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Review article

Involvement of memory T-cells in the pathophysiology of chronic lymphocytic leukemia

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ABSTRACT

The role of T-cells in the pathogenesis of chronic lymphocytic leukemia has recently gained much attention due to the importance of the constant interaction between neoplastic B-cells with microenvironment substratum and T-cells. It is believed that these interactions modulate the clinical course of the disease, mainly through the regulation of the expansion, differentiation, and survival of chronic lymphocytic leukemia B-cells. Importantly, this crosstalk may also change the number, function, and memory phenotype of normal T-cells, thereby altering the amplitude and/or efficiency of adaptive immunity in chronic lymphocytic leukemia patients. The present study presents an overview on important aspects of this immunological crosstalk, particularly on the abnormalities of chronic lymphocytic leukemia B-cells and the alterations in normal T-cells, with focus on the CD4 memory T-cell compartment that could offer survival signals to chronic lymphocytic leukemia B-cell clone(s) and contribute to the establishment and progression of the disease. The authors believe that understanding the biological consequences of the interaction between normal T- and neoplastic B-cells in chronic lymphocytic leukemia may allow for improvements in the prognostic information and therapeutic approaches for this disease.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common mature B-cell neoplasm in Western countries. It is characterized by the appearance of monoclonal $CD5^+CD19^+$ mature B-cells in the peripheral blood, lymphoid system, and bone marrow.[1] The prevalence of the disease is higher in men compared to women and the estimated incidence is two to six cases per 100,000 people annually. At the time of diagnosis,

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approximately 31% of the patients are younger than 64 years and the average age is 72 years.[1,2]

The clinical course of CLL is heterogeneous, and survival can vary from months to decades. Although most patients have an asymptomatic disease, there is a group of patients with aggressive CLL characterized by autoimmune hemolytic anemia, recurrent infections, immunodeficiency, and transformation to aggressive lymphoma, with an average life expectancy of less than three years.[1,3]

Several factors play an important role in the etiology of CLL, such as genetic predisposition related to the familiar history, environmental factors, and antigens/auto-antigens promoting division of precursor cells and clonal evolution.[1,4] Moreover, the study of CLL genome by sequencing approaches revealed novel mutated genes, such as MYD88, NOTCH1, SF3B1, and XPO1, among others. Importantly, some of these genes may be considered as prognostic factors.[5-6]

Another important aspect that modulates the outcome of the disease in CLL patients is the interaction between neoplastic B-cells with microenvironment substratum and T-cells. These interactions occur in organized structures termed pseudofollicular proliferative centers (PC), which are clusters of small lymphocytes dispersed in lymph nodes and bone marrow. Interestingly, PC are not visualized in any other B-cell neoplasm, and this structure is considered a hallmark of CLL.[7] Data in the literature suggest that the crosstalk between CLL B-cells, extracellular components of the microenvironment, and T-cells has an important impact on the physiopathology and evolution of the disease, mainly through regulation of CLL B-cell expansion, differentiation, and survival. Conversely, this crosstalk may also induce qualitative and quantitative changes in normal T-cells that could impact the fitness of the immune system of CLL patients.[7-10]

Tables 1 and 2 summarize some characteristics of neoplastic B-cells and normal T-cells, respectively, that may impact in CLL physiopathology.

Table 1 - Characteristics of CLL B-cells.

Characteristics	Implications
Reduction in CD80/CD86 expression	CLL B-cells are poor antigen presenting cells[11]
CD200 expression	Inhibition of T-helper-1 and induction of regulatory T-cells (Tregs)[12,13]
Expression of FASL with downregulation of FAS	Protection of CLL B-cells from FAS-mediated cell death; promotion of T-cell apoptosis[9]
Increase of soluble FAS	Related to the progressive CLL[14]
Secretion of soluble interleukin-2 receptor and interleukin-10	Inhibition of T-helper-1 differentiation[15,16]
Interleukin-6 secretion	Protection of CLL B-cells from spontaneous apoptosis; secretion of interleukin-4 by T-cells and consequent positive impact on CLL B-cell survival[17,18]

CLL: chronic lymphocytic leukemia.

Table 2 - Qualitative and quantitative changes in T-cells induced by CLL B-cells.

Changes in T-cell	Comments
Increase in CD4 and CD8 T-cell absolute number	Due to leukocytosis[9,10,19]
Inversion of the CD4/CD8 ratio in peripheral blood	CD4 T-cells are more sensitive to FAS mediated cell death[20,21]
Elevated expression of FAS	Increased rates of T-cell apoptosis induced by FASL on CLL B-cells[20]
Deficiency acquired in CD40L expression	CLL cells induce downregulation of CD40L on the T-cell surface[22]
Abnormal profile of cytokine and/or cytokine receptor expression[10]	-
Expansion of regulatory T-cells (Tregs)	Induced by CD200 expression in CLL B-cells[12,13]
Reduction in T-cell receptor repertoire	T-cell oligloclonal expansion[23]
Interleukin-4 secretion	Induced by interleukin-6 secretion of CLL B-cells[17,18, 24]
Cytoskeleton changes	Defective immune synapse[25]
Alterations in genes involved in CD8 T-cell cytotoxicity	Inefficient CD8 T-cell cytotoxicity[26,27]
Defective lymphocyte function-associated antigen 1-directed T-cell motility	CLL B-cells alter the Rho GTPase signaling[28,29]

CLL: chronic lymphocytic leukemia.

In addition to these changes in the T-cell compartment, recent data suggest an accumulation of memory T-cells in CLL patients that is associated with a more aggressive course of the disease.[19,21,30,31] Therefore, this study aimed to discuss the possible involvement of memory T-cells in the physiopathology and clinical course of CLL.

Memory T-cells

T-cells play a crucial role in the immune system; they are critical for combating and controlling tumors and intracellular and extracellular pathogens, acting as cytotoxic cells (cytotoxic T-lymphocytes [CTL]) or assisting other immune cells (T-helper [Th] lymphocytes). Importantly, Th lymphocytes differentiate into subsets capable of producing different cytokine patterns and, therefore, exerting diverse helper functions.[8]

The course of immune response can be briefly summarized by initial antigen-specific stimulation of naïve T-cells that results in activation, vigorous proliferation, and differentiation to specific effector T-cell subpopulations, which are capable of fighting pathogens and tumor cells.[8]

After pathogen clearance, the majority of effector T-cells die due to lack of stimulation with participation of the pro-apoptotic protein B-cell lymphoma 2 interacting mediator of cell death (BIM).[32] In the case of chronic activation of T-cells, these may undergo activation-induced cell death (AICD),