Post-Graduate Course: Lung innate immunity

Lung Dendritic Cells Link Innate and Adaptive Immunity

Graduate School of Biomedical Science and Engineering, KAIST

You-Me Kim

Dendritic cells are professional antigen presenting cells that play critical roles in both innate and adaptive immune responses. Although present at relatively low numbers in peripheral tissues and lymphoid organs, dendritic cells are specialized in sensing environmental changes caused by pathogenic infection or non-microbial cellular stress and initiate appropriate innate immune responses. In addition, dendritic cells efficiently take up antigens, process them for presentation on MHC class-I or -II molecules, migrate into the nearby draining lymph nodes, and activate naive T cells, thereby initiating the adaptive immune responses. Coordination of proper innate and adaptive immune responses by dendritic cells is a key to the successful host defense against microbial infection, anti-tumor immunity, as well as tissue homeostasis. Deficiency or uncontrolled activation of dendritic cell function are often associated with various pathologic conditions, including lung infection, allergy, asthma, and cancer.

Innate Immune Functions of Dendritic Cells

Along with macrophages, dendritic cells serve as sentinels for pathogenic infection in the peripheral tissue by detecting pathogen-associated molecular patterns (PAMPs), which are proteins, lipids, and carbohydrates uniquely present in a wide variety of microorganisms. Dendritic cells also sense cellular stress and tissue dysfunction by recognizing danger-associated molecular patterns (DAMPs), which generally are intracellular molecules actively or passively secreted by damaged cells. Receptors for PAMPs and DAMPs are called pattern recognition receptors (PRRs) and a single PRR can often detect both PAMPs and DAMPs. Major PRRs include Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), c-type lectin receptors, and NOD-like receptors (NLRs). Ligation and signaling of PRRs result in activation of dendritic cells. Activated dendritic cells exhibit heightened endocytosis and phagocytosis for antigen uptake and pathogen removal. They also

secret various innate cytokines and chemokines, such as IL-1β, IL-6, IL-8, and IL-12, to stimulate and recruit other immune cells from blood for enhancing innate immune responses in the tissue.

Special molecular structures of PAMPs from different types of microorganisms are recognized by specific PRRs preferentially expressed by a relevant dendritic cell subset, whose activation results in the tailored innate immune responses against the particular forms of insult. For example, lipopolysaccharides, a major structural component of the outer membrane of all gram-negative bacteria are recognized by TLR4 on conventional (or classical) dendritic cell (cDC) and promote secretion of proinflammatory cytokines for activating and recruiting macrophages and neutrophils for bacterial removal. On the other hand, single-stranded RNA (ssRNA), presence of which often suggests viral infection, activates plasmacytoid dendritic cells (pDC) by binding to TLR7 highly expressed in pDC and induces production of type I interferon for anti-viral defense mechanisms.

Adaptive Immune Functions of Dendritic Cells

Not only promoting innate immune responses upon recognition of pathogens or tissue malfunction in the periphery, activated dendritic cells also uptake antigens, upregulate T cell costimulatory molecules such as CD80 and CD86, express CCR7 for migration into draining lymph nodes, and stimulate naïve T cell. Due to its unique migratory ability and strong expression of T cell costimulatory molecules, dendritic cells among professional antigen presenting cells are most efficient in priming naïve T cells. Antigens synthesized inside dendritic cells, for example self antigens or viral proteins, are processed by proteasomes in the cytoplasm, loaded onto MHC class I in the ER, and presented to $CD8^+$ T cells, whereas exogenous antigens taken up by dendritic cells are degraded by endosomal proteases and usually presented on MHC class II to activate $CD4^+$ T cells. In addition, dendritic cells, especially cDC1 subset, can present peptides derived from exogenous antigens to $CD8^+$ T cells by a process termed cross-presentation. Antigens subjected to the cross-presentation are internalized into dendritic cells in the form of soluble proteins, immune complexes, or dead cells expressing the antigen. Some of the antigens escape from endosomes or phagosomes into cytoplasm and degraded by cytoplasmic proteasomes while other antigens are processed by endolysosomal proteases, and the resulting peptides from both pathways are loaded onto MHC class I and presented to $CD8^+$ T cells.

During T cell priming, the lack of proper costimulatory signals delivered by dendritic cells cause T cell inactivation or anergy, which is an important mechanism for inducing the peripheral tolerance against self antigens. Therefore, dendritic cells control the balance between immune activation and tolerance.

Activated $CD4^+$ TH cells undergo clonal expansion and differentiation into various T_H cell subsets, including T_H1, T_H2, T_H17, T_{FH}, and Treg. A decision for differentiation into a particular T_H subset is influenced by the strength and duration of T cell receptor signaling (signal 1). In addition, the quality and

the quantity of costimulatory signals (signal 2) and the cytokine milieu (signal 3) during the T cell priming and activation critically regulate the TH cell differentiation. Dendritic cells play a decisive role in the TH cell differentiation by providing the all three signals (signal 1, 2, and 3). Especially, upregulation of costimulatory molecules and the varieties of cytokines secreted by dendritic cells depend on the nature and strength of PRR signaling. Therefore, dendritic cells recognize and distinguish various infectious and cellular stress conditions and relay that information into the adaptive immune system.

Dendritic Cell Subsets

Dendritic cells can be classified into several subsets according to their origin, function, and cell surface molecule expression. All dendritic cells seem to be derived from common myeloid progenitors (CMPs) in the bone marrow. CMPs differentiate into either committed monocyte progenitor (cMoP) or common dendritic cell progenitor (CDP). In the steady state, both cDCs and pDCs are derived from CDPs. All cDCs express the transcription factor Zbtb46 and are often further divided into cDC1 and cDC2. cDC1 subset expresses the transcription factors IRF8 and Batf3, secretes a high level of IL-12 upon activation, and is very good at uptake of dead or damaged cells and cross-presentation, thereby efficiently promoting the TH1 differentiation and type I immune responses. In mice, cDC1 in the spleen and lymph nodes expresses CD8, whereas cDC1 in the peripheral tissues is generally marked by cell surface expression of CD103. Compared to cDC1, cDC2 depends on IRF4 for its own differentiation and expresses CD4 or CD11b on the surface. In mice, cDC2 subset is comprised of heterogeneous cell populations and promotes either T_H2 or T_H17 cell differentiation. In humans, $CD141^+$ DCs and CD1C+ DCs are thought to be equivalent to mouse cDC1 and cDC2, respectively.

Both cDC1 and cDC2 seem to differentiate from the dedicated precursor cells, pre-cDC1 and pre-cDC2, respectively. In contrast, committed pDC progenitor cells are yet to be identified and the differentiation of pDC from CDP depends on the transcription factors E2-2 and Spi-B. pDC is unique in its morphology, cell surface molecule expression, and function. It resembles antibody-secreting plasma cells with the highly developed rough ER structure, shows a low CD11c and high B220 expression pattern. pDCs are most well known for secreting a tremendous amount of type I interferon upon viral infection, thereby coordinating early anti-viral immune responses. Instead, antigen presentation by pDC seems to be less efficient compared to cDCs. Nonetheless, several studies reported efficient antigen presentation by pDCs in certain pathological conditions and its role in promoting either immune activation or tolerance induction.

Unlike the steady state condition in which all DC subsets are differentiated from CDPs in the bone marrow, dendritic cells can also be generated from circulating monocytes in the inflammatory settings. These monocyte-derived dendritic cells (moDCs) are generated by GM-CSF and IL-4 signaling and actively recruited from blood to the inflamed tissues. They resemble cDCs in their functions and the inflammatory

cytokine production. moDCs can be distinguished from bona fide cDCs by expression Ly6C. In certain cases, moDCs are also called TNF-α/iNOS-producing dendritic cells (Tip-DCs).

Lung Dendritic Cells

Compared to dendritic cells in other tissues, lung dendritic cells are exposed to unique environment factors such as high levels of surfactants and mucins. In addition, pulmonary epithelial cells secrete IL-25, IL-33 and thymic stromal lymphopoietin (TSLP), which are known to promote type 2 immune responses. These factors likely influence the activation and function of lung dendritic cells.

In the healthy lung, most dendritic cells are present in the tissue rather than in the airspaces. $CD103^+$ cDC1 are predominantly found in association with the pulmonary epithelium, while CD11b+ cDC2 are mostly found beneath the basement membrane. In mice, soluble antigens were shown to be preferentially acquired by cDC2 and transported to mediastinal lymph nodes, whereas cDC1 was more efficient in taking up particulate antigens. pDCs in the lung, like pDCs in other tissues, is responsible for secreting type I interferons and amounting anti-viral innate immune responses.

During lung inflammation, moDCs as well as the total dendritic cell numbers are increased in the lung tissue and bronchoalveolar lavage (BAL). Given the clear importance of dendritic cells in T cell priming and TH cell differentiation, it would be necessary to identify the exact dendritic subsets and their functions in balancing immune responses and mounting tolerance in the various pathological conditions of the lung. One of the particular interests is how cDC2 and/or moDCs are activated and regulate eosinophilic versus neutrophilic (or T_H2 versus T_H17) inflammation in several allergic diseases. In addition, how lung cDC1 subset play a role in promoting anti-viral and anti-tumor immune responses needs further investigation.