

# Immune Microenvironment in Hematologic Malignancies

The role of the tumor microenvironment (TME), especially immune cell compartments, in tumor progression is inevitable and the heterogeneity and complexity of the TME-associated immune cells make it challenging to provide appropriate treatments for hematologic malignancies.<sup>1</sup>

The reciprocal interactions between tumor and immune cells essentially regulate tumor cell survival and growth, invasion and metastasis, as well as drug resistance and tumor escape from the immune system.<sup>2</sup> Although accumulation of the different immune cell subsets, such as solid tumors, has been observed in hematologic malignancies, hematologic malignancies exploit various strategies to alter the immune cell compartments in the TME to avoid efficient recognition and subsequent eradication of malignant cells by the immune system, a dynamic process known as “cancer immunoeediting”.<sup>2</sup>

Depending on the context, the dual interaction between infiltrated leukocytes and lymphoma cells might influence the pro- and/or anti-tumorigenic signals. T cell infiltration has been seen in HL patients; however, they are unable to destroy tumor cells *in vitro*, indicating that infiltrated T cells are less responsive and/or energetic in these patients.<sup>3</sup> This is in the case that Reed Sternberg (HRS) cells release immunosuppressive cytokines including IL-10 and transforming growth factor beta (TGF- $\beta$ ), which shift T cell differentiation towards Th2 cells and Tregs while keeping effector T-cells exhausted.<sup>4</sup>

One of the most important features of HL patients is the overexpression of the PD-L1 gene, which can interact with both CD4<sup>+</sup> and CD8<sup>+</sup> T-cells that are expressing PD-1 within the TME, rendering them ineffectiveness and promoting their exhaustion.<sup>3</sup> Lymphoma tumor cells can also increase IL-10 secretion, which stimulates CD40L expression on surrounded T cells and supports HL tumor cell proliferation through CD40–CD40 ligand (CD40L) interactions.<sup>5</sup> Actually, IL-10RA or IL-10RB gene amplifications have been observed in DLBCL, promoting tumor cell survival.<sup>6</sup>

Tregs are more frequent in B-cell NHL, such as follicular lymphoma (FL) or diffuse large B-cell lymphoma (DLBCL), resulting in an immunoregulatory TME. The clinical impact of the tumor-infiltrating Tregs on disease outcomes, however, is debatable and unknown. In FL and DLBCL, high infiltration of the FOXP3<sup>+</sup> and Tim-3<sup>+</sup>Foxp3<sup>+</sup> Tregs, respectively, has been identified as a poor prognostic factor, while their accumulation is associated with favorable outcomes in HL and other lymphoma subtypes.<sup>3</sup> Despite this, a meta-analysis found that the elevated intratumor CD25<sup>+</sup>FOXP3<sup>+</sup> Tregs infiltration was positively correlated with a better prognosis in DLBCL patients.<sup>3</sup>

In lymphoma, CD8<sup>+</sup> cytotoxic T lymphocytes (CTLs) have varying degrees of anti-tumor activity. While CTLs are more effective at preventing the progression of Epstein–Barr virus (EBV)<sup>+</sup> HL or B-cell NHL, they are unable to control the malignant transformation of CD8<sup>+</sup> lymphomas, such as nodal cytotoxic T-cell lymphoma and cutaneous T-cell lymphoma (CTCL).<sup>3</sup> In addition to T cell defect, dysregulation of the NK cells, both quantitative and functional, has been observed in lymphoma patients, which prevents the NK cells from effectively eradicating tumor cells.<sup>3</sup> Moreover, a higher accumulation of M2 macrophages and myeloid-derived suppressor cells (MDSCs) in TME from lymphoma patients has been observed, which is associated with a poor prognosis in both HL and NHL patients.<sup>3</sup>

Multiple myeloma (MM) patients' bone marrow (BM) contains mesenchymal stem cells (MSCs), which secrete C-X-C motif chemokine ligand 12 (CXCL12) (CXCR4 ligand), as well as more interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF). Thus, these actions facilitate plasma cells (PCs) homing into BM.<sup>7</sup> The mutual interactions between PCs and MSCs promote MM progression and favor the accumulation of chemoresistant malignant PCs.<sup>7</sup>

Furthermore, it has been discovered that NK cells from MM patients express fewer NK cell activating receptors while having higher levels of PD-1 receptors, which prevents NK cell-mediated cytotoxicity against MM cells.<sup>7, 8</sup>

Defects in T cell frequency and function, including CD4<sup>+</sup> and CD8<sup>+</sup> T cells, abnormal Th1/Th2 ratio (as a result of reduced Th1 phenotype and Th2 population dominance), and impaired T cell functions have all been reported in MM.<sup>7,9</sup> Additionally, myeloma cells overexpress PD-L1 receptors, which actively block the effector activity of the infiltrated PD-1-expressing T cells, which is associated with a poor prognosis.<sup>7,9</sup> Moreover, higher levels of Tregs were seen in bone marrow microenvironment (BMME) of MM patients, which along with infiltrated MDSCs and M2 macrophages, contribute to the creation of an immunosuppressive environment through secretion of IL-10 and TGF- $\beta$  cytokines.<sup>7,9</sup> There is little information on how regulatory B cells (Bregs) are distributed in the BM of MM patients. However, it was shown that Bregs are more prevalent in BMME of MM patients than peripheral blood, indicating that Bregs preferentially infiltrate the BMME.<sup>7,9</sup>

In Acute myeloid leukemia (AML), AML blasts downregulate antigen presentation molecules, upregulate ligands for T cell inhibitory receptors such as PD-L1, TIM-3, and Gal-9, and stimulate the production of inhibitory mediators/enzymes including reactive oxygen species (ROS), indoleamine 2,3-dioxygenase (IDO), and arginase (Arg) in the BM niche.<sup>10</sup> Consequently, these factors impair and inhibit the cytotoxic function of CD8<sup>+</sup> T cells and NK cells, trigger exhaustion of effector T cell (Teff), and ultimately their apoptosis, raise Tregs and MDSCs populations, and promote macrophages polarization from M1 toward immune suppressive M2 phenotype.<sup>10</sup> Higher frequency of T cells (both CD4<sup>+</sup> and CD8<sup>+</sup> T cells) expressing inhibitory checkpoint receptors alone and/or in combination with other checkpoint receptors (such as PD-1/TIM3 and PD-1/LAG3) display exhausted phenotype, which was associated with disease progression and a poor prognosis in AML patients.<sup>10</sup>

In Myelodysplastic Syndrome (MDS), abnormal innate immune system activation and numerous cytokines, including TNF $\alpha$ , IFN- $\gamma$ , TGF- $\beta$ , IL-6, IL-1 $\beta$ , IL-7, and IL-8, indicating abnormal inflammatory signaling and myeloid differentiation and leading to dysfunctional hematopoiesis and cytogenetic abnormalities.<sup>11</sup>

In acute T cell lymphoblastic leukemia (T-ALL), Interleukin-7, which is produced by thymic and stromal cells, might activate the STAT5, PI3K/AKT/mTOR, and MEK/ERK pathways, and lead to leukemia formation and progression.<sup>12</sup>

T-cell compartments (CD4<sup>+</sup> T helper cells) and cytokines including IL-6, IL-10, and CCL2 change microenvironmental cells in chronic lymphocytic leukemia (CLL), inducing a tumor-supportive niche. Besides, hypoxia-inducible factor 1 $\alpha$  attenuates Tregs and regulates the balance between T regulatory (Treg) and TH17 differentiation.<sup>13</sup> High levels of BCR-ABL, CD4<sup>+</sup> CD25<sup>+</sup> FOXP3<sup>+</sup> T-regulatory cells are observed in chronic myeloid leukemia, which is crucial in the initiation and progression of the disease.<sup>14</sup>

Accordingly, given the critical role of the immune cells in the regulation of tumor cell growth and progression, most current therapeutic strategies focus not only on eradicating the tumor cells themselves but also significantly target the tumor immune microenvironment, which has been successfully applied to hematological malignancies and is associated with promising results.

**Conflict of Interest:** None declared.

Nargess Arandi<sup>1</sup>, PhD;  Mehdi Dehghani<sup>1,2</sup>, MD 

<sup>1</sup>Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran;

<sup>2</sup>Department of Hematology and Medical Oncology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

**Correspondence:**

Mehdi Dehghani, MD;

Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

**Tel:** +98 71 36122263

**Email:** dehghanim@sums.ac.ir

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