Response to Comment on "Expansion of Effector Memory Regulatory T Cells Represents a Novel Prognostic Factor in Lower Risk Myelodysplastic Syndrome"

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Letters to the Editor

Comment on “Expansion of Effector Memory Regulatory T Cells Represents a Novel Prognostic Factor in Lower Risk Myelodysplastic Syndrome”

The article by Mailloux et al. (1) is informative in defining the immune microenvironment and illustrating the independent prognostic value of effector memory regulatory T cells’ (TregEM) expansion in myelodysplastic syndromes (MDS). However, we wonder: 1) because functional Tregs primarily reside in the bone marrow (2), it might be prudent to use bone marrow samples rather than peripheral blood to analyze Treg subsets (3); 2) the suppression assay performed clearly delineates the high suppressive potential of TregEM, but it is important to demonstrate suppression of tumor-specific responses by cytotoxic T cells by addition of either autologous bone marrow or MDS cell lines as an Ag source and subsequently quantifying CD8+ IFN-γ-producing CFSElow CD8+ T cells (4); 3) the time point from diagnosis at which patient samples were collected would impact disease progression; and 4) the rate of leukemic transformation is critical in determining disease progression.

This study is clearly a step in the right direction in that TregEM expansion may serve as an effective immune marker for patients with MDS that might be used to monitor the response to currently available immunomodulatory therapies such as lenalidomide (5). However, the addition of TregEM expansion has limited utility in improving prognostication already provided by contemporary prognostic models (6), particularly in light of the recent discovery of prognostically relevant mutations in MDS (7).

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Response to Comment on “Expansion of Effector Memory Regulatory T Cells Represents a Novel Prognostic Factor in Lower Risk Myelodysplastic Syndrome”

The letter by Gangat and Patnaik in response to the paper by Mailloux et al. (1) raises several interesting questions about effector memory regulatory T cells (TregEM) in myelodysplastic syndromes (MDS). First, we agree that the bone marrow (BM) naturally contains a higher number of Tregs relative to peripheral blood or other organs (2) and should be examined in MDS. Because Tregs traffic to the BM through similar chemokine/receptor axes as conventional T cells following activation (2), it is likely that BM Tregs are phenotypically and functionally different in this disease.

With regard to Ag-specific Treg responses, recent studies indicate that many “tumor-specific” Ags stimulate both T effector and Treg populations (3). Preleukemic BM Ag presentation and activation is hypothesized to be the cause of effector memory Treg class switching in MDS. The results suggest that a shift toward TregEM cells identifies a specific point in which the immunosuppressive networks are active and contribute to leukemia immune evasion (1). This explains the close association of TregEM frequency and blast percentage (i.e., disease progression/leukemic transformation). To study whether Tregs specifically recognize MDS BM Ags, a valid “tumor” Ag must first be identified. Wilms tumor 1 (WT1), located on chromosome 11, appears to be such an Ag in MDS patients with a trisomy 8 chromosomal abnormality as recently defined by Sloand et al. (4). Increased expression of WT1 was shown to stimulate a WT1-specific response by autologous CD8+ effector cells using combined physical and functional assays (4). Because this effector T cell response occurs endogenously, it is possible that WT1 may prove useful in defining Ag specificity within the Treg population. Interestingly, trisomy 8 MDS patients are sensitive to immunosuppressive therapy, suggesting that the presence of activated effector T cells inhibits hematopoiesis in this subset of patients.

Concerning prognostic value, rigorous statistical analyses were applied in the study by Mailloux et al. (1) and TregEM
numbers were identified as an independent risk factor associated with worse overall survival in MDS in a multivariable model (hazard ratio 3.7, 95% CI 1.1–12.2; \( p = 0.036 \)). In addition to the traditional International Prognostic Scoring System (IPSS), the MD Anderson Risk Model was used to classify patients and proved to be significantly better than IPSS at defining prognostication. The status of Treg\(_{EM}\) cells significantly improved the MD Anderson model (1). Whereas it is true that numerous novel mutations have been identified in MDS since the advent of exome sequencing (5), these mutations have demonstrated variable prognostic significance. Based on the study by Bejar et al. (6) in lower-risk MDS, only \( EZH2 \) mutation status out of 22 gene mutations studied retained prognostic significance in a multivariable model (hazard ratio 2.90, 95% CI, 1.85–4.52). We argue that Treg measurement is easily accomplished and cost-effective using standard flow cytometry techniques and may offer unique prognostic information. It is also possible that Treg\(_{EM}\) status may prove to be informative for the selection of patients for immunosuppressive agents and should be further explored for this purpose.

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