkus WJ, Zitvogel L, Celluzzi C, Falo LD et al. Bone marrow-derived dendritic cells pulsed with synthetic tumour peptides elicit protective and therapeutic antitumour immunity. Nat Med. 1995; 1:1297-302.
122 Ingulli E, Mondino A, Khoruts A, Jenkins MK. In vivo detection of dendritic cell antigen presentation to CD4 (+) T cells. J Exp Med. 1997; 185:2133-41.
123 Shortman K, Wu L.Parentage and heritage of dendritic cells. Blood. 2001; 97:3325.
124 Ruedl C, Bachmann MF.CTL priming by CD8 (+) and CD8 (-) dendritic cells in vivo. Eur J Immunol. 1999; 29:3762-7.
125 Maldonado-Lopez R , De Smedt T, Michel P, Godfroid J, Pajak B, Heirman C et al. CD8alpha+ and CD8alpha- subclasses of dendritic cells direct the development of distinct T helper cells in vivo. J Exp Med. 1999; 189:587-92.
126 Maldonado-Lopez, R., Maliszewski C, Urbain J, Moser M.Cytokines regulate the capacity of CD8alpha (+) and CD8alpha (-) dendritic cells to prime Th1/Th2 cells in vivo. J Immunol. 2001; 167:4345-50.
127 Inaba K., Pack M, Inaba M, Sakuta H, Isdell F, Steinman RM. High levels of a major histocompatibility complex II-self peptide complex on dendritic cells from the T cell areas of lymph nodes. J Exp Med. 1997; 186:665-72.
128 Hart DN. Dendritic cells: unique leukocyte populations which control the primary immune response. Blood. 1997; 90:3245-87.
129 Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol. 2005; 23:515-48.
130 Ridge JP, Di Rosa F, Matzinger P. A conditioned dendritic cell can be a temporal bridge between a CD4+ T-helper and a T-killer cell. Nature. 1998; 393:474-8.
131 Bennett SR, Carbone FR, Karamalis F, Flavell RA, Miller JF, Heath WR. Help for cytotoxic-T-cell responses is mediated by CD40 signalling. Nature. 1998; 393:478-80.
132 Schoenberger SP, Toes RE, van der Voort EI, Offringa R, Melief CJ. T-cell help for cytotoxic T lymphocytes is mediated by CD40-CD40L interactions. Nature. 1998; 393:480-3.
133 Caux C, Massacrier C, Vanbervliet B, Dubois B, Van Kooten C, Durand I et al. Activation of human dendritic cells through CD40 cross-linking. J Exp Med. 1994; 180:1263-72.

134 Yamazaki S, Iyoda T, Tarbell K, Olson K, Velinzon K, Inaba K et al. Direct expansion of functional CD25+ CD4+ regulatory T cells by antigen-processing dendritic cells. J Exp Med. 2003; 198:235-47.
135 Lutz MB, Schuler G.Immature, semi-mature and fully mature dendritic cells: which signals induce tolerance or immunity? Trends Immunol. 2002; 23:445-9.
136 Smits HH, de Jong EC, Wierenga EA, Kapsenberg ML. Different faces of regulatory DCs in homeostasis and immunity. Trends Immunol. 2005; 26:123-9.
137 Akbari O, DeKruyff RH, Umetsu DT. Pulmonary dendritic cells producing IL-10 mediate tolerance induced by respiratory exposure to antigen. Nat Immunol. 2001; 2:725-31.
138 Rutella S, Lemoli RM. Regulatory T cells and tolerogenic dendritic cells: from basic biology to clinical applications. Immunol Lett. 2004 ;94:11-26.
139 Wick M, Dubey P, Koeppen H, Siegel CT, Fields PE, Chen L et al. Antigenic cancer cells grow progressively in immune hosts without evidence for T cell exhaustion or systemic anergy. J Exp Med. 1997; 186:229-38.
140 Ochsenbein AF, Klenerman P, Karrer U, Ludewig B, Pericin M, Hengartner H et al.Immune surveillance against a solid tumor fails because of immunological ignorance. Proc Natl Acad Sci U S A. 1999; 96:2233-8.
141 Enk AH, Jonuleit H, Saloga J, Knop J.Dendritic cells as mediators of tumor-induced tolerance in metastatic melanoma. Int J Cancer. 1997; 73:309-16.
142 Lee PP, Yee C, Savage PA, Fong L, Brockstedt D, Weber JS et al. Characterization of circulating T cells specific for tumor-associated antigens in melanoma patients. Nat Med. 1999; 5:677-85.
143 Garcia-Lora A, Algarra I, Garrido F. MHC class I antigens, immune surveillance, and tumor immune escape. J Cell Physiol. 2003; 195:346-55.
144 Qin Z, Blankenstein T. CD4+ T cell--mediated tumor rejection involves inhibition of angiogenesis that is dependent on IFN gamma receptor expression by nonhematopoietic cells. Immunity. 2000; 12:677-86.
145 Dembic Z, Schenck K, Bogen B. Dendritic cells purified from myeloma are primed with tumor-specific antigen (idiotype) and activate CD4+ T cells. Proc Natl Acad Sci U S A. 2000; 97:2697-702.
146 Hung K, Hayashi R, Lafond-Walker A, Lowenstein C, Pardoll D, Levitsky H. The central role of CD4(+) T cells in the anti-tumor immune response. J Exp Med. 1998; 188:2357-68.
147 Terheyden P, Straten P, Brocker EB, Kampgen E, Becker JC. CD40-ligated dendritic cells effectively expand melanoma-specific CD8+ CTLs and CD4+ IFN-gamma-producing T cells from tumor-infiltrating lymphocytes. J Immunol. 2000; 164:6633-9.
148 Celluzzi CM, Mayordomo JI, Storkus WJ, Lotze MT, Falo LD Jr. Peptide-pulsed dendritic cells induce antigen-specific CTL-mediated protective tumor immunity. J Exp Med. 1996; 183:283-7.
149 Jenne L, Arrighi JF, Jonuleit H, Saurat JH, Hauser C. Dendritic cells containing apoptotic melanoma cells prime human CD8+ T cells for efficient tumor cell lysis. Cancer Res. 2000; 60:4446-52.
150 Fernandez NC, Lozier A, Flament C, Ricciardi-Castagnoli P, Bellet D, Suter M et al. Dendritic cells directly trigger NK cell functions: cross-talk relevant in innate anti-tumor immune responses in vivo. Nat Med. 1999; 5:405-11.
151 Fanger NA, Maliszewski CR, Schooley K, Griffith TS. Human dendritic cells mediate cellular apoptosis via tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). J Exp Med. 1999; 190:1155-64.
152 Chapoval AI, Tamada K, Chen L. In vitro growth inhibition of a broad spectrum of tumor cell lines by activated human dendritic cells. Blood. 2000; 95:2346-51.
153 Janjic BM, Lu G, Pimenov A, Whiteside TL, Storkus WJ, Vujanovic NL. Innate direct anticancer effector function of human immature dendritic cells. I. Involvement of an apoptosis-inducing pathway. J Immunol. 2002; 168:1823-30.
154 Lu G, Janjic BM, Janjic J, Whiteside TL, Storkus WJ, Vujanovic NL. Innate direct anticancer effector function of human immature dendritic cells. II. Role of TNF, lymphotoxin-alpha(1)beta(2), Fas ligand, and TNF-related apoptosis-inducing ligand. J Immunol. 2002; 168:1831-9.
155 Stary G, Bangert C, Tauber M, Strohal R, Kopp T, Stingl G.Tumoricidal activity of TLR7/8-activated inflammatory dendritic cells. J Exp Med. 2007; 204:1441-51.
156 Jalili A, Stoklosa T, Giermasz A, Olszewska D, Wilczynski G, Jakobisiak M et al.A single injection of immature dendritic cells is able to induce antitumour response against a murine colon adenocarcinoma with a low apoptotic index. Oncol Rep. 2002; 9:991-4.
157 Banchereau J, Palucka AK. Dendritic cells as therapeutic vaccines against cancer. Nat Rev Immunol.2005; 5:296-306.
158 Gunzer M, Grabbe S. Dendritic cells in cancer immunotherapy. Crit Rev Immunol. 2001; 21:133-45.
159 Lynch DH, Andreasen A, Maraskovsky E, Whitmore J, Miller RE, Schuh JC. Flt3 ligand induces tumor regression and anti-tumor immune responses in vivo. Nat Med. 1997; 3:625-31.
160 Borges L, Miller RE, Jones J, Ariail K, Whitmore J, Fanslow W et al. Synergistic action of fms-like tyrosine kinase 3 ligand and CD40 ligand in the induction of dendritic cells and generation of antitumor immunity in vivo. J Immunol. 1999; 163:1289-97.
161 Pulendran B, Banchereau J, Burkeholder S, Kraus E, Guinet E, Chalouni C et al. Flt3-ligand and granulocyte colony-stimulating factor mobilize distinct human dendritic cell subsets in vivo. J Immunol. 2000; 165:566-72.
162 Daro E, Pulendran B, Brasel K, Teepe M, Pettit D, Lynch DH et al. Polyethylene glycol-modified GM-CSF expands CD11b(high)CD11c(high) butnotCD11b(low)CD11c(high) murine dendritic cells in vivo: a comparative analysis with Flt3 ligand. J Immunol. 2000; 165:566-72.
163 Mackey MF, Gunn JR, Maliszewsky C, Kikutani H, Noelle RJ, Barth RJ Jr. Dendritic cells require maturation via CD40 to generate protective antitumor immunity. J Immunol. 1998; 161:2094-8.
164 Pulendran B, Smith JL, Jenkins M, Schoenborn M, Maraskovsky E, Maliszewski and CR. Prevention of peripheral tolerance by a dendritic cell growth factor: flt3 ligand as an adjuvant. J Exp Med. 1998; 188:2075-82.
165 Banchereau J, Schuler-Thurner B, Palucka AK, Schuler G. Dendritic cells as vectors for therapy. Cell. 2001; 106:271-4.
166 Schuler G, Steinman RM. Dendritic cells as adjuvants for immune-mediated resistance to tumors. J Exp Med. 1997; 186:1183-7.
167 Paglia P, Medina E, Arioli I, Guzman CA, Colombo MP. Gene transfer in dendritic cells, induced by oral DNA vaccination with Salmonella typhimurium, results in protective immunity against a murine fibrosarcoma. Blood. 1998; 92:3172-6.
168 Pan ZK, Ikonomidis G, Lazenby A, Pardoll D, Paterson Y.A recombinant Listeria monocytogenes vaccine expressing a model tumour antigen protects mice against lethal tumour cell challenge and causes regression of established tumours. Nat Med. 1995; 1:471-7.
169 Baskar S, Glimcher L, Nabavi N, Jones RT, Ostrand-Rosenberg S. Major histocompatibility complex class II+B7-1+ tumor cells are potent vaccines for stimulating tumor rejection in tumor-bearing mice. J Exp Med. 1995; 181:619-29.

170 Baskar S. Gene-modified tumor cells as cellular vaccine. Cancer Immunol Immunother. 1996; 43:165-73.
171 Lasek W, Mackiewicz A, Czajka A, Switaj T, Gol b J, Wiznerowicz M et al. Antitumor effects of the combination therapy with TNF-alpha gene-modified tumor cells and interleukin 12 in a melanoma model in mice. Cancer Gene Ther. 2000; 7:1581-90.
172 Chiodoni C, Paglia P, Stoppacciaro A, Rodolfo M, Parenza M, Colombo MP. Dendritic cells infiltrating tumors cotransduced with granulocyte/macrophage colony-stimulating factor (GM-CSF) and CD40 ligand genes take up and present endogenous tumor-associated antigens, and prime naive mice for a cytotoxic T lymphocyte response. J Exp Med. 1999; 190:125-33.
173 Huang AY, Golumbek P, Ahmadzadeh M, Jaffee E, Pardoll D, Levitsky H. Role of bone marrow-derived cells in presenting MHC class I-restricted tumor antigens. Science. 1994; 264:961-5.
174 Klein C, Bueler H, Mulligan RC. Comparative analysis of genetically modified dendritic cells and tumor cells as therapeutic cancer vaccines. J Exp Med. 2000; 191:1699-708.
175 Mach N, Dranoff G. Cytokine-secreting tumor cell vaccines. Curr Opin Immunol. 2000;12:571-5.
176 Moller P, Sun Y, Dorbic T, Alijagic S, Makki A, Jurgovsky K et al. Vaccination with IL-7 gene-modified autologous melanoma cells can enhance the anti-melanoma lytic activity in peripheral blood of patients with a good clinical performance status: a clinical phase I study. Br J Cancer. 1998; 77:1907-16.
177 Dhodapkar MV, Steinman RM, Krasovsky J, Munz C, Bhardwaj N. Antigen-specific inhibition of effector T cell function in humans after injection of immature dendritic cells. J Exp Med. 2001; 193:233-8.
178 Steinbrink K, Jonuleit H, Muller G, Schuler G, Knop J, Enk AH. Interleukin-10-treated human dendritic cells induce a melanoma-antigen-specific anergy in CD8 (+) T cells resulting in a failure to lyse tumor cells. Blood. 1999; 93:1634-42.
179 Gilboa E. DC-based cancer vaccines. J Clin Invest. 2007; 117:1195-203.
180 Moser M, Murphy KM. Dendritic cell regulation of TH1-TH2 development. Nat Immunol. 2000; 1:199-205.
181 Rissoan MC, Soumelis V, Kadowaki N, Grouard G, Briere F, de Waal Malefyt R et al. Reciprocal control of T helper cell and dendritic cell differentiation. Science. 1999; 283:1183-6.
182 Langenkamp A, Messi M, Lanzavecchia A, Sallusto F. Kinetics of dendritic cell activation: impact on priming of TH1, TH2 and nonpolarized T cells. Nat Immunol. 2000; 1:311-6.
183 Mukherji B, Chakraborty NG, Yamasaki S, Okino T, Yamase H, Sporn JR et al. Induction of antigen-specific cytolytic T cells in situ in human melanoma by immunization with synthetic peptide-pulsed autologous antigen presenting cells. Proc Natl Acad Sci U S A. 1995; 92:8078-82.
184 Thurner B, Haendle I, Roder C, Dieckmann D, Keikavoussi P, Jonuleit H et al. Vaccination with mage-3A1 peptide-pulsed mature, monocyte-derived dendritic cells expands specific cytotoxic T cells and induces regression of some metastases in advanced stage IV melanoma. J Exp Med. 1999; 190:1669-78.
185 Schuler-Thurner B, Dieckmann D, Keikavoussi P, Bender A, Maczek C, Jonuleit H et al. Mage-3 and influenza-matrix peptide-specific cytotoxic T cells are inducible in terminal stage HLA-A2.1+ melanoma patients by mature monocyte-derived dendritic cells. J Immunol. 2000; 165:3492-6.
186 Nestle FO, Alijagic S, Gilliet M, Sun Y, Grabbe S, Dummer R et al. Vaccination of melanoma patients with peptide- or tumor lysate-pulsed dendritic cells. Nat Med.1998; 4:328-332.
187 Hsu FJ, Benike C, Fagnoni F, Liles TM, Czerwinski D, Taidi B et al. Vaccination of patients with B-cell lymphoma using autologous antigen-pulsed dendritic cells. Nat Med. 1996; 2:52-8.
188 Boczkowski D, Nair SK, Nam JH, Lyerly HK, Gilboa E. Induction of tumor immunity and cytotoxic T lymphocyte responses using dendritic cells transfected with messenger RNA amplified from tumor cells. Cancer Res. 2000; 60:1028-34.
189 Nair SK, Hull S, Coleman D, Gilboa E, Lyerly HK, Morse MA.Induction of carcinoembryonic antigen (CEA)-specific cytotoxic T-lymphocyte responses in vitro using autologous dendritic cells loaded with CEA peptide or CEA RNA in patients with metastatic malignancies expressing CEA. Int J Cancer. 1999; 82:121-4.
190 Grunebach F, Muller MR, Brossart P. New developments in dendritic cell-based vaccinations: RNA translated into clinics. Cancer Immunol Immunother. 2005; 54:517-25.
191 Song W, Kong HL, Carpenter H, Torii H, Granstein R, Rafii S et al.Dendritic cells genetically modified with an adenovirus vector encoding the cDNA for a model antigen induce protective and therapeutic antitumor immunity. J Exp Med. 1997; 186:1247-56.
192 Specht JM, Wang G, Do MT, Lam JS, Royal RE, Reeves ME et al. Dendritic cells retrovirally transduced with a model antigen gene are therapeutically effective against established pulmonary metastases. J Exp Med.1997; 186:1213-21.
193 Tuting T, Wilson CC, Martin DM, Kasamon YL, Rowles J, Ma DI et al. Autologous human monocyte-derived dendritic cells genetically modified to express melanoma antigens elicit primary cytotoxic T cell responses in vitro: enhancement by cotransfection of genes encoding the Th1-biasing cytokines IL-12 and IFN-alpha. J Immunol.1998; 160:1139-47.
194 Bot A, Stan AC, Inaba K, Steinman R, Bona C.Dendritic cells at a DNA vaccination site express the encoded influenza nucleoprotein and prime MHC class I-restricted cytolytic lymphocytes upon adoptive transfer. Int Immunol. 2000; 12:825-32.
195 Albert ML, Sauter B, Bhardwaj N. Dendritic cells acquire antigen from apoptotic cells and induce class I-restricted CTLs. Nature. 1998; 392:86-9.
196 Paczesny S, Beranger S, Salzmann JL, Klatzmann D, Colombo BM. Protection of mice against leukemia after vaccination with bone marrow-derived dendritic cells loaded with apoptotic leukemia cells. Cancer Res. 2001; 61:2386-9.
197 Jalili A, Makowski M, Switaj T, Nowis D, Wilczynski GM, Wilczek E et al. Effective photoimmunotherapy of murine colon carcinoma induced by the combination of photodynamic therapy and dendritic cells. Clin Cancer Res. 2004; 10:4498-508.
198 Saji H, Song W, Furumoto K, Kato H, Engleman EG. Systemic antitumor effect of intratumoral injection of dendritic cells in combination with local photodynamic therapy. Clin Cancer Res. 2006; 12:2568-74.
199 Schadendorf D, Ugurel S, Schuler-Thurner B, Nestle FO, Enk A, Brocker EB et al. Dacarbazine (DTIC) versus vaccination with autologous peptide-pulsed dendritic cells (DC) in first-line treatment of patients with metastatic melanoma: a randomized phase III trial of the DC study group of the DeCOG. Ann Oncol.2006; 17:563-70.
200 Klammer M, Waterfall M, Samuel K, Turner ML, Roddie PH. Fusion hybrids of dendritic cells and autologous myeloid blasts as a potential cellular vaccine for acute myeloid leukaemia. Br J Haematol.2005; 129:340-9.
201 Kohler T, Plettig R, Wetzstein W, Schmitz M, Ritter M, Mohr B et al. Cytokine-driven differentiation of blasts from patients with acute myelogenous and lymphoblastic leukemia into dendritic cells. Stem Cells. 2000; 18:139-47.
202 Choudhury BA, Liang JC, Thomas EK, Flores-Romo L, Xie QS, Agusala K et al. Dendritic cells derived in vitro from acute myelogenous leukemia cells stimulate autologous, antileukemic T-cell responses. Blood. 1999; 93:780-6.
203 Cignetti A, Bryant E, Allione B, Vitale A, Foa R, Cheever MA. CD34 (+) acute myeloid and lymphoid leukemic blasts can be induced to differentiate into dendritic cells. Blood. 1999; 94:2048-55.

204 Robinson SP, English N, Jaju R, Kearney L, Knight SC, Reid CD. The in-vitro generation of dendritic cells from blast cells in acute leukaemia. Br J Haematol. 1998; 103:763-71.
205 Engels FH, Koski GK, Bedrosian I, Xu S, Luger S, Nowell PC et al. Calcium signaling induces acquisition of dendritic cell characteristics in chronic myelogenous leukemia myeloid progenitor cells. Proc Natl Acad Sci U S A. 1999; 96:10332-7.
206 Choudhury A, Gajewski JL, Liang JC, Popat U, Claxton DF, Kliche KO et al. Use of leukemic dendritic cells for the generation of antileukemic cellular cytotoxicity against Philadelphia chromosome-positive chronic myelogenous leukemia. Blood. 1997 ;89:1133-42.
207 Okada N, Tsujino M, Hagiwara Y, Tada A, Tamura Y, Mori K et al. Administration route-dependent vaccine efficiency of murine dendritic cells pulsed with antigens. Br J Cancer. 2001; 84:1564-70.
208 Fong L, Brockstedt D, Benike C, Wu L, Engleman EG. Dendritic cells injected via different routes induce immunity in cancer patients. J Immunol. 2001; 166:4254-9.
209 Lambert LA, Gibson GR, Maloney M, Durell B, Noelle RJ, Barth RJ Jr. Intranodal immunization with tumor lysate-pulsed dendritic cells enhances protective antitumor immunity. Cancer Res. 2001; 61:641-6.
210 Zoller M, Christ O. Prophylactic tumor vaccination: comparison of effector mechanisms initiated by protein versus DNA vaccination. J Immunol. 2001; 166:3440-50.
211 Fong L, Engleman EG. Dendritic cells in cancer immunotherapy. Annu Rev Immunol. 2000; 18:245-73.
212 Wang TL, Ling M, Shih IM, Pham T, Pai SI, Lu Z et al. Intramuscular administration of E7-transfected dendritic cells generates the most potent E7-specific anti-tumor immunity. Gene Ther. 2000; 7:726-33.
213 Serody JS, Collins EJ, Tisch RM, Kuhns JJ, Frelinger JA. T cell activity after dendritic cell vaccination is dependent on both the type of antigen and the mode of delivery. J Immunol. 2000; 164:4961-7.