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Pillars of Immunology

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Monocyte-Derived Dendritic Cells: A Transendothelial Trip Launches the Quest To Understand Heterogeneity in the APC Family

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The paper featured in *Pillars of Immunology* in this issue of *The Journal of Immunology*, "Differentiation of Monocytes into Dendritic Cells in a Model of Transendothelial Trafficking" by Randolph et al. (1), was published in *Science* in 1998. This paper revealed that monocytes could respond to a variety of cues, including noncytokine, to differentiate into dendritic cells.

APCs are an essential link between the point of exposure to a pathogen or insult and the army of immune cells that launch a specific attack to remove invaders from the body. Immune protection depends critically on sparsely distributed specialized cells—dendritic cells—which can ingest and display Ags on their surface, allowing them to activate adaptive immune cells. A key step in this activation process depends on the ability of the dendritic cell to migrate from peripheral tissues, where they encounter Ags, to a regional lymph node, where T cells reside awaiting their instruction. Dendritic cells were first described by Steinman and Cohn in 1973 (2). Ralph Steinman was later awarded the Nobel Prize in Physiology or Medicine (2011) for his dogged pursuit to unravel the critical pathways by which this novel cell type could trigger the adaptive immune system.

In the early days, the progenitor cells and signals that give rise to monocytes and dendritic cells were largely unknown, and it was quite unclear how one could make these cells efficiently in the laboratory. Sallusto and Lanzavecchia, however, had already shown that dendritic cells capable of presenting Ags could be generated in vitro from blood mononuclear cells by supplementing cultures with GM-CSF and IL-4 (3). This system provided a very significant step forward for the field. Nevertheless, amplification of these cells was relatively slow and relied on the continuous supply of exogenous cytokines, leaving some investigators questioning whether it was a process that normally occurred in vivo, and if so, when? Equally unclear was how dendritic cells accessed the peripheral tissues to allow subsequent transmission of signals to adaptive immune cells. It was appreciated that dendritic cells could gain access to lymphoid tissues via either the blood or lymph (4). Despite this, it was completely unknown how dendritic cells then enter the afferent lymphatic vessels, which are pivotal for collecting interstitial fluid and cells from the tissues, to travel into the lymph node.

Randolph et al. (1) investigated the migration of monocytes through the vascular endothelium in vitro. They identified that these monocytes were capable of differentiating very rapidly into dendritic-type cells through a process that did not require the massive amounts of exogenous cytokines necessary in previous culture systems. The identified abluminal-to-luminal migration pathway mimicked that described for migratory dendritic cells as they navigated their way from the peripheral tissues into the lymphatics. It is this fine network of lymphatics that would convey them to the draining lymph nodes to interact with T cells. The origins of lymph-borne dendritic cells, at the time often referred to as veiled cells due to their long cellular processes, was completely unknown. Now it seemed that an apparently homogenous population of blood-derived monocytes had two, not one, potential fate outcomes: dendritic cells and macrophages. This differentiation step unexpectedly depended on the processes of phagocytosis and transendothelial transport, and highlighted that tissue-specific cues could play a central role in driving the developmental fates of monocytes, dendritic cells, and macrophages.

Dendritic processes, in all their beauty, were considered a definitive hallmark of classical dendritic cells. Confusingly, these projections now also appeared on monocyte-derived dendritic cells when exposed to a stimulus. This made these monocyte-derived dendritic cells almost impossible to distinguish from the classical Steinman dendritic cells. Indeed, initially this must have been very puzzling to Ralph Steinman and his colleagues in the laboratory, who had taken great pains to demonstrate that classical dendritic cells were a unique cell type that "do not represent morphological variants of either lymphocytes or macrophages" but exhibit exceptional Ag presentation properties (5). Paradoxically, the evidence of Randolph et al. (1) now suggested that dendritic cells might actually be related to monocytes and macrophages.

Our understanding of monocytes and dendritic cells has progressed significantly since this initial work. It is now clear that these two cell types are quite distinct lineages, although the origins of the various mononuclear cells have been vigorously debated. This is attributable to the fact that both subsets are highly heterogeneous; they are composed of multiple subsets and exhibit significantly overlapping phenotypic features. Thus, they are not readily distinguishable from each other based on a single marker or attribute.

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Dendritic cells are diverse and can develop into very specialized subpopulations that localize to both lymphoid and nonlymphoid tissues. They arise from a specific progenitor, the predendritic cell, found in the bone marrow and spleen, which has lost the capacity to give rise to monocytes (6–8). They also depend critically on the nonredundant role of Fms-like tyrosine kinase receptor 3 and Flt3 ligand for their differentiation and maintenance, both in vitro and in vivo (9–11). Intriguingly though, at steady-state, most tissue-resident APCs are classical dendritic cells and are not derived from monocytes (6, 12, 13).

Monocytes are found in the circulation, and can exit the blood and enter the tissues under inflammatory conditions and form monocyte-derived dendritic cells and macrophages (12, 14–16). The monocyte-derived dendritic cells exhibit many dendritic cell–like properties, including the ability to process and present Ag to T cells, whereas the macrophage progeny generally take up long-term residency in tissues (and are also known as tissue-resident macrophages). Both of these cell types were generated in the cultures of Randolph et al. (1) with the activated monocytes developing dendrites. These cells are derived from the macrophage/dendritic cell progenitor, which is now known to only give rise to the monocyte and macrophage lineages, rather than classical dendritic cells (17) as was initially assumed. This progenitor is found in the bone marrow and expresses the monocyte-associated chemokine receptor CX_3CR1 (also known as fractalkine) (18). Circulating monocytes can constitutively traffic to the skin and lungs and recirculate through the lymph nodes, but at steady-state, relatively few of them differentiate into dendritic cells or tissue-resident macrophages (19). This implies that circulating monocytes are poised to rapidly differentiate in response to infection, inflammation, and trauma, and quickly augment defense against an invader as necessary effector cells. In other settings, monocytes can also initiate tissue repair such as occurs during ischemia where they express vascular endothelial growth factor that promotes myofibroblast accumulation, angiogenesis, and collagen deposition (20).

In summary, the discovery of Randolph et al. (1) has been instrumental in laying the groundwork for understanding the immense diversity that exists in monocytes and dendritic cells. It has taken the better part of the intervening 19 y for very detailed, tedious, and elegant dissection of the monocyte/dendritic cell network by multiple laboratories worldwide to unravel the origins, development, and diverse and complex functions of dendritic cells, inflammatory monocytes, and macrophages. These contributions have shed light on the division of labor that characterizes these specific subsets in effecting immune protection, tolerance, and tissue repair. It also now opens the doorway for new approaches to treatments for immunological diseases where the field has been stymied and perplexed that a one-hit approach targeting dendritic cells and monocytes as a single cell type have almost universally failed.

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Disclosures

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