Dendritic cell subsets: the ultimate T cell differentiation decision makers?


Abstract
It is not known whether subsets of dendritic cells provide different cytokine microenvironments that determine the differentiation of either type-1 T helper (Th1) or Th2 cells. Human monocyte (pDC1)-derived dendritic cells (DC1) were found to induce Th1 differentiation, whereas dendritic cells (DC2) derived from CD4+CD3–CD11c– plasmacytoid cells (pDC2) induced Th2 differentiation by use of a mechanism unaffected by interleukin-4 (IL-4) or IL-12. The Th2 cytokine IL-4 enhanced DC1 maturation and killed pDC2, an effect potentiated by IL-10 but blocked by CD40 ligand and interferon-gamma. Thus, a negative feedback loop from the mature T helper cells may selectively inhibit prolonged Th1 or Th2 responses by regulating survival of the appropriate dendritic cell subset.

Comment
Identifying the factors that determine Th1 versus Th2 lymphocyte differentiation is the goal of many scientists, and in recent years it seemed that a modicum of understanding was finally within reach. Contributions from many different sources have helped to determine beyond reasonable doubt that it is the local cytokine microenvironment that plays the most important role in directing T helper cell differentiation during the immune response. Text books and journals are full of good examples of how Th0 cells are directed towards a Th1 phenotype by cytokines such as interleukin (IL) 12, whereas cytokines like IL-4 promote differentiation towards a Th2 phenotype. Furthermore, it is well accepted that the Th1 cells produce cytokines that will encourage more Th0 cells towards a Th1 differentiation pathway, and likewise the Th2 cells produce cytokines that direct more Th0 cells towards a Th2 differentiation pathway. Although these positive autocrine mechanisms make sense in the context of an ongoing immune response, the initial effects which cause a pool of naive T cells to be driven selectively down a particular pathway are still not well understood. A recent study by Rissoan and colleagues may have brought us one step closer to understanding this phenomenon.

Rissoan et al make a very good argument that Th cell differentiation is controlled by specific dendritic cell (DC) subsets. The authors describe two major DC subsets—monocyte derived DC1 cells and plasmacytoid derived DC2 cells which, as their names suggest, are purported to drive Th1 and Th2 differentiation, respectively. These DC subsets are apparently able to drive differentiation of naïve Th0 cells down the Th1 or Th2 pathways independently of the cytokines that were traditionally believed to be important. DC1 cells secrete copious amounts of IL-12, thus creating a microenvironment conducive to Th1 cell differentiation, but the authors clearly show that DC1 cells can induce Th1 differentiation even in the absence of IL-12. A striking argument for Th differentiation being mediated by specific interactions with DC subsets and not cytokines comes from analysis of DC2 cells. DC2 cells selectively direct Th0 cells towards a Th2 phenotype, yet seem to be totally devoid of IL-4. Although the selectivity of the DC1 and DC2 subsets for driving Th1 and Th2 responses seems to be definitive, there is as yet no insight into the precise mechanism driving the differentiation. It will be interesting to learn whether these DC subsets mediate their activity via direct cell–cell contact or via novel soluble mediators.

A fascinating twist to the story comes when the authors provide evidence of a negative feedback mechanism to maintain the balance between Th1 and Th2 responses. DC1 maturation and survival seem to be enhanced by the Th2 cytokine IL-4, whereas DC2 maturation and survival is inhibited by the Th2 cytokines IL-4 and IL-10. In fact, IL-4 and IL-10 appear to induce apoptosis of DC2 precursor cells. The authors also show that CD40L can prevent IL-4 induced killing of mature DC2 cells, presumably a safety mechanism to prevent the accidental death of a DC once it is engaged with a T cell. Interferon (IFN) γ, a Th1 cytokine, seems to promote the survival and maturation of DC2 cells. The overall result is a rather strange negative regulation which deviates away from Th1 cell development during Th1 responses and from Th2 cell development during Th2 responses. Overall, these new data provide evidence of yet another tier of control in the regulation of the homoeostatic balance between Th1 and Th2 responses.

Why should gastroenterologists and mucosal immunologists be interested in DC1 and DC2 cells? Elucidating the mechanisms regulating active immunity versus tolerance in the intestine has proved to be difficult. Quite how mucosal immune cells decide when to mount an active response to a pathogenic micro-organism while at the same time remaining tolerant to food proteins and the enteric flora is a mystery that still needs to be solved. It is probable that the selectivity of mucosal immune responsiveness is controlled by the precise nature of the antigen presenting cells in the organised gut associated lymphoid tissue. There are many DCs situated throughout all of the gut compartments, although there is little evidence that DCs in the gut are grossly different to DCs elsewhere. Functionally, it is of course possible that gut DCs may behave differently from their peripheral counterparts, as has been shown for DCs residing in the lung. It is also feasible that DC1 and DC2 cells reside in different locations within the gut itself. Perhaps one subset of DC localises beneath M cells in the dome region of Peyer’s patches, picks up antigen derived from invading pathogens and then migrates towards the
interfollicular T cell area of the Peyer’s patch to direct differentiation. The other DC subset might preferentially localise beneath the enterocytes in the lamina propria, pick up antigen that has passed through the epithelial barrier and effect differentiation of another type of response. In mice it has been shown that DCs in the dome region of the Peyer’s patch have a different phenotype to those in the interfollicular areas, and it will be interesting to learn whether these correlate with human DC subsets. With more reagents becoming available, it should be relatively easy to look at whether DC1 and DC2 cells localise to discrete compartments of the gut in humans.

An alternative hypothesis for how DC subsets specifically direct intestinal responses would be if DC1 and DC2 cells had different antigen capture capabilities. Perhaps DC1 cells preferentially capture particulate antigens derived from invading pathogens and thus direct potent inflammatory Th1 responses, whereas DC2 cells preferentially capture soluble food proteins and initiate Th2 type responses. Another potential explanation for the biasing of responses by DC1 and DC2 cells might arise from selective expression of chemokines. The gut is a particularly rich source of chemokines, and it is likely that there are strong gradients even in the absence of inflammatory challenge. It is not yet clear whether DC1 and DC2 cells bear sets of chemokine receptors which might direct them to different gut localities, or whether the subsets themselves are able to produce chemokines that effect differential function on naïve cells. Either way, there is evidence that DCs can both respond to and produce chemokines. Again, the chemokine and chemokine receptor profile of DC1 and DC2 cells should be relatively easy to resolve.

In summary, these studies have provided us with new avenues for research. Understanding the role mucosal DCs play in determining selective T cell responses in the gut will probably prove to be a particularly fascinating area of study. It may now be pertinent to analyse gut DC subpopulations in healthy and diseased people to determine whether the adverse immune responses that lead to inflammatory bowel disease or food allergy arise because of an imbalance in the DC subsets driving the Th differentiation process.

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