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Review

Tumor-induced host immunosuppression: Special focus on CLL

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ABSTRACT

Malignant cells are able to suppress host immune responses in an effort to avoid immune detection *in vivo*. Tumor-induced immunosuppression can be achieved at the molecular, cellular, and/or physiological levels. Herein the contribution of immune-tolerant genes and regulatory cells to immunosuppression related to alterations of T-cells and antigen-presentation is reviewed. Furthermore, key advances in countering tumor-induced immunosuppression are described in reference to immune evasion mechanisms used by chronic lymphocytic leukemia (CLL) cells. Lastly, the challenges associated with targeting the tumor microenvironment coupled with the usefulness of immunomodulatory drugs are discussed. This review summarizes select immune evasion tactics orchestrated by the conversation between CLL cells and their microenvironment.

Contents

1. Etiology and characteristics of CLL

Chronic lymphocytic leukemia (CLL), the most common adult leukemia, is a heterogeneous disease. CLL predominantly affects the elderly with a mean age of 72 at diagnosis, and is characterized by clonal expansion of malignant B cells [1]. There exists a well-established immunodeficiency in CLL, evident by the manifestation of several complications including changes in immunophenotype, impaired immune synapse formation, hypogammaglobulinemia, and an altered cytokine milieu.

Previously, the etiology of CLL cells was postulated to be of a bipotential origin bearing the phenotype of both T and B cells [2]. However, recent studies suggest that CLL cells are of a B cell origin, particularly from B-1 cells [3–6]. The development of CLL from B-1 cells is highly likely due to the expression of both CD5 and CXCR5 on the cell surface, and the sensitivity to interleukin-10 (IL-10). IL-10 most likely contributes to the autocrine self-renewal and survival of CLL cells [7,8]. Moreover, the most widely accepted murine model for aggressive CLL, Eμ-*TCL1*, has a lymphoproliferative disorder of B-1 cells [9]. Nordgren and Joshi [4] provide a comprehensive review of the likelihood of B-1 cells as the cell of origin for CLL [10,11]. Others have supported the idea of a malignant transformation in patients with monoclonal B lymphocytosis [12]. Typically, Bregs are described in the context of autoimmune disease. CLL has been suspected to be an autoimmune disorder, and the phenocopy observed between CLL cells and typical B-1 cells is remarkable. B-1 and CLL cells both produce IL-10 and are positive for CD5 and CD19 [9]. Even though CLL cells resemble B-1/B-10/Breg cells, few reports

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have considered the possibility of CLL cells actually functioning as these regulatory cells. However, the results from Vu et al., [13] suggest a role for CLL as a B-10 cell due to the apparent immunosuppression elicited by CLL. Consequently, the amount of B-10 cells increases significantly before full-blown CLL in the *TCL1*-Tg model of CLL [11]; thereby suggesting a similarity between the immunosuppressive effects that take place in human CLL and CLL recapitulated *in vivo*. Although the precise etiology of CLL in patients remains unconfirmed, the progression of CLL, gene expression signature changes, and prognostic markers have been studied comprehensively.

CLL cells rely on the tumor microenvironment (TME) for their proliferation and survival. This is demonstrated by the fact that when cultured *ex vivo*, CLL cells readily undergo apoptosis [14]. CLL cells upregulate self-antigen and the tumor-associated antigen *ROR1* [15]. Also, some patients with CLL have an expanded population of regulatory T cells (Tregs) and a shorter time to their first treatment; lastly, formation of the immune synapse with T-lymphocytes is impaired [16–18]. Therefore, there exists an intricate interaction between CLL cells and the surrounding TME. Based on the changes in gene expression and immunophenotype during CLL progression, CLL cells directly participate in immunomodulation. CLL-induced immunosuppression is mediated by several factors including molecular mechanisms, environmental influence, and immune evasion (Fig. 1). To be focused, this review will discuss only cellular, cytoskeletal-regulation, and the contribution of human leukocyte antigen-G (HLA-G) to immunosuppression. Recently, a review discussing CLL TME and apoptosis was published, so that information is already summarized [19]. Currently, there is not a cure for CLL since a major complication is the contribution of the tumor to immunosuppression. Most CLL patients are elderly and thus may already be immunosuppressed and many therapies exacerbate this problem. As a consequence, CLL cells escape immunosurveillance and facilitate immunosuppression.

2. Tumor-induced immunosuppression

The immune system has many immunological brakes in place to hinder foreign invaders from taking up residence, but an imbalance of these brakes (i.e. cancer) leads to immune dysregulation. As a consequence, patient susceptibility to opportunistic and/or nosocomial infections and malignancies increases [1,14]. CLL cells are no exception, they exploit the TME to maintain survival and receive proliferation signals. Three methods of CLL-induced immunosuppression discussed herein include mechanisms mediated by: suppressor cells, cytoskeletal-associated molecules, and HLA-G.

2.1. Mechanisms of immunosuppression in CLL mediated by suppressor cells

Generally, CLL cells proliferate within pseudofollicles in lymphoid organs and then disseminate to other sites. Since CLL cells undergo apoptosis quickly *ex vivo*, a pseudofollicle model was developed to identify the influence of CD154, IL-2, IL-10, and stromal cells on CLL cells [20]. Burger et al., [21] demonstrated the importance of nurse-like cells (NLC) or monocyte/macrophage-like cells that support CLL cell survival via CD38 and CD49d and facilitate the recruitment of more monocytes and macrophages than CLL cells lacking these molecules [22]. The upregulation of cytokines and chemokines from CLL cells in different sites of the body undoubtedly contributes to CLL progression due to recruited support from these NLCs. Also, the direct interaction between CD38 on CLL cells with the CD31 ligand expressed by NLC and stromal cells leads to increased proliferation and migratory potential of CLL cells [23]. Lastly, the upregulation of CCL3/CCL4 by CLL cells leads to increased NLC recruitment and prolonged survival of CLL cells [21]. CLL cells form these protective niches to avoid immune detection, change the function of key immune

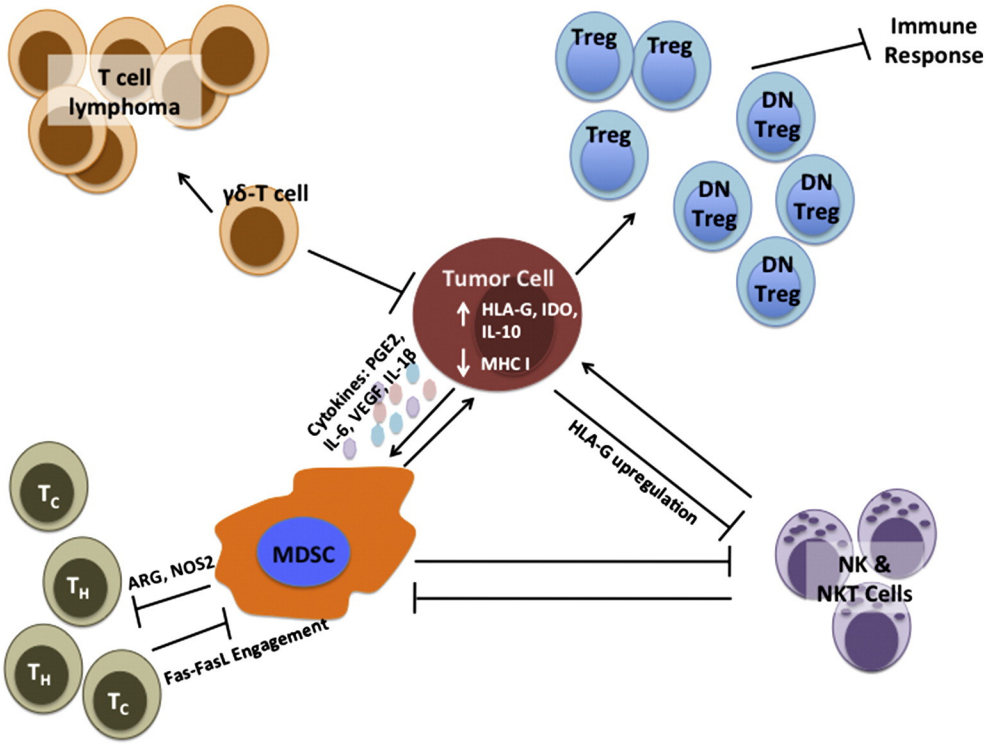

Fig. 1. Summary of potential mechanisms of immune subversion deployed by cancer cells. Tumor cells produce cytokines that recruit and expand myeloid-derived suppressor cells (MDSC), which arrest T-cell activation via production of ARG and NOS2. Engagement between the Fas receptor on MDSCs with Fas ligand on the T-cell causes apoptosis of MDSCs. Tumor cells can also recruit gamma-delta suppressor T cells and if these cells proliferate without inhibition, they may lead to T-cell lymphomas. Tumor cells can also recruit other immune suppressors such as Tregs and double negative (DN) T cells [13–15]. However, natural killer (NK) cells target tumor cells for apoptosis, but the malignant cell thus evading another immunological checkpoint can inhibit apoptosis.