Commentary

The Role of B Cells in the Programming of T Cells for IL-4 Synthesis

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In this issue of the Journal of Experimental Medicine, Stockinger and her colleagues describe their work on the role of B cells, dendritic cells, and macrophages in the induction of IL-4 synthesis by T cells (1). Two clear conclusions emerged from this study. First, whereas there was a requirement for DC in the primary activation of T cells, B cells played an essential role in the induction of IL-4 gene expression by the T cells that provided helper activity for antibody synthesis. Second, DC and macrophages together were the most potent inducers of IFN-γ.

As the authors remark, experiments to establish the role of B cells in the programming of T cells to produce IL-4 have given apparently conflicting results, and the subject has an interesting history. Early experiments in vitro (for review see 2) showed that the induction of IL-4–producing T cells required the presence of IL-4 in the culture medium. Were this to be the case in vivo, then there would be the problem of how IL-4 synthesis was ever initiated. Whereas it was recognized that basophils produced IL-4 (3), they were not attractive candidates for the apparently essential initial source of IL-4, because their anatomical location was inappropriate to such a role. However, two possible alternative solutions were apparent.

First, it was shown that the activation of Th-2 T cell clones in vitro was dependent on the presence of B cells, whereas the proliferation of Th-1 clones was favored by costimulation with adherent cells (4). These observations led to the hypothesis that both Th-1 and Th-2 clones derived from a common precursor but that after primary activation, the subsequent contact with different types of APC determined which way the differentiation proceeded (4). Support for these in vitro experiments came from earlier experiments in vivo that had shown that the polyclonal activation of murine B cells by the injection of rabbit anti–mouse IgD induced high levels of IL-4 synthesis and IgE production (5).

Second, although these experiments seemed to establish a role for B cells in the induction of IL-4 synthesis by T cells, they did not exclude other mechanisms for such induction. B cells might be sufficient, but were they necessary? The discovery of a small subset of murine thymocytes that promptly secreted IL-4 on activation and that expressed the NK cell antigen NK1.1 (6) indicated that an atypical subset of T cells existed that were already programmed for the synthesis of this cytokine. These cells had other unusual characteristics; some were $CD4^+$, whereas others were $CD4^-CD8^-$, but all were apparently restricted to the non-MHC–linked, class I–like antigen, CD1. The capacity of these cells to produce large amounts of IL-4 on primary activation has lead to the suggestion that they may promote Th-2–like T cell responses (7), but currently there is no established role for these cells (6). Further, recent studies on mice in which class II MHC antigen expression has been eliminated by homologous recombination have demonstrated that these animals contain CD1-restricted TCR-α/β^+ $CD4^+$ T cells, only some of which express NK1.1 (8). Consequently, it may be that in normal mice there are more CD1-restricted T cells than have been recognized hitherto, and this possibility makes identification of the function of these cells a pressing matter. However, with regard to the question of the role of B cells in the induction of T cell cytokines, three features of these atypical T cells were remarkable: first, some were found in the B cell areas of lymphoid tissue; second, of seven T cell lines derived from these cells, two were activated by B cells; third, the activation of these cells in vitro with B cells induced the latter to proliferate but not to terminally differentiate into antibody-secreting cells (9). These results await a full interpretation, but since it has been shown that B cell activation by cross-linking of surface Ig primes B cells for IL-4–induced proliferation (10) and that activated B cells upregulate their expression of CD1 (11), it is reasonable to suggest that the physiological role of the CD1-restricted $CD4^+$ T cells in B cell follicles is to induce the expansion of antigen-activated B cells. Such a mechanism retains the classical T cell control of antibody synthesis, since the CD1-restricted T cells can induce B cell proliferation but not antibody synthesis. The physiological significance of such a process is clear: it implies that B cells, like T cells, may undergo clonal expansion before the two cell types interact, the result being that the probability that such antigen-specific interactions will actually occur is greatly augmented.

This hypothesis would predict that antibody synthesis in animals that lack CD1-restricted T cells would be greatly impaired. In the experiments of Stockinger and her coworkers, the mice used were transgenic for the T cell receptor that recognized a peptide fragment of murine C5 in the context of $I\text{-}E^k$, and consequently they would be deficient in CD1-restricted T cells. Interestingly, these mice,

which were genetically lacking lacking C5 and therefore are not tolerant to it, were unable to make an antibody response to this antigen when immunized, whereas nontransgenic congenic mice were able to do so. This result is consistent with a role for CD1-restricted T cells in antibody synthesis, but other explanations are also possible. As Stockinger observes, in the TCR transgenic mice the C5-specific T cells greatly outnumber any C5-specific B cells, and this imbalance may have impaired antibody production, possibly by the hyperproduction of IFN-γ (12).

However, in two experimental systems it has proved possible to induce IL-4 synthesis in the absence of B cells. In the first of these, SCID mice were injected with highly purified T cells from normal donors and immunized with KHL in alum. Control SCID mice received both B and T cells before immunization (13). The induction of IL-4 synthesis was found to be independent of the presence of B cells in the donor inoculum. Furthermore, it was shown that normal mice could be primed for IL-4 synthesis by injecting them with purified DCs pulsed in vitro with KLH. Whereas these results appeared to show that B cells were not essential for priming T cells for IL-4 synthesis, it could be argued that in all these experiments the T cells had already been primed by cross-reactive environmental antigens. Given the high level of cross-reactivity among T cells (14), this possibility cannot be completely dismissed. However, such a caveat could not apply to the second series of experiments. In these, mice rendered genetically B cell–deficient by the introduction of a deletion mutation in the transmembrane region of B cell surface IgM were immunized with KLH in CFA. As with the SCID mice, priming for IL-4 synthesis in these deletion mutants was comparable to that of controls (15). Although these B cell–deficient mice have not been examined for their content of CD1-restricted $CD4^+$ T cells, there is no reason at present to suppose that these cells are also lacking, and they remain therefore a possible explanation for the apparent difference between the TCR transgenic experiments of Stockinger and the experiments with B cell–deficient mice.

If this explanation proves to be the case, are we able to conclude that there are at least two ways that T cells may be induced to differentiate into IL-4–secreting cells with one depending only on B cells and the other on CD1-restricted, IL-4–producing T cells? At present this question remains to be resolved. In the TCR transgenic mice of Stockinger and her colleagues, the T cells expressing the TCR transgene were induced into IL-4 gene expression in vitro by culturing them with specific antigen in the presence of DCs and B cells that had been activated with LPS. Further, in the in vivo experiments, B cells primed in nontransgenic donors were used to induce IL-4 synthesis in the TCR transgenic T cells. These experiments lead to an important conclusion, specifically, that after primary B cell activation has taken place, these cells are competent to induce IL-4 synthesis in T cells. However, the experiments do not address the question of whether B cell priming for T cell–dependent responses is itself an autonomous function of naive resting B cells requiring only antigen. An alternate view might be that such priming requires the clonal expansion of B cells driven by IL-4 produced by CD1-restricted T cells. Further developments in this very active field are anticipated with interest.

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Note added in proof: Direct evidence for the involvement of $CD4^+$, $NK.1.1^+$ T cells in the induction of IL-4–dependent responses has been reported. (Yoshimoto, T., A. Bendelac, J. Hu-Li, and W.E. Paul. 1995. Abstract IX International Congress of Immunology. San Francisco, CA.) The absence of $CD4^+$, $NK.1.1^+$ T cells in $\beta 2\text{-}m^{-/-}$ mice accounts for their failure to produce IgE in response to anti-IgD.

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