**EPH - International Journal of Medical and Health Science**

ISSN (Online): 2456-6063
Volume 05 Issue 03 September 2019

DOI: https://doi.org/10.53555/eijmhs.v5i3.81

# REVIEW ARTICLE: THE ROLE OF DENDRITIC CELLS IN THE CONTROL ON INNATE IMMUNITY

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## Abstract:

*Dendritic cells play an important role in host immunity by inducing innate inflammatory responses to pathogens, efficiently priming immature T cells, activating memory T cells and promoting B cell activation. Dendritic cells are also integral in maintaining steady- state immune homeostasis by continually presenting tissue-derived selfantigens to $CD4^+$ and $CD8^+$ T cells in the absence of inflammatory signals, leading to tolerance against those self-antigens. The important of innate immunity lies not only in directly confronting pathogenic and non-pathogenic insults but also in instructing the development of an efficient adaptive immune response.*

**Keywords:-** *innate inflammatory responses, T cells and B cells, adaptive immune response, innate immunity*

## INTRODUCTION

Dendritic cells is named because of their probing 'tree –like' or dendritic shapes, they are responsible for the intiation of adaptive immune responses and hence function as the
'Sentinels' of the immune system (Billiard, 2016). Paul Langerhans first described dendritic cells in human skin in 1868 but he thought that they were cutaneous nerve cells. Dendritic cells are bone marrow (BM)- derived leukocytes and are the most potent type of antigen- presenting cells(Ferris, 2017). They can also be propagated in vitro from bone marrow and blood using various combinations of growth factors, such as granulocyte macrophage- colony stimulating factor (GM-CSF) and Flt3 ligand (Billiard, 2016). Dendritic cells are specialised to capture and process antigens, converting proteins to peptides that are presented on major histocompatibility complex (MHC) molecules recognised by T cells (Castelli, 2018). Dendritic cells are heterogenous for example myeloid and plasmacytoid dendritic cells; although all dendritic cells are capable of antigen uptake, processing and in location, migratory pathways, detailed immunological function and dependence on infections or inflammatory stimuli for their generation (Rowland, 2018). During the development of an adaptive immune response, the phenotype and function of dendritic cells play an extremely important role in initiating tolerance, memory and polarised T-helper 1(Th1), Th2 and Th17 differentiation (Peng, 2018).

## DENDRITIC CELLS BRING ABOUT INNATE AND ADAPTIVE IMMUNITY:

Since dendritic cells have numerous cytoplasmic processes, they have a high surface area permitting intimate contact with a large number of surrounding cells, for example T cells, natural killer cells, Neutrophils, epithelial cells (Abram, 2016). For instant, only one mature dendritic cell (mDC) is required to stimulate 100-3000 T cells. Dendritic cell precursors migrate from bone marrow (BM) through the blood stream to almost every non- lymphoid tissue, where they reside in an immature state (iDC), continuously sampling their environment by endocytosis, macropinocytosis and phagocytosis (Wlodarczyk, 2017). They can extend their processes through the tight junctions of epithelia to increase capture of antigens even when there is no overt infection/inflammation (Bourges, 2016).
During pathogen invasion, resident immature dendritic cells (iDCs) detect intruders via pattern recognition receptor (e.g TLRs) capture antigens and quickly leave the tissue (Ferris, 2017). They crawl through the cells, cross the endothelium of lymphatic vessels and migrate to the draining lymph nodes (DLN) in response to a number of chemokines such as (CCL19) and CCL21 (Jakubzick, 2016). During their migration from the peripheral tissues, dendritic cells undergo phenotypical and functional maturation (Diana, 2017).

## THE ROLE OF DENDRITIC CELL SUBSETS AND INNATE IMMUNITY IN THE PATHOGENESIS:

Dendritic cells (DCs) are key antigen-presenting cells that have an important role in autoimmune pathogenesis (Pelletier, 2016). Dendritic cells control both steady- state T cell tolerance and activation of pathogenic responses (Price, 2016). The balance between these two outcomes depends on different factors, including genetic susceptibility; environmental signals that stimulate varied innate responses, and which dendritic cell (DC) subset is presenting antigen (Morel, 2017). Although the specific dendritic cell phenotype can separate depending on the tissue location and context, there are four main subsets established in both mouse and human: conventional dendritc cell1 cDC1 and cDC2, plasmacytoid DCs and monocytes-derived DCs (Guilliams, 2016).
Dendritic cells play a vital role in host immunity by inducing innate inflammatory responses to pathogens, efficiently,activating memory T cells and promoting B cell activation (Teichmann, 2016). Nonetheless, dendritic cells are also integral in maintaining steady-state immune homeostasis by continually presenting tissue-derived self-antigens to $CD4^t$ and $CD8^t$ T cells in the absence of inflammatory signals, leading to tolerance against those self-antigens (Yang, 2016). Dendritic cells can affect induction of both immunity and tolerance in several ways, including at the level of dendritic cell development, the relative composition of dendritic cell subsets and the extent of dentritic maturation (Belkaid, 2016).
Autoimmune diseases occur when autoreactive T and B cells escape negative selection in the thymus and bone marrow, respectively followed by breaks in peripheral tolerance mechanisms that disrupt immune system homeostasis (Hammer, 2017). Antigen- presenting cells (APCs), including dendritic cells play a central role both in the initial thymic selection of the T cell repertoire and in maintaining peripheral T cell tolerance for autoreactive cells (Stranges, 2016).
Early interaction between innate immunity and target tissues is often a mark of autoimmune disease. The effects of dendritic cell on autoimmune disease centers on the possibility that dendritic cells could either induce or suppress autoreactive T cell responses and focuses on dendritic cell protein that will affect those interactions (Loschko, 2016). In both autoimmune patients and murine models of autoimmunity, dentrtic cells exhibit alterations in phenotype or function that could be due to underlying genetic defects or the chronic inflammatory environment and can affect both the initiation of disease and later failure of tolerance mechanisms that lead to destruction such as loss of insulin-producing beta cells in T1D (Welzen, 2016).

## PLASMACYTOID DENDRITIC CELLS:

Plasmacytoid dendritic cells are significant contributors of type 1 IFN after stimulation via TLR7 or TLR9 and as much can facilitate autoimmunity as is clearly the easy with SLE. However, they can also play a significant role in regulation of immune responses by secreting IDO, inducing Tregs or inhibiting pathogenic responses (Rowland, 2016). Even though evidence suggests that IFN=α from pDCs in the pancreas of NOD mice early (2-4 weeks of age) is important for initiation of autoimmune diabetes, some groups show that pDCs are present only in the islets later in the disease and play a protective role via IDO (Pelletier,

2017). recently a study on human shows increased IFN-α from peripheral blood pDCs in patients with type 1 diabetes. It is possible that pDCs may be playing both pathogenic and a regulatory role in type 1 diabetes, depending on the disease stage and microenvironment.

**MONOCYTE-DERIVED CELLS:**

There are also several monocyte-derived cell populations that happen to have therapeutic potential and the ability to derive T cell tolerance via cell-intrinsic mechanisms or T reg induction (Guilliams, 2016). Some studies identifying roles for CD11 b cells may actually be studying a monocyte-related population, but not cDCs. Bone marrow dendritic cells generated invitro with GM-CSF are monocytes derived GM-CSF bone marrow dendritic cells efficiently stimulate proliferation of self-specific T regs that can effectively block and reverse pathogenesis (Calderon, 2016). Both GM-CSF/IL-4- derived dendritic cells and IL-10derived dendritic cells are tolerogenic monocyte-derived populations that can alter T reg populations and inhibit autoreactivity (Welzen, 2016). These tolerogenic dendritic cells are being actively studied for possible therapies in human autoimmunity and for stopping medical complications such as graft-versus- host disease (Scroggins, 2016). On the other side T1D patients have activated monocytes in the peripheral blood that make high levels of proinflammatory cytokines. Therefore, monocyte-derived dendritic cells, like other dendritic cell subsets can also provide both tolerogenic and immune activating signals that alter autoimmune pathogenesis (Billiard, 2016).

**ALTERATIONS IN DENDRITIC CELLS DUE TO CHRONIC INFLAMMATION: COMPARISON TO INFECTION**

The inflammation that occurs during autoimmune pathogenesis may have the same responses with T cells during chronic infection because long lasting effectors T cell responses can alter the inflammatory state of host, both pro- and anti-inflammatory mechanisms (Abrams, 2016). The generation of antimicrobial T cells can produce responses that have inflammatory effects on host tissues, as well as regulatory mechanisms to reduce host tissue damage (Santin, 2016). Autoimmune diseases that have environmental etiologies may have infectious triggers and secondary autoimmunity can be triggered together with molecular mimicry or pathogeninduced inflammatory environment (Diana, 2017). Indeed, altering the inflammatory status of dendritic cells alters T cell responses and autoimmune pathology. Increased inflammation observed during autoimmune pathogenesis has many similarities to the host response to infection and emerging studies have demonstrated that dendritic subsets play distinct roles during infection as well as during autoimmunity (Rowland, 2016).

**THE CONTROL OF INNATE IMMUNITY:**

The ability of innate immune system to respond to a variety of stimuli is central to its function in pathogen clearance and tissue repair (Halle, 2016). Upon activation, cells of the innate immune system up regulate inflammatory mediators and induce increased expression of costimulatory and adhesion molecules which can derive the activation of the adaptive arm of the immune system (Nakahira, 2016). Supposing the role of innate immune system was thought to recognize harmful conditions such as the presence of microbes through its ability to distinguish pathogens as ‘’ non-self’’ (Kofoed, 2017) however, this cannot account for the activation that follows sterile insults where in the inflammatory response is triggered in the absence of invading pathogens (Gasse, 2016). It is now understandable that the ability of cells of the innate immune system to execute their inflammatory and tissue repair programs is dependent upon germ-line encoded pattern recognition receptors (PRR) that identify molecular structures associated with cellular stress and death, known as damage associated molecular patterns, as well as conserved pathogen derived structures or pathogen associated molecular patterns (Kawai, 2016).

Damage associated molecular patterns (DAMPs) can be cytosolic or nuclear components, such as the chromatin-associated protein high mobility group (HMG1), or the chaperone heat shock protein 60 (Hsp60) which under homeostatic conditions do not come into contact with pattern recognition receptors (PRRs) (Bauernfeind, 2016). The inflammatory response can cause bystander host tissue damage and has a high metabolic cost, thus multiple regulatory mechanisms control the extent, duration and the type of response. To prevent unwanted responses, interactions of these intracellular and extracellular molecules with pattern recognition receptors (PRRs) must occur under conditions in which an inflammatory response is required allowing cells of the innate immune system to activate in an appropriate and timely (Kumar, 2016).

Organisms fight an infection or disease with the help of an intricate system of immunity classified as an innate and adaptive in nature. Innate immunity is an evolutionarily conserved defence mechanism capable of fighting a diverse threat of viral, prokaryotic and eukaryotic parasites and pathogens in plants and invertebrate animals (Brydges, 2016). In some conditions, the adaptive immune elements restrain innate immune responses. In some the combination of innate and adaptive immunity maximizes host defense while minimizing collateral damage to the host tissues; adaptive immunity provides specific responses to the insult that directly attack the pathogenic process or recruit other powerful innate effector cells that even though not specific by themselves but can act specifically by their selective recruitment (Hise, 2016). More than this linear progression from innate to adaptive immunity by innate signals following tissue insult triggering adaptive immune cells to respond to the pathogen or disease, several studies now demonstrate an adaptive control of effector mechanisms of host defence by specifically recruiting, activating or blocking innate effectors (McKee, 2016).

**SUMMARY:**

The mechanisms by which the immune system respond to an infection or disease depends on a complex interplay between the elements of innate and adaptive immunity. While most of the focus so far has been on the innate instruction of the adaptive immune responses, considerable evidence now suggests an equally important adaptive control of the innate

immunity by initiating an antigen-specific response can compensate, suppress and activate innate responses at the site of tissue antigen. Here we also discussed recent advances in understanding of the adaptive control of immune effector function in various pathological and physiological conditions.

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