Reply to Dr. Woodward

Dear Editor,

Dr. Woodward questioned whether the results of our study (1) can address questions specific to dendritic cells, or any other type of specific antigen-presenting cell. In particular, he expressed concern about our finding (Table 2) that 3.1 and 2.4% of nucleated spleen cells from control and malnourished mice, respectively, were dendritic cells. He contended that the number of spleen dendritic cells should be 0.5–1.0% of nucleated spleen cells. However, other investigators have reported various frequencies of dendritic cells. Roberts et al. (2) and Abe et al. (3) detected 2.39 ± 0.48% of CD11c+ highly purified spleen dendritic cells and 3.95% of CD11c+, MHC class II+ spleen dendritic cells, respectively, in nucleated spleen cells of normal mice. Therefore, our results are consistent with published data.

Dr. Woodward also suggested that our assay of antigen-presenting cells may not be specific to dendritic cells. Spleen dendritic cell populations may contain variable percentages of T cells, B cells, macrophages, and natural killer cells, when density centrifugation and adherence steps are used for isolation. Accordingly, dendritic cells, as well as contaminating cells, may influence cytokine production and the proliferation of hepatitis B surface antigen (HBsAg)-specific T cells. However, we found that the proliferative capacities of B cells and T cells were similar in malnourished and control mice. To verify that dendritic cells were mainly, if not solely, responsible for diminished immune responses in malnourished mice, we also provided data from an in vitro study. We prepared HBsAg-pulsed dendritic cells by culturing spleen dendritic cells with HBsAg in vitro. It is known that mainly dendritic cells, but not other contaminating cells, internalize antigens, process them at their endosomal compartments, and express antigenic peptides on their surface. In comparison to HBsAg-pulsed dendritic cells from control mice, those from malnourished mice had significantly lower capacity to stimulate HBsAg-specific T cells. This supports our concept that impaired antigen processing and presenting capacities of spleen dendritic cells from malnourished mice were mainly responsible for the impaired antigen-specific immune responses of these mice.

Finally, we would like to mention the data of an in vivo study in which control mice and malnourished mice were immunized with a vaccine containing HBsAg to induce HBsAg-specific primary humoral and cellular immune responses. Contaminating cells in a spleen dendritic cell population may induce antigen-specific memory responses, but only dendritic cells are endowed with an excellent capacity to induce antigen-specific primary immune responses. Immunization with HBsAg resulted in anti-HBs production in all control mice (10 of 10), with high levels of anti-HBs (138.6 ± 51.3 IU/L, n = 10). However, very low levels of anti-HBs (8.3 ± 5.5 IU/L, n = 10) were detected in only 2 of 10 malnourished mice. Also, the levels of HBsAg-specific primary cellular immune responses were significantly diminished in malnourished mice compared with control mice. These data indicate that disruption of dendritic cell function in malnourished mice contributed to impaired antigen-specific immune responses.

We recently isolated 95% pure CD11c+ spleen dendritic cells and CD11c+ liver dendritic cells from malnourished mice and control mice using magnetic beads, as described previously (4). Highly purified CD11c+ dendritic cells from the spleen and the liver from malnourished mice exhibited lower cytokine production and impaired T cell stimulatory capacities than those from control mice (our unpublished data).

Conzen and Janeway (5) reported that chronic murine protein deficiency reduced the antigen presenting capacity of the dendritic cell compartment in vitro. In our study, we found that antigen-specific immune responses in vivo are also diminished in malnourished mice. Subsequently, we have shown that dendritic cells are mainly responsible for impaired antigen-specific immune responses of malnourished mice. We conclude that the impact of nutrition on functional capacities of human dendritic cells should be studied in detail. This may reveal a new field of dendritic cell-based interventional strategies against nutritional anomalies, because we have recently reported that human blood dendritic cells (partially purified) are safe and can overcome immune response defects in immune-competent subjects, such as human hepatitis B vaccine nonresponders (6).


Literature Cited