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Dendritic Cells in Pulmonary Hypertension: Foot Soldiers or Hidden Enemies?

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Editorials: *American Journal of Respiratory Cell and Molecular Biology* – Red-2019-0443OC – ‘DNDR1-Cre-mediated deletion of *Tnfrsf25/A20* in conventional dendritic cells induces pulmonary hypertension in mice.’ by T. Koudstaal, J.A.C. van Hulst, T. Das, S.F.H. Neys, D. Merkus, I.M. Bergen, M.A. de Raaf, H.J. Bogaard, L. Boon, G. van Loo, J.G.J.V. Aerts, R.W. Hendriks, K.A. Boomars, M. Kool.

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Dendritic cells (DCs) constitute a heterogeneous and versatile group of hematopoietic antigen-presenting cells indispensable for a healthy immune system. At the crossroads of innate and adaptive immunity, DCs have indeed a prominent role in immune surveillance for self- and non-self-antigens, and in the initiation and orchestration of different types of antigen specific adaptive immune responses. This first line of defense is therefore critical at barrier sites, particularly in the lungs. However, they are also involved in the pathogenesis and progression of highly prevalent respiratory conditions (1). In this issue, Thomas Koudstaal and colleagues obtained evidence that enhanced nuclear factor-kappa B (NF- κ B) activation in DCs in mice is sufficient to cause interleukin (IL)-6-dependent pulmonary arterial muscularization and mild pulmonary hypertension (PH).

Even if DCs express high expression of major histocompatibility complex class II (MHC-II) molecules and CD11c, additional markers are essential to identify DCs and to categorize them into specific subtypes. Even if a multitude of phenotypically and functionally distinct DC subtypes have been described, they are classically divided into five distinct major subsets, namely the conventional DCs (cDCs), comprising cDC1s and cDC2s, the plasmacytoid DCs (pDCs), Langerhans cells, and the monocyte-derived DCs (moDCs) (2). The cDC1 subset, identified in Human by the expression of IRF8, CD141, and XCR1, is the most efficient at priming cytotoxic CD8⁺ T-cells to exogenously-derived antigens (cross-presentation) and to polarize CD4⁺ T-cells toward a Th1 phenotype (3). IRF4, CD1c, and CD172a identify Human cDC2s that are the most efficient to differentiate CD4⁺ T-cell into Th1, Th2, and Th17 in specific contexts. Human pDCs, positive for CD303, CD304 and CD123, secrete high amounts of interferon and support B-cell differentiation. However, such identification can be challenging because DC subset composition, maturation, and migration is dependent on multiple tissue-specific factors and can rapidly be adapted depending of the micro-environmental milieu (4, 5).

Alterations in DC subset composition and activation state are present in lungs of patients with pulmonary arterial hypertension (PAH) (6-13). While DCs accumulate around remodeled pulmonary vessels (6, 9, 11, 12), their numbers decrease in blood of PAH patients (7, 8, 10), suggesting that they are likely recruited in pulmonary lymph nodes and tertiary lymphoid organs (TLOs). Consistent with this notion, Perros and colleagues have reported increased levels of CCL20, a potent chemoattractant for immature DCs, in explanted lungs of PAH patients. They also reported the presence of CCR7 and its ligands CCL19 and CCL21, an axis that is essential for the development and maintenance of bronchus associated-TLOs (14). In addition to increased DC numbers and

complexity in PAH lungs, Hautefort and colleagues have demonstrated that PAH-moDCs are functionally different from control-moDCs, as reflected by a higher capacity to induce activation and proliferation of CD4⁺ T-cells, a lower IL-4 expression (Th2-response) and a higher IL-17 expression (Th17-response) (7). Finally, as previously reviewed (13), additional DC alterations are also found in other PAH clinical subgroups, especially those associated with connective tissue disorders. Collectively, these findings support that DC homeostasis is altered in PAH; however, it is unclear whether such alterations are the cause of disease development and/or progression or a consequence of it, and precisely how DCs contribute to PAH pathogenesis remains unknown.

In their most recent study published in this issue, Thomas Koudstaal and colleagues examined the lung and cardiac effects of enhanced cDC activation in adult mice, through DC-mediated deletion of the NF- κ B negative regulatory protein A20 (encoded by *Tnfaip3*). To this aim, they crossed mice with loxP-flanked *Tnfaip3* alleles with mice expressing Cre under the control of a promoter region of *Clec9a* (encoding DNGR1) that has a restricted expression profile in cDCs. Using histology and immunohistology, they found that *Tnfaip3*^{DNGR1} KO mice display pronounced lung accumulation of activated cDC1s, cDC2s and moDCs, accompanied by peribronchial and perivascular infiltration of activated T- and B-cells, macrophages and of IgA-producing plasma cells. Furthermore, they showed that these mice developed spontaneous PH with mild RV hypertrophy. They also noted high levels of IL-1 β , IL-6, IL-10 and TGF β , and high proportions of IL-10- and IFN γ -producing CD4⁺ and CD8⁺ T-cells and of IL-17A-producing CD4⁺ T-cells in *Tnfaip3*^{DNGR1} KO mouse heart and lungs. Using indirect immunofluorescence assay on HEp-2 cells and *Rag1* deficient mice, the authors showed that autoreactive IgA recognizing lung vasculature are present in the serum of *Tnfaip3*^{DNGR1} KO mice. Remarkably, the PH phenotype was markedly attenuated in the groups receiving IL-6 neutralizing antibodies versus the control antibodies.

A key finding of this study was the demonstration that changes in DC composition, maturation, and migration in mice are sufficient to cause structural and functional changes of the pulmonary vasculature. Spontaneous DC activation and subsequently T- and B-cell activation induced by the loss of A20 in DCs were indeed found to be sufficient to produce the PH phenotype in ~50% of *Tnfaip3*^{DNGR1} KO mice in the absence of other stimuli. These findings taken with the observation that arterial DC accumulation precedes vascular and hemodynamic alterations in monocrotaline-injected rats (12), are strong arguments supporting that DCs are critical in the maintenance of immune

surveillance and lung homeostasis, and also in the PAH pathogenesis. Interestingly, mice lacking the DC homing-receptor CCR7 display also a marked lung inflammatory phenotype and develop spontaneous PH (15). Moreover, although anti-IL-6 receptor therapy does not translate into beneficial effects on pulmonary vascular resistance in PAH patients, in this study the anti-IL-6 treatment was associated with a normalization of pulmonary pressures and RV hypertrophy in *Tnfaip3^{DNGR1}* KO mice. Since IL-6 influences antigen-specific immune responses and inflammatory reactions, but also pro-survival signals in pulmonary vascular smooth muscle cells (16), these findings offer new insight into the complexity of the link between dysregulated immunity and adverse PAH pulmonary arterial remodeling.

Although the findings presented in this study are exiting, a number of questions remain. For obscure reasons, only ~50% *Tnfaip3^{DNGR1}* KO mice develop PH with variable phenotypic severity. Because these mice display chronic liver inflammation associated with collagen deposition (17), it would be important to explore possible relationships between these two different manifestations. Similarly, because *Tnfaip3^{DNGR1}* KO mice display RV hypertrophy before hemodynamic changes, further work is also needed to dissect the role of DCs in cardiac remodeling and function. To reinforce the translational relevance of these findings, it would also be important to determine how the local PAH environment and the current therapies affect the NF- κ B pathway and the specific characteristics of DC subsets.

Despite these remaining questions, the observations reported by Thomas Koudstaal and colleagues should encourage a better understanding of the contribution of DCs in PAH. Clarifying these questions would be a milestone in the development of effective anti-inflammatory and immunomodulatory therapies for PAH and other cardiovascular disorders.

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