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Commentary Open Access

Modulation of the CD141/DC-SIGN/CD1c Monocyte by the Airway Epithelium

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Commentary

It has been suggested more than 20 years ago that epithelial cells (ECs) are the major culprit in some lung diseases including asthma. Although their role in chronic lung diseases is undoubtedly unquestionable, the mechanisms by which ECs orchestrate the immune response are far from being fully understood today. Besides the production of mucus, surfactant, and periciliary fluids which have an important innate immune protection [1-3], one of the mechanisms that has earned important recognition concerns the molecular crosstalk between ECs and immune cells such as monocytes and dendritic cells (DCs). However, questions have arisen on how the modulation induced by direct cell contact *vs.* soluble components can be dissected *in vivo*. Recently published aspects regarding the modulation of monocyte derived DCs (ModDCs) by ECs in humans obtained from *in vitro* and *ex vivo* studies will be commented on the forthcoming sections.

Role of the Epithelium Inducing ModDCs

It is widely recognised that during homeostasis ECs produce a broad spectrum of chemokines and growth factors including CCL20, IL-8, MCP-1 and GM-CSF that attract monocytes and are involved in ModDC differentiation, stage in which ModDCs are recognized for maintaining tissue surveillance [4-6]. However, in humans little is known regarding the modulation of monocytes by ECs or whether the epithelium is involved in the transition of monocytes to ModDCs. The recently published characterization of phagocytes in cadaveric nondiseased lungs has contributed to the ability to dissect tissue and blood mononuclear cells. Upon arrival in the lung parenchyma, $CD14^+$ monocytes were shown to undergo an important transformation. Extravascular $CD14^+$ monocytes increased, at different intensities, the expression of HLA-DR, CD206, CD163, CD141, CD11c, CD1c, CD1a and CCR7 when compared to their counterparts in blood [7]. This group of receptors including CD172a and FcεRI have been used to define the ModDC phenotype in humans [8,9]. A similar monocyte derived population expressing $CD14^+$ CD1c and CD141 markers was reported in lung tissues and BALF from healthy individuals, highlighting the fact that this population already exists at steady state and can be modulated by the lung environment [10]. However, it is unclear whether all the monocyte cell surface modulation depends on cell-contact or soluble-derived molecules and what the role of the epithelium could be. Recently, *in vitro* studies have demonstrated that soluble components released by bronchial epithelial cells (BECs) can induce a particular modulation in monocytes observed by an increased expression of CD141, DC-SIGN and CD123 but not of CD1c [6,11]. One particular aspect is that BEC-conditioned media also modulates on monocytes the expression of FLT3 (CD135), a receptor involved in DC differentiation and maintenance in the periphery. This result was of importance because it suggests that the bronchial epithelium at steady state is able to participate in the transition of monocytes towards a ModDC phenotype [11].

Role of EC Soluble Molecules on ModDC Function

Beside the phenotypic modulation, endogenous molecules released constitutively by BECs have shown to be sufficient to induce functional modifications on monocytes. BEC-conditioned monocytes without microbial stimulus released significant amounts of IL-6 and IL-1β and were capable of inducing Th17 cell differentiation. It is currently unknown whether the secreted IL-17 has a protective or a pathogenic role. Nevertheless, since IL-23 was not a cytokine produced by conditioned monocytes even upon LPS stimulation, it is thought that the induced IL-17 might have a homeostatic immune function [11]. Indeed, numerous studies have shown that BEC-soluble components have an important anti-inflammatory activity. The effect has been better described in human and mouse GM-CSF/IL-4-ModDCs in which BEC-conditioned ModDCs increased the expression of IL-10 upon LPS stimulation, but reduced the expression of IL-12 and TNF-α. Furthermore, conditioned ModDCs showed a decreased capacity to induce T cell proliferation, but they are able to expand Tr1 cells and Tregs [12,13]. With regard to monocytes, it has been reported that BEC-conditioned monocytes also failed to induce inflammatory cytokines such as TNF-α, IL-12p70 and IL-23 upon stimulation with LPS, poly-IC, and ssRNA. Additionally, they are not capable of upregulating the maturation markers CD80, CD83 and CD86 upon the different TLR-stimulations [6,14]. Unexpectedly, these tolerogenic features were still maintained in monocytes cultured in conditioned media obtained from respiratory syncytial virus (RSV)-infected airway epithelial cells. These results highlighted the capacity of the epithelial cell soluble components in maintaining homeostasis despite the large amounts of cytokines and growth factors released by RSV-infected airway epithelial cells. Several cytokines and metabolites released by EC such as IL-10, TGF-β, retinoic and acid and Prostaglandin E2 (PGE2) have been associated with the anti-inflammatory role of ECs [15,16]. PGE2, for example, was shown to specifically dampen LPS-induced inflammatory cytokine release in monocytes and ModDCs [12].

Role of EC-ModDC Direct Cell Contact in Inflammation

In contrast to the tolerogenic state of ModDCs induced by soluble molecules released by EC at steady state, the modulation induced by cell-cell contact has shown an opposite effect. ModDCs cultured in contact with airway epithelial cells have shown to upregulate the expression of co-stimulatory markers HLA-DR, CD80, CD86 as well as increased the release of chemokines involved in Th1 cell recruitment [17,18]. Monocytes or ModDCs in co-cultures with ECs also demonstrated an enhanced responsiveness to LPS stimulation as well as to rhinovirus and RSV infection [14,17-19]. It has been interesting to observe that in *ex vivo* experiments, co-cultures of ModDCs with primary BECs from control subjects upregulated the release of CXCL-10 and CCL2 chemoattractant proteins and to some extent IL-8 and TLSP [20]. However, co-cultures of ModDCs with primary BECs from patients with severe asthma significantly upregulated IL-8, TSLP and IL-33 compared to those of the co-cultures of the same ModDCs with control BECs, suggesting a specific difference of EC activation in asthma patients [20].

These results highlighted the complex modulation induced by ECs even at steady state in ModDC. These results have led us to speculate that both soluble and cell-contact components may be involved in a specific transformation of monocytes towards a ModDC phenotype, which is particularly observed by the upregulation of CD1c, CD141, DC-SIGN, CD206 and FLT3 on CD14 monocytes. However, soluble components of BECs seem to play a major role in maintaining ModDCs hyporesponsiveness or tolerant state to different TLR-ligands. It can be speculated that the cell contact reveals the capacity of ModDCs to induce inflammation and increase the ability of cells to mount a rapid immune response against pathogens. Furthermore, in patients with chronic lung diseases such as asthma, in whom the epithelial activation threshold is altered, the direct cell contact may contribute to the exaggerated inflammatory response.

MoDCs in Chronic Lung Diseases

ModDCs in the lungs have been poorly investigated due to the lack of specific markers. Nevertheless, HLA-DR$^+$CD14$^+$ monocytes that express the DC receptors CD1c and CD141 have been characterized as ModDCs. Recently, an important percentage of CD14$^+$monocytes that express CD141$^+$DC-SIGN$^+$CD1c$^+$ markers were found to be increased in the BALF of patients with sarcoidosis [11]. Similarly, CD14$^+$ monocytes expressing CD1c$^+$FceRI$^+$ markers were shown to be markedly increase in tissues obtained from explanted lungs of patients who developed idiopatic pulmonary fibrosis, hypersensitivity pneumonitis and also, but to a lesser extent, in COPD [21]. It has been suggested that this population may play a role in the pathogenesis of these chronic lung diseases.

Does the CD141/DC-SIGN/CD1c monocyte subset represent a dysregulated mechanism in chronic inflammatory lung disorders? With regard to monocytes, *in vivo* and *in vitro* studies have begun to shed light on a role that ModDCs are most probably involved in: regulation of adaptive immunity in addition to providing anti- and pro-inflammatory mediators to their environment. However, it would be important to look at the epithelial aspect of the question and focus on the contact dependent regulation. Although a variety of airway EC sources and cell cultures have been use and some of these studies have shown contradictory results, there are three factors that we consider highly relevant in the field. 1. The epithelium is able to modulate monocyte differentiation and function; 2. The direct contact between ModDC and ECs showed to be a key factor in the amplification of immune response. 3. The accumulation of pulmonary ModDCs has been shown to be associated with lung inflammation in chronic lung diseases. Thus, these important evidences might indicate that the ModDC-EC direct contact may play a major role in the accumulation of ModDCs in the lungs. The goal now is to identify the involvement of CD141, DC-SIGN, CD206 and CD1c receptors during cell-cell direct contact, as well as to determine how the activation of adhesion molecules such as integrins, cadherins and C-type lectins may modulate the activation threshold of ModDC at steady state and inflammation. The identification of these pathways is needed to target specifically the receptor or molecule on ModDCs, and hence limit their migration into the tissue or retention into the airways and decrease the burden of chronic lung diseases.

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