

Role and Status of Dendritic Cells in Pulmonary Arterial Hypertension: A Literature Review

Kaustav Chakraborty^{1*} and Pallab Chakraborty²

¹Department of Zoology, S.B.S. Government College, Hili, West Bengal, India

²Department of Zoology, Ramakrishna Mission Vidyamandira, Belur Math, Howrah, West Bengal, India

***Corresponding Author:** Kaustav Chakraborty, Assistant Professor (W.B.E.S.), Department of Zoology, S.B.S. Government College, Hili, West Bengal, India.

Received: March 16 2020; **Published:** April 17, 2020

Abstract

It is well known to us that dendritic cells (DCs) are one of the most crucial immune cells of our body and so-called antigen presenting cells (APC) that not only activate T cells but also link the adaptive immune system with innate immune system. Involvement of DCs in various lung inflammatory diseases led the scientists force to explore its role in pulmonary arterial hypertension (PAH). Dendritic cells have different subsets such as conventional dendritic cells which are lower in number in PAH patients as compared with control. Interestingly, plasmacytoid dendritic cells show increased prevalence in PAH lungs compared to donors. The number and function of another DC subset, monocyte-derived dendritic cells are also compromised in PAH. All these DC subsets together influence the immunopathology of PAH extensively. Relationship between DC and PAH opens up a new avenue for investigating the pathology of PAH. Here in this review article we focus on the role and status of DCs such as expression of their different subsets, their functional activity, phenotypic changes, and migration in PAH.

Keywords: Dendritic Cells; Myeloid Dendritic Cells; Plasmacytoid Dendritic Cells; Lung; Pulmonary Arterial Hypertension

Abbreviations

DC: Dendritic Cell; mDC: Myeloid Dendritic Cells; pDC: Plasmacytoid Dendritic Cell; cDC: Conventional Dendritic Cell; moDC: Monocyte-derived Dendritic Cell; PAH: Pulmonary Arterial Hypertension; PH: Pulmonary Hypertension; IPAH: Idiopathic Pulmonary Arterial Hypertension; AD: Autoimmune Disease; CTD: Connective Tissue Diseases; TLOs: Tertiary Lymphoid Organs.

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by a pathological condition where a mean pulmonary arterial pressure (PAP) of ≥ 25 mmHg at rest and a mean capillary wedge pressure of ≤ 15 mmHg [1]. The high PAP causes the right ventricle (RV) hypertrophy that leads eventually to RV dilatation, heart failure, and finally death. Specifically, small pulmonary arteries (PAs) and arterioles are affected. PAH is the collective term for a combination of diseases that have several pathophysiologic, histologic, and prognostic features in common [2]. Patients belong to PAH can be subdivided into groups based on associated conditions and risk factors. However, a few PAH patients show no cause or associated conditions i.e. idiopathic PAH (IPAH). Sometimes, PAH is associated with autoimmune diseases (AD) such as connective tissue disease (CTD) which includes systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA). SSc is the most common AD associated with PAH, followed by SLE [3-5]. The survival rate for PAH patients are low, just 1 year. Clinical data suggests only 82% of SSc-PAH patients and 93% of IPAH patients are still alive after 1 year [6].

From immunopathological aspect of PAH, inflammation is the major phenomenon [7, 8] in IPAH and that initiate lots of ongoing clinical research for the treatment of IPAH with immunosuppressive therapy [9-12]. Among various inflammatory cells, dendritic cells (DCs) play some vital role in IPAH as suggested by Perros., *et al.* (2007) [13]. Relationship between DC and PAH opens up a new avenue for investigating the pathology of IPAH.

Dendritic cells

DCs are acting as a bridge between innate and adaptive immune system. They are most potent antigen-presenting cells in the immune system and are crucial for the activation of naïve T cells [14,15]. There are two distinct DC subtypes of circulating DC precursors are identified in human [16]: (1) myeloid dendritic cells (mDCs), are characterized by the markers CD11c and CD33, develop into become DC1, secrete interleukin (IL)-12, and direct Th1 polarization of naïve T cells; and (2) plasmacytoid dendritic cells (pDCs), are characterized by the marker CD123, mature to become DC2 and drive a potent Th2 polarized immune responses. DCs are shown to be critical in multiple cardiovascular diseases as well as exposure to hypoxia [17-19]. DCs were shown to accumulate at perivascular regions in PH suggesting their involvement in PH progression [20].

It has been reported that CD209 (C-type lectin receptor) positive cells are dramatically increased in lungs of IPAH patients compared with donor lungs. In addition, the number of infiltrating dendritic cells is much higher in small, medium as well as large pulmonary arteries of IPAH lungs compared with donor lungs. These infiltrating dendritic cells are found in the adventitia of pulmonary arteries of IPAH patients [21].

Role of different dendritic cell subsets in PAH

Conventional dendritic cells (cDCs)/Myeloid dendritic cells (mDCs) in PAH

Among different types of DC, conventional dendritic cells influence the disease very much. It has been reported that the number of circulating cDCs are lower in PAH patients compared with control [22], which could indicate an increased cDCs migration toward lung tertiary lymphoid organs (TLOs). IPAH patients possess DCs inside T-cell zones of lung TLO which suggest that they promote T-cell activation [23]. From the study of Fleige., *et al.* (2018), it can be assumed that DCs may gather in tissue and contribute to TLO formation as they fail to reach to lymph nodes [24]. Perros., *et al.* (2019) reported that CCL19 and CCL21 in IPAH patients facilitate DC attraction [20]. It is also found that a CCR7 (migratory receptor of DCs which control DCs response to CCL19 and CCL21)-deficient mice, show sign of PH that also relate the link of DC with the disease formation [24,25]. DC-secreting cytokines such as IL-6, IL-10, and TNF- α [26], play a central role in the immunopathology of PAH [27]. This subtype is currently in focus of research to find out its overall role in PAH.

Recently, an investigation from Rohm., *et al.* (2019) reveals that the number of circulating DCs are decreased significantly in the PH group compared to the control group ($p = 0.008$). They performed subgroup analysis to investigate this observation of a decrease in circulating mDC during PH and they found significant differences in the number of circulating mDCs compared to healthy controls for patients with PH group I, II, III, II&III (mixed genesis), but not for group IV. Most interestingly, no significant differences were reported in the subgroup analyses for pDCs. Along with circulating DCs, they suggested also a reduction of myeloid DCs number in PH [28].

Plasmacytoid dendritic cells (pDCs) in PAH

It has been reported that PAH has autoimmune features [29,30]. pDCs have a key role in the regulation of autoimmunity and are at the crossroads of innate and adaptive immunity [31]. So, research analysis for pDCs in PH is very important criteria. Marsh., *et al.* (2018) confirmed increased prevalence of pDCs (CD123+CD304+) in lungs of IPAH patients compared to donors and these pDCs were localized predominantly in the alveolar space in proximity to vessels. They further investigated whether the increased pDC numbers, as observed

in IPAH lungs, were also found in the circulation. They found no changes in pDC numbers in the peripheral blood, which is similar to the results of Wang, *et al.* (2009) [32].

pDCs are the most potent producers of antiviral type-I interferons [33], which have been implicated in PH pathogenesis [34]. Therefore, pDCs might represent the missing link between the associations of PH with both autoimmunity and viral infections [35]. Alternatively, pDCs can also induce regulatory or anti-inflammatory responses [36]. It is therefore possible that the increased pDCs in the IPAH lungs may thus represent a mechanism to oppose ongoing inflammation [32]. It has been found that the number of pDC is decreased in blood sample of IPAH patients which suggest that they might migrate to the particular affected tissue [23,37]. pDCs secrete CXCL4 and together they promote this disorder [38]. All these data suggest that pDCs also play crucial role in PAH and IPAH.

Monocyte-derived dendritic cells (moDCs)

According to Wang, *et al.* 2009; the monocyte-derived DC subset, especially moDCs, is implicated in the pathogenesis of IPAH as their number and functions get compromised [22]. Monocytes expressing both CD14 and CD16 are termed intermediate monocytes, can also produce pro-inflammatory cytokines [39]. Intermediate monocytes specifically promote pro-inflammatory Th17-cell responses which also contribute to PAH development [39]. However, the immunopathology of IPAH still needs further investigation to relate the role of moDCs directly in IPAH development [22].

Discussion

Although the morbidity rate is only 1 - 2/million, it is a lethal disease. Without treatment, the median life expectancy from the time of diagnosis in patients with IPAH was 2.8 years. Modern treatment has markedly improved physical function and has extended survival, so the 5-year mortality rate is 50%. However, the pathogenesis of IPAH is still unexplained, and at present, no therapy can cure this disease [22]. The present review summarizes that the dendritic cells influence comprehensively the immunopathology of pulmonary arterial hypertension.

As it was observed that the number of myeloid DCs are significantly decreased in PH patients compared to control group, so there may be possibility for using myeloid DCs as a biomarker in PH. However, it needs to be evaluated in the near future [28]. On the other hand, we can assume that pDCs have pivotal role in PAH. From different studies, it has been suggested that pDCs generally counteract the inflammation procedures which are initiated by cDCs or mDCs and other important immune inflammatory cells. By that time pDCs also regulate autoimmune features of PAH (Figure 1).

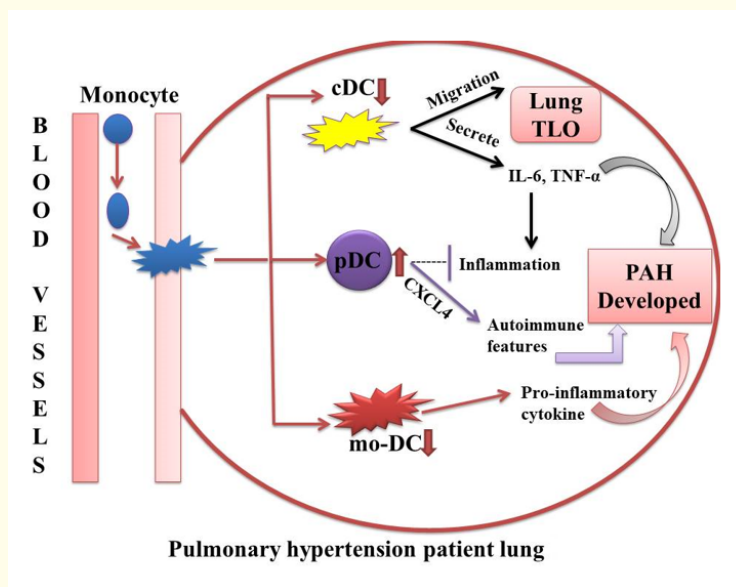


Figure 1: Role of different DC subsets in pulmonary arterial hypertension.

The result from the research done by Perros, *et al.* (2007) suggested that immature DCs accumulate in remodelled pulmonary vessels in human and experimental pulmonary hypertension. They observed the mean numbers of arterial DCs increased during the development of vasculopathy in monocrotaline-exposed rats. Accumulation of arterial DCs precedes pulmonary arterial thickening and haemodynamic alteration. Furthermore, they found DCs are constantly present in remodelled vessels, which indicate that the DC influx is not just a consequence of increased pulmonary arterial pressure. It has been assumed that DCs accumulation in lesions of pulmonary hypertension patient lung may be the consequence of recruitment but also of local proliferation, decreased efflux from the pulmonary vascular wall [13]. Among the different lineage of inflammatory cells, DCs have been related to various vascular disorders. In systemic arteries, vascular-associated DCs make a crowd in arterial regions that are under major haemodynamic stress via turbulent flow conditions [40]. It has been observed that the DC infiltration mostly occurs in plexiform lesions. Along with haemodynamic changes, occurrence of oxidative stress in PAH might act as a DC-attracting “danger signal” [41].

It has been reported that different DC subsets are involved not only in the pathobiology of ADs but appear to play a role in the pathobiology of IPAH and CTD-PAH as well [23]. The increasing knowledge on DC biology obtained by advanced immunological techniques has led to a more combined method to identify DC subsets and the discovery of new DC subsets. Exploring the role of all currently known DC populations may help to unravel the pathobiology of PAH. This might lead to new immunotherapeutic approaches for targeting specific DC subsets, their activation, and/or their effectors function [23].

Conclusion

In conclusion, DC and their different subsets have significant role in PAH. DCs contribute extensively in both human as well as experimental pulmonary arterial hypertension.

Acknowledgement

Authors want to thank Prof. Arindam Bhattacharyya (Immunology Lab., D/o Zoology, University of Calcutta), Dr. Narbu Sherpa (Principal, S.B.S. Govt. College, Hili) and Maharaj Swami Shastrajnananda (Principal, R.K.M.V., Belur Math) for their supports.

Conflicts of Interests

None.

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Volume 9 Issue 5 May 2020

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