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Pillars of Immunology

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There was a time when consensus on the existence of dendritic cells (DCs) was tenuous, when many researchers in the field did not believe that "professional" APCs are involved in the priming of T cell responses. Until the late 1980s, the cellular basis that links Ags, which are generally present in tissues (e.g., pathogens or infected cells) to the initiation of immune responses (which occurs in lymph nodes) was unclear. Everybody assumed that soluble Ags drained from tissues to lymph nodes through the lymph, but the question was more delicate for cell-associated Ags. In both cases, the nature of the cells that present Ags to naive T cells for the initiation of T cell immune responses in lymph nodes was an open question.

The 1980s witnessed a change in how we understand the initiation of adaptive immune responses. This change was initiated by the discovery of DCs by Steinman and Cohn (1). It took over 15 y before Steinman proposed a unifying model: DCs pick up Ags by endocytosis and phagocytosis in tissues and then migrate through the lymph to lymph nodes, where they present Ags to naive T cells. This model was based largely on ex vivo experiments showing that, after extraction from tissues (mainly the skin), DCs spontaneously change phenotype, lose endocytic capacities, and gain the ability to costimulate and activate T cells (2). This spontaneous change in phenotype after isolation suggested that DCs existed in two alternative functional states that were rapidly referred to as "immature" and "mature."

Maturation is now known to be a common property of all DC types and subtypes. Indeed, DCs do not represent a homogeneous lineage; instead, they are a set of heterogeneous populations of cells with common characteristics. Spectacular advances in understanding DC ontogeny have been made in the last 10 y, but we still do not fully understand the molecular programs involved. We know that DCs include multiple subpopulations that differentiate in tissues and then migrate to lymph nodes (migratory DCs) or differentiate and reside in lymphoid organs (resident DCs). In the early 1990s, it had already been shown that DCs derive from bone marrow precursors (3), although the precise precursor was still unknown. However, like the primary DCs isolated from tissues (1, 4), in vitro–generated mouse DCs spontaneously matured in culture (5), hampering the molecular characterization of the maturation process.

In this context, the featured article by Sallusto and Lanzavecchia (6), published in 1994, made at least three critical contributions to the field. First, it showed that cells with all of the morphological and functional characteristics of DCs can develop from adult blood monocytes. How and why were these monocyte-derived cells classified as DCs? From very early on, Steinman (2) proposed a functional definition of DCs as cells whose "distinctive role is to initiate T-dependent responses from quiescent lymphocytes." Indeed, the monocyte-derived DCs generated by Sallusto and Lanzavecchia primed resting cord blood T cells to actively proliferate. The monocyte-derived cells were also highly phagocytic and lost their uptake capacities upon maturation while gaining expression of costimulatory molecules and T cell priming capacity. These characteristics very precisely match those of mouse tissue–derived DCs. The finding that DCs can differentiate from monocytes was at that time, and still is, quite confusing.

Are monocyte-derived cells "real" DCs? This question still preoccupies the field, and the debate on the subject is still active. Some researchers believe that the name "DC" should be restricted to cells derived from dedicated precursors, pre-DCs, whereas all cells derived from monocytes should be referred to as monocyte-derived cells (7, 8). This does not exclude that monocytes can differentiate into cells that have macrophage- or DC-like functions. A unifying view, which is gaining increasing experimental support, is that DCs and macrophages have dedicated precursors in adults and embryos, respectively, whereas monocytes can adopt either fate under specific tissue environments, such as inflammation or damage. Alternative development of monocytes into macrophage- or DC-like cells has been shown, but the precise classification of the resulting cells is still debated. Hopefully, identification of the molecular mechanisms that control the two alternative differentiation pathways will clarify the issue.

Second, Sallusto and Lanzavecchia provided a unique culture system to generate immature DCs in vitro, paving the road to understanding the biology of DC maturation. Monocyte-derived human immature DCs presented all of the characteristics previously reported for mouse tissue DCs (i.e., high endocytic capacity and low costimulation). Sallusto and Lanzavecchia showed that TNF-α (an inflammatory cytokine) induced the very same changes in monocyte-derived DCs that were reported previously as a "spontaneous" maturation in mouse DCs (9). Therefore, DC maturation is not only a spontaneous process, but it is a regulated response to specific inflammatory stimuli. These results confirmed the hypothesis that DCs exist under two alternative developmental stages: immature and mature, with distinct markers, morphologies,

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Abbreviation used in this article: DC, dendritic cell.

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and functions. Importantly, they showed that inflammation controls the transition between the two maturation stages. This paradigm will have strong impact on future research in immunology (including, for example, in vaccination or autoimmunity). This idea still guides research in the field over 20 y later, even if the precise molecular programs at play during DC maturation are still incompletely understood.

Indeed, we know today that DC maturation can be triggered by multiple stimuli, including pathogen- and danger-associated molecular patterns, and that the ability to developmentally respond to these stimuli is a common feature of all DCs, even if the maturation responses also depend on the nature of the maturation stimuli and types of DCs (10). Maturation is a true developmental, irreversible response, and not just a transient activation of the cells. The outcome of the maturation process includes a "core response" that endows DCs with all the functional attributes to find rare Ag-specific T cells and prime them (active migration, adhesion, and costimulation). Other functional consequences of DC maturation are specific to either a subgroup of maturation stimuli, or a subtype of DCs. These more "specific" responses to maturation stimuli are mostly secretion of specific cytokines or expression of surface costimulatory molecules. They probably do not determine naive T cell priming per se, but orient T cell development to different fates (Th1, Th2, Tregs, CTLs, etc.).

Third, Sallusto and Lanzavecchia showed that DCs use specific receptors to take up Ags and efficiently present them to $CD4^+$ T cells. Building on their previous findings that B cells present cognate Ags with efficacies up to several logs higher than non-specific Ags (11), they compared soluble tetanus toxin with the same Ag complexed to specific IgG to form immune complexes. They showed that IgG-complexed Ags are presented to T cells at concentrations up to three logs lower than soluble Ag. These results establish a link between Ag-specific immune responses (Abs) and Ag presentation by DCs, providing a molecular mechanism for the preferential presentation of non-self Ags.

Most importantly, this paper showed that efficient Ag presentation is lost after DCs are treated with TNF-α and become mature. At the same time, the authors showed that TNF-α-treated DCs induce more efficient MLR (a direct consequence of T cell stimulation that does not require processing of endocytosed Ags). These results established what later became an important paradigm in DC biology: maturation induces a shift between high Ag uptake and processing/low T cell activation (immature DCs), and low Ag uptake/highly efficient T cell activation (mature DCs). Reduced Ag presentation in mature DCs is largely due to decreased Ag uptake, and also a consequence of reduced FcγR expression (in the system used in this article). Changes in the intracellular distribution of MHC class II molecules are mentioned in the paper, but not actually documented (the results were published a few years later) (12). Although reduced Ag processing had been shown after migration to lymph nodes or "spontaneous" maturation in vitro in mouse DCs, the present paper introduced the important notion that TNF-α produced at the site of infection can trigger increased DC migration to lymph nodes, where DCs initiate adaptive T cell-mediated immune responses.

This paper represented an important step in our understanding of DC biology. It came at a time when the importance of DCs was still questioned, and provided spectacular confirmation in humans of different critical properties of mouse DCs. It also provided the first demonstration that inflammatory cytokines induce DC maturation, and thereby control the initiation of T cell priming by DCs. The idea that DCs provide a link between innate and adaptive immune responses had been proposed earlier (2), but the results from Sallusto and Lanzavecchia provided precise cellular bases for that link. These findings not only established some of the most solid roots for future fundamental research in the field, but they also guided translational use of DCs and adjuvants in vaccination, both for cancer and infectious diseases.

Disclosures

The authors have no financial conflicts of interest.

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