Response

Recipient plasmacytoid dendritic cells and graft-versus-host disease

The issues raised by Markey et al are important and help to further clarify the role of plasmacytoid dendritic cells (pDCs) in graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HSCT).[1] They found that recipient pDCs were highly sensitive to myeloablative total body irradiation (TBI) and were hardly detectable in the spleen and bone marrow 24 hours after TBI. In our experiments, pDCs were detectable in the spleen, lymph nodes, and bone marrow 10 hours after TBI but, consistent with the observation of Markey et al, were not detectable at 25 hours. It has been shown that conventional DCs (cDCs) are also sensitive to irradiation; DCs disappear quickly within 5 days after TBI.[1] Paradoxically, TBI induces activation of preterminal DCs, resulting in donor T-cell activation to initiate GVHD before their disappearance.[2] This is not surprising because only brief contact between naive T cells and cDCs or mature pDCs for several hours in lymph nodes is sufficient to generate antigen-specific effector T cells.[3,4]

The aim of our study was to determine whether pDCs could have the ability to mediate tolerance after allogeneic HSCT as in cardiac allografts[5] or to induce GVHD in the absence of cDCs. To address this issue, pDCs were injected into major histocompatibility complex (MHC)–deficient mice immediately after TBI to maximize the effect of pDCs because the numbers of MHC-expressing pDCs injected in these mice were far less than those resident in normal mice. pDCs were detectable 72 hours after an add-back of pDCs.

Markey et al also showed that selective depletion of pDCs with 120G8 mAb did not reduce donor T-cell activation, indicating that pDCs were not required to prime donor T cells in the presence of cDCs. This result is consistent with our observation that cDCs alone can activate donor T cells to cause GVHD in the absence of other antigen-presenting cell (APC) subsets including pDCs.

Collectively, the observations of Markey et al and our results suggest that pDCs might not be the dominant APCs in the presence of cDCs, but have the capacity to prime donor T cells and are capable of initiating GVHD in the absence of other functional APC (DC) subsets. It is possible that pDCs survive longer after non-TBI conditioning or reduced-intensity conditioning regimen and may contribute to GVHD along with cDCs. Moreover, it remains to be elucidated whether recipient pDCs or cDCs disappear quickly in humans as they do in mice. We concur that insights from all animal models must be extrapolated to clinical studies with caution.

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