Abstract

In recent years, a great effort has been deployed towards a better understanding of the molecular changes in cells and in the bone marrow (BM) environment that contribute to the development and progression of myelodysplastic syndrome (MDS) to acute myeloid leukemia (AML). Among others, the aberrant hematopoietic stem cells in MDS often display increase in DNA double strand breaks, genomic instability with common loss or rearrangement of chromosomes and an ineffective response to DNA damage, a phenomenon that has been linked to the onset of cellular senescence. Additionally, the BM microenvironment can become more pro-inflammatory.

In our effort to better understand the contribution of the BM microenvironment on MDS progression, we analyzed the expression profiles of cytokines in the BM microenvironment in all stages of MDS/AML and found several proinflammatory cytokines that increase with disease progression. Also, by repeated sampling of patients over the course of 5-azacytidine therapy, we were able to assess the changes in the proinflammatory cytokine milieu with the progression of the disease.

Additionally, we aimed to identify the candidate markers for the improvement of MDS prognosis. We focused on naturally occurring germline polymorphism of NAD(P)H dehydrogenase (quinone 1) gene (NQO1*2) that diminishes the ability to reduce oxidative stress. We uncovered that patients with NQO1*2 genotype progress faster and have a shorter overall expression, especially pronounced in low-risk MDS with normal karyotype. Moreover, the NQO1*2 genotype was associated with higher sensitivity to increased ferritin levels. We suggest that NQO1*2 polymorphism can be used as a prognostic marker.

Further, in a subset of low-risk MDS patients treated with lenalidomide, we found that the combination of lenalidomide and prednisone and/or erythropoietin had a positive impact on relapsed and refractory patients with del(5q) MDS.

Next, we focused on the characterization of virtual memory (VM) CD8+ T cells. The diminishment of this population was recently identified in chronic myeloid leukemia. Thus it is possible that VM T cells could play a role in MDS pathology as well. We discovered that VM T cell development is determined by their T cell receptor self-reactivity. Moreover, by analyzing the expression profiles of antigen-experienced memory T cells and VM T cells, we uncovered that VM T cells acquire a partial memory program. However, this does not make them more potent in inducing autoimmunity when compared to naïve cells with the same T cell receptor. Thus, we postulate that VM T cell formation from highly self-reactive T cell receptor clones could function as a novel self-tolerance mechanism.

Finally, we compared findings of the different subsets of antigen-inexperienced memory T cells and concluded that VM T cells and lymphopenia-induced memory T cells likely represent one subset of antigen-inexperienced memory T cells. We have proposed to call this subset “homeostatic memory T cells”.