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Review Article

The Role of Dendritic Cells in Lung Defense and the Development of Dendritic Cell-Based Therapies

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Abstract

Lung as the most important organ for gas exchange in our body has a very large surface area. This continually exposes our lung to potential dangers. Therefore, it requires good defense mechanisms. Dendritic cells are the component of our body's defense system that is important in bridging the innate and adaptive immune systems. Dendritic cells function primarily to present antigen to T cells otherwise known as antigen-presenting cells. Dendritic cells are also known to secrete mediator molecules that are important in the body's immune response. It is now known that there are several types of dendritic cells and their subsets, including plasmacytoid, classical, and monocyte-derived dendritic cells. Dendritic cells can also be identified by their location in the body. Understanding the role and function of dendritic cells is paramount, especially in developing medical technology and dendritic cell-based therapies. This literature review will discuss dendritic cells, their function, classification, and recent developments in dendritic cell-based therapy.

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Introduction

Lungs are the most important organ in the respiratory system, serving as the site of gas exchange. To perform their function, the lungs have a very large surface area to maximize gas exchange. It is estimated that the surface area of the lungs reaches 70m^2, or the size of a badminton court, under normal conditions and can reach 100m^2 during maximum inspiration.[1] This causes the lungs to be constantly exposed to the outside world, necessitating a robust defense mechanism. These mechanisms are played by the innate and adaptive immune systems.

Air inhaled through the nose or mouth provides the oxygen needed by the body for aerobic respiration to produce energy. However, inhaled air also carries many particles, toxic gases, and microorganisms that pose potential dangers to the body. For gas exchange to occur smoothly, foreign substances and harmful substances must be eliminated without causing excessive inflammation.[2]

The first line of defense for the lungs consists of a mechanical barrier and the innate immune system.[2] The mechanical barrier in question is the mucociliary layer and its clearance mechanisms. The innate immune system is primarily played by airway epithelial cells, alveolar macrophages, and neutrophils. The body also has an adaptive immune system, powered by T and B lymphocytes. The adaptive immune system responds more specifically to foreign substances and microorganisms, but its activation must first be initiated by components of the innate immune system.

Dendritic cells are a crucial component of the body's defense system, triggering the adaptive immune response. First discovered by Ralph Steinman in 1973, dendritic cells resemble tree branches, hence the name dendritic cells.[3] Dendritic cells function primarily as antigen-presenting cells to T cells.[4] It is now known that there are several types of dendritic cells and their subsets, such as plasmacytoid dendritic cells, which primarily secrete interferon.[1,5]

Understanding the role and function of dendritic cells is crucial, especially in the development of health technologies and dendritic cell-based therapies. Currently, therapies using dendritic cells as the basis of their work have been developed, such as dendritic cell therapy for cancer.[6] Dendritic cells also

have the potential to be biomarkers for cancer prognosis.[7] This literature review will discuss dendritic cells in general, types of dendritic cell subsets, the function of dendritic cells, the role of dendritic cells as antigen presenting cells, and the development of dendritic cell-based therapies in the future.

Dendritic Cell Development and Migration

Dendritic cells were first discovered by Paul Langerhans in skin tissue in 1868, but were still considered nerve cells in skin tissue. The function of dendritic cells as APCs was first studied by Ralph Steinman in 1973. Dendritic cells are so named because of their tree-like shape (dendron = tree in Greek).[3]

Most dendritic cells originate from common myeloid progenitor (CMP) cells, but they can also be derived from common lymphoid progenitor (CLP) cells.[4] This is a unique feature of the dendritic cell lineage compared to other leukocyte cells, such as neutrophils, which can only be derived from CMP. CMP cells differentiate into monocyte-DC progenitor (MDP) cells, which are the progenitor cells of monocytes and dendritic cells. CMP cells can then differentiate into common DC progenitor (CDP) cells, which can give rise to classical dendritic cells (cDC) and plasmacytoid cells (pDC). Monocyte cells can also differentiate into dendritic cells called monocyte-derived dendritic cells (moDC) in inflammatory conditions with the help of granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin 4 (IL-4).[8,9] The differentiation pathway of dendritic cells can be seen in Figure 1.

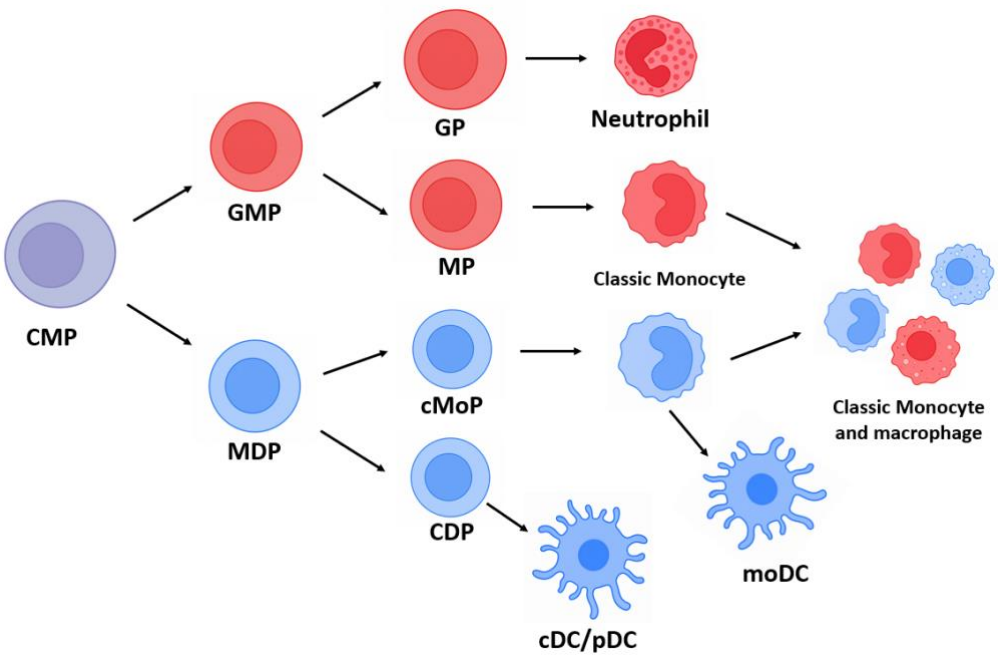

Figure 1. Pathway of differentiation of common myeloid progenitor cells into dendritic cells. CMP: common myeloid progenitor, GMP: granulocyte-monocyte progenitor, MDP: monocyte-DC progenitor, GP: granulocyte progenitor, MP: monocyte progenitor, cMoP: monocyte-committed progenitor, CDP: common DC progenitor; Adapted from Wolf et al.[8], under the Creative Commons Attribution 4.0 International License (CC BY 4.0)

Dendritic cells have phagocytic capabilities and are widely distributed in lymphoid, epithelial, mucosal, and parenchymal tissues.[10] This widespread distribution is achieved through the migration of cells called preDC cells from the spinal cord through the blood. CDP cells can differentiate into preDC cells that migrate to lymphoid organs and peripheral tissues through the blood. PreDC cells then differentiate into dendritic cells. Maturation of dendritic cells depends on a cytokine called Flt3 ligand. Flt3 ligand binds to tyrosine kinase receptors on precursor cells.

Dendritic Cell Subset

There are two major types of dendritic cells based on their phenotype and function: classical dendritic cells (cDC) and plasmacytoid dendritic cells (pDC).[10] Classical dendritic cells primarily capture microbes that enter through the epithelium and present them to T cells. Plasmacytoid dendritic cells primarily produce the cytokine interferon (IFN) type 1 in response to viruses. pDC also phagocytose blood-borne antigens and transport them to the spleen for presentation to T cells.

Classical dendritic cells were first identified based on their dendritic morphology and ability to stimulate a strong T cell response. The cDC are the most abundant type of dendritic cell in epithelial and lymphoid organs. Most cDC originate from myeloid precursors that migrate from the spinal cord and differentiate locally into resident dendritic cells in lymphoid and non-lymphoid organs. cDC function to monitor and detect pathogens in surrounding tissues. In the digestive tract, cDC cells have a cell segment that extends through the epithelial cells of the digestive tract into the lumen to detect antigens. This function is similar to that of Langerhans cells.[10]

Table 1. Summary of Dendritic Cell Subsets, Surface Markers, Cytokines, and Major Functionss

Dendritic cell subset	Major surface markers / transcription factors	Major cytokines	Primary functions	Predominant location
Plasmacytoid dendritic cell (pDC)	No specific markers discussed in the manuscript	Type I interferons (IFN-α/β)	Rapid antiviral response; produces large amounts of type I interferons; captures blood-borne antigens and transports them to the spleen for antigen presentation	Blood and secondary lymphoid organs
Classical dendritic cell type 1 (cDC1)	BDCA-3 (CD141), IRF8, TLR3	IL-12 (high production)	Cross-presentation of antigens to $CD8^+$ T cells; induces cytotoxic T lymphocyte (CTL) responses; pathogen surveillance	Predominantly lymph nodes (T-cell zone/medulla)
Classical dendritic cell type 2 (cDC2)	BDCA-1 (CD1c)	Lower IL-12 production than cDC1	Presentation of antigens to $CD4^+$ T cells; activation of helper T-cell responses	Predominantly peripheral tissues; interfollicular zone (IFZ) of lymph nodes
Monocyte-derived dendritic cell (moDC)	Derived from monocytes under the influence of GM-CSF and IL-4	Not specifically discussed	Differentiate during inflammation; potent antigen-presenting cells; widely used for dendritic cell vaccine development because they are readily generated ex vivo	Inflammatory tissues
Migratory dendritic cells*	CD11c^int MHC II^hi	Depends on subset	Capture antigens in peripheral tissues and migrate to lymph nodes to activate naïve T cells	Peripheral tissues
Resident dendritic cells*	CD11c^hi MHC II^int	Depends on subset	Sentinel cells that sample antigens arriving through lymphatic flow and activate T cells within lymph nodes	Lymph nodes and secondary lymphoid organs

Classical dendritic cells can be further divided into two types: type 1 cDC cells and type 2 cDC cells. Type 1 cDC cells express Blood Dendritic Cell Antigens 3 (BDCA-3) and the transcription factor Interferon Regulatory Factor (IRF 8). Type 1 cDC cells play a role in presenting antigens to CD8+ T cells and triggering their differentiation into cytotoxic T cells. Type 1 cDC cells also produce more IL-12 than cDC 2 cells and express toll-like receptor 3 (TLR3).[11] Type 2 cDC cells express BDCA-1/CD1c and play a role in presenting antigens to CD4+ T cells.[10–12] cDC1 cells are predominantly found in lymph nodes, while cDC2 cells are predominantly found in peripheral tissues.[13]

Plasmacytoid dendritic cells (pDC) produce the cytokine interferon (IFN) type-1 in response to pathogen attack. pDC can also capture and transport antigens from the blood to the spleen for presentation to T cells. pDC are so named because their shape resembles plasma cells after activation.[10] pDC are the largest producers of IFN-type 1 in the human body. In addition to cDC and pDC, under inflammatory conditions monocyte cells can differentiate into dendritic cells called moDC.

Types of Dendritic Cells Based on Location

In addition to being differentiated into classical and plasmacytoid dendritic cells, dendritic cells are also divided into migratory and resident dendritic cells based on their location under normal conditions. Migratory dendritic cells reside in the parenchyma of peripheral tissues and must migrate to lymph nodes or secondary lymphoid organs to interact with naive T cells. Resident dendritic cells, on the other hand, reside in lymph nodes or secondary lymphoid organs and act as sentinels, detecting pathogens in the lymph flow.[11] These two cells can be distinguished based on the number of markers they express. Migratory dendritic cells are CD11cintMHCIIhi, while resident dendritic cells are CD11chiMHCIIint.[11]

Within secondary lymphoid organs and lymph nodes, cDC1 and cDC2 cells are also distinguished based on their location. cDC1 cells congregate in the medulla of the lymph node, which is the T cell zone (TCZ). The presence of cDC1 cells in the TCZ facilitates access for cDC1 cells to cytotoxic T cells. Meanwhile, cDC2 cells congregate in the paracortex, specifically in the interfollicular zone (IFZ), which is the boundary between the T cell zone (TCZ) and the B cell zone (BCZ). The interfollicular zone is where B lymphocytes and helper T cells gather. This facilitates cDC2 cells' ability to activate CD4+ cells.

Dendritic Cells as Antigen Presenting Cells

Dendritic cells serve as a primary link between the innate and adaptive immune systems. This function is primarily achieved through their role as antigen-presenting cells (APCs). As antigen-presenting cells, dendritic cells possess receptors that detect molecular patterns found on microbes and damaged cells, also known as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns

(DAMPs). The cellular receptors that detect these patterns are pattern recognition receptors (PRRs).[10]

Different types of microbes (bacteria, viruses, and fungi) express different PAMPs. However, the PAMPs detected are usually microbial components essential for their survival, so it is unlikely that the microbe will undergo mutations that would render these components undetectable by the PRRs. For example, viral DNA and RNA are essential for replication, or lipopolysaccharides and polyteichoic acids are essential components of bacterial cell walls. This represents an evolutionary adaptation of the innate immune system to ensure that microbes remain detectable by the body's immune system. Unlike specific ligands in the adaptive immune system, which can mutate and thus become undetectable.[10]

The innate immune system can also detect endogenous molecules produced or released by damaged cells. These molecules are called damage-associated molecular patterns (DAMPs). Examples of DAMPs include heat-shock proteins, proteoglycan peptides, monosodium urate, and mitochondrial components. DAMP molecules are not typically produced by cells that die through apoptosis. Cells can also produce molecules that are produced under healthy conditions and released upon damage. These molecules are a subset of DAMPs called alarmins.[10]

Dendritic cells and other phagocytic cells (macrophages and neutrophils) have the ability to detect the presence of PAMPs and DAMPs through pattern recognition receptors (PRRs). These receptors are expressed on the surface of cell membranes, phagocytic vesicles, and in the cytosol (sites where microbes can invade). When PRRs detect the presence of PAMPs and DAMPs, pro-inflammatory and antimicrobial signal transduction pathways are activated.[10]

Dendritic cells are highly efficient antigen-presenting cells. They can phagocytose antigens and present them via major histocompatibility complex (MHC) peptides expressed on their surface membranes.[14] Dendritic cells can detect antigens through three mechanisms: receptor-mediated endocytosis, phagocytosis, and macropinocytosis. Macropinocytosis is continuously carried out by dendritic cells (constitutive macropinocytosis) and is an important mechanism for detecting extracellular antigens.[15] Macropinocytosis is the primary mechanism by which dendritic cells detect antigens, in contrast to macrophages, which use phagocytosis, and B cells, which use endocytosis with the help of antigen-specific receptors.[15]

In conditions of infection and inflammation, antigens internalized by dendritic cells are degraded into peptides and presented via MHC type II to CD4+ T cells. CD4+ T cells then activate the adaptive immune system. However, under healthy conditions, immature dendritic cells will still perform macropinocytosis. Macropinocytosis in healthy conditions continuously captures self-antigens for presentation to regulatory T cells in lymphoid organs. This implies that dendritic cells play a role in establishing the immune system's self-tolerance to the body's own antigens.[15,16]

Dendritic Cell-Based Therapy

The properties of dendritic cells as T cell activators can be utilized for immunotherapy. Dendritic cell-based immunotherapy aims to activate tumor-specific cytotoxic T cells to attack tumor cells. Tumor cells express distinct self-antigens compared to normal cells, enabling them to be detected by the immune system for elimination. However, to avoid immune elimination, tumor cells have the ability to evade T cell recognition, create an immunosuppressive environment, and actively hijack immune cells to support tumor tissue progression.[17] Dendritic cell vaccination aims to support T cell function in recognizing tumor cells.

Dendritic cell vaccination is performed by exposing autologous dendritic cells ex vivo to tumor-associated antigens (TAAs). The source of TAAs varies and can be tumor tissue lysates, cancer cell line lysates, tumor-associated peptides, viral vectors, mRNA transfer, and others. Dendritic cell maturation techniques also vary, for example, using cytokines, CD40 ligands, and TLR agonists.[18]

Of the known dendritic cell subsets, monocyte-derived moDC are the most widely used in dendritic cell vaccine development. This is due to logistical reasons. Because dendritic cells constitute less than 1% of peripheral blood mononuclear cells, obtaining sufficient numbers for therapeutic applications is challenging. A solution to this problem is to use purified monocyte cells, which are then cultured using GM-CSF and IL-4 to form moDC. Data on the efficacy of moDC as a dendritic cell vaccine compared to other dendritic cell subsets are not available.[18] The purification, culture, and exposure techniques of dendritic cell vaccines are known to influence vaccine efficacy.

The route of administration of dendritic cell vaccines also influences vaccine effectiveness. Dendritic cells must reach the lymph nodes to present TAA-specific T cell antigens. Various routes of dendritic cell vaccination have been studied, including intradermal, intranodal, subcutaneous, or near-nodal. Based on preclinical studies in mice, only the intranodal route significantly prolonged survival.[19] However, in clinical studies, the superiority of the intranodal route was not clearly demonstrated. One study found that 4% of dendritic cells administered intradermally migrated to the lymph nodes.

With the intranodal route, the number of dendritic cells that migrated varied between 0 and 56%.[20] This high variation is likely due to the higher difficulty of intranodal injection compared to intradermal injection.[18] The use of recall antigens, familiar antigens such as tetanus toxoid antigen from the Td vaccine, as pretreatment has been shown to promote dendritic cell migration to the lymph nodes.[19] Therefore, the technique and route of dendritic cell vaccination still require further research.

A phase 1 dendritic cell vaccine study was conducted by Ge et al. in 2017 to demonstrate the vaccine's safety.[21] This study found the dendritic cell vaccine to be well tolerated. The most common side effects were a flu-like syndrome with fever, fatigue, myalgia, and nausea, which did not require intervention. A total of 15 patients with stage I to IIIA non-small cell lung cancer (NSCLC) after tumor resection were enrolled in this study. Three patients received a low dose, three received a medium dose, and nine received a high dose.[21]

In this study, the percentage of CD3+CD4+CD25+Foxp3+ regulatory T cells was significantly reduced. Meanwhile, TNF-alpha and IL-6 levels significantly increased in two of the 15 patients. Clinically, quality of life scores significantly improved in the high-dose group. During long-term follow-up using response evaluation criteria in solid tumors (RECIST), one patient died, one patient developed progressive disease, and seven patients experienced no recurrence in the high-dose group. These results were significantly better than those in the low-dose group (one patient died, one had progressive disease, and one had no recurrence). However, given the small number of subjects, further research is needed.[21]

Conclusion

Dendritic cells play a crucial role in linking the innate and adaptive immune systems, primarily as antigen-presenting cells and mediator molecules that play a crucial role in the body's immune response. Dendritic cells have several subsets, each with specific but interrelated functions. Furthermore, dendritic cells' ability to act as T-cell activators could be utilized as immunotherapy in cancer treatment, although further research is needed.

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