Pharmacology & Therapeutics 144 (2014) 338–348

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: B. Teicher

Microenvironment dependency in Chronic Lymphocytic Leukemia: The basis for new targeted therapies

Elisa ten Hacken, Jan A. Burger *

Department of Leukemia, MD Anderson Cancer Center, Houston, TX, USA

ARTICLE INFO

Available online 19 July 2014

Keywords:
Chronic Lymphocytic Leukemia
microenvironment
nurselike cells
stromal cells
CXCR4
CXCL12
B cell receptor
SYK
BTK
PI3Kδ

ABSTRACT

Chronic Lymphocytic Leukemia (CLL) is a prototype microenvironment-dependent B-cell malignancy, in which the neoplastic B cells co-evolve together with a supportive tissue microenvironment, which promotes leukemia cell survival, growth, and drug-resistance. Chemo-immunotherapy is an established treatment modality for CLL patients, resulting in high rates of responses and improved survival, especially in low-risk CLL. New, alternative treatments target B-cell receptor (BCR) signaling and the Chemokine (C–X–C motif) Receptor 4 (CXCR4)–Chemokine (C–X–C motif) Ligand 12 (CXCL12) axis, which are key pathways of CLL-microenvironment cross talk. The remarkable clinical efficacy of inhibitors targeting the BCR-associated kinases Bruton's tyrosine kinase (BTK) and phosphoinositide 3-kinase delta (PI3Kδ) challenges established therapeutic paradigms and corroborates the central role of BCR signaling in CLL pathogenesis. In this review, we discuss the cellular and molecular components of the CLL microenvironment. We also describe the emerging therapeutic options for CLL patients, with a focus on inhibitors of CXCR4–CXCL12 and BCR signaling.

Contents

1. Introduction

The microenvironment is the compilation of accessory cells and extracellular matrix that, within individual organs, provides a structural and molecular scaffolding ("stroma") to support parenchymal cells. Similar complex interactions exist between tumor cells and surrounding non-tumoral tissue stromal cells, which contribute to tumor progression, a concept that was originally proposed as "seed and soil" theory formulated by Paget in 1889 (reviewed in Langley & Fidler, 2011). Extending this concept into B cell malignancies, neoplastic B cells are the seeds, which thrive in a supportive soil microenvironment, which provides growth and survival signals.

Blood cancers develop in specialized tissue microenvironments, such as bone marrow (BM) and secondary lymphoid organs. These microenvironments contain different distinct populations of stromal cells and non-malignant lymphocytes that interact with the malignant B cells (Burger et al., 2009). Malignant blood cells apparently have variable degrees of dependency upon signals from the microenvironment. Burkitt's lymphoma B cells, for example, are more autonomous due to the c-Myc chromosomal translocation into the immunoglobulin heavy chain locus that leads to constitutive oncoprotein activation. In contrast, malignant B cells from patients with Chronic Lymphocytic Leukemia (CLL), follicular lymphoma, mucosa-associated-lymphoid-tissue lymphomas, and multiple myeloma are more dependent on signals from the microenvironment to proliferate and survive.

* Corresponding author at: Department of Leukemia, The University of Texas, MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 428, Houston, TX 77030, USA. Tel.: 713 563 1487.
E-mail address: jaburger@mdanderson.org (J.A. Burger).

http://dx.doi.org/10.1016/j.pharmthera.2014.07.003
0163-7258/

2. The cellular and molecular components of the microenvironment

2.1. Bone marrow stromal cells and nurselike cells

Signals coming from tissue compartments, including the BM and secondary lymphoid organs, are essential for the proliferation, homing and survival of CLL cells. Proliferation of CLL cells occurs in tissue areas termed "pseudofollicles" and accounts for a daily birth rate of approximately 1–2% of the entire clone, as determined by deuterated water labeling (Messmer et al., 2005). When removed from the microenvironment and placed into in vitro culture, CLL cells undergo spontaneous apoptosis, but they can be rescued by coculture with bone marrow stromal cells (BMSC) (Panayiotidis et al., 1996; Lagneaux et al., 1998; Kurtova et al., 2009) or nurse like cells (NLC) (Burger et al., 2000) (Fig. 1). Marrow stromal cells regulate the survival of normal and malignant hematopoietic cells, including B cells. Adhesion through very late antigen 4 (VLA-4) integrin to the corresponding ligand vascular cell adhesion molecule 1 (VCAM-1) on BMSCs (Panayiotidis et al., 1996; Lagneaux et al., 1998) favors CLL–stroma interactions, with subsequent upregulation of the anti-apoptotic protein myeloid cell leukemia 1 (MCL1) (Kurtova et al., 2009) and of the proto-oncogene T-cell leukemia/lymphoma 1 (TCL1) (Sivina et al., 2012). BMSCs secrete high levels of the chemokine Chemokine (C–X–C motif) Ligand 12 (CXCL12) (Bleul et al., 1996), and interaction with the corresponding chemokine receptor Chemokine (C–X–C motif) Receptor 4 (CXCR4) on CLL cells is critically involved in trafficking and tissue homing of CLL cells (J.A. Burger et al., 1999). A model to mimic CLL interactions with BMSCs is pseudo-emperipoiesis, an in vitro phenomenon of spontaneous migration of CLL cells beneath CXCL12-secreting BMSCs in a CXCR4-dependent fashion (Burger et al, 1999). CLL cells, in turn, can activate BMSCs through direct cell–cell contact with induction of protein kinase C beta II (PKCβII) expression and subsequent nuclear factor kappa B (NFκB) pathway activation in BMSCs (Lutzny et al., 2013).

Another crucial component of the CLL microenvironment are NLCs, which are found in secondary lymphoid organs of CLL patients (Burkle et al., 2007), in animal models of CLL (Reinart et al., 2012; Troeger et al., 2012) and can be generated in vitro from the monocyte fraction of CLL peripheral blood mononuclear cells (Burger et al., 2000). The mechanism through which NLCs differentiate from blood monocytes is still under investigation, although a recent report showed that the nuclear protein high mobility group box 1 (HMGB1), released by CLL cells, can stimulate NLC differentiation in vitro by activating the receptor for advanced glycation endproducts (RAGE)-Toll Like receptor 9 (TLR9) pathway (Jia et al., 2014). NLCs activate BCR signalling in CLL cells (Burger et al., 2009) and secrete the chemokines CXCL12 (Burger et al., 2000) and CXCL13 (Burkle et al., 2007), which attract CLL cells into the tissue microenvironment. Besides BCR pathway activation and chemokines, NLCs also express the tumor necrosis factor (TNF)-family members B cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) which activate B cell maturation (BCMA),

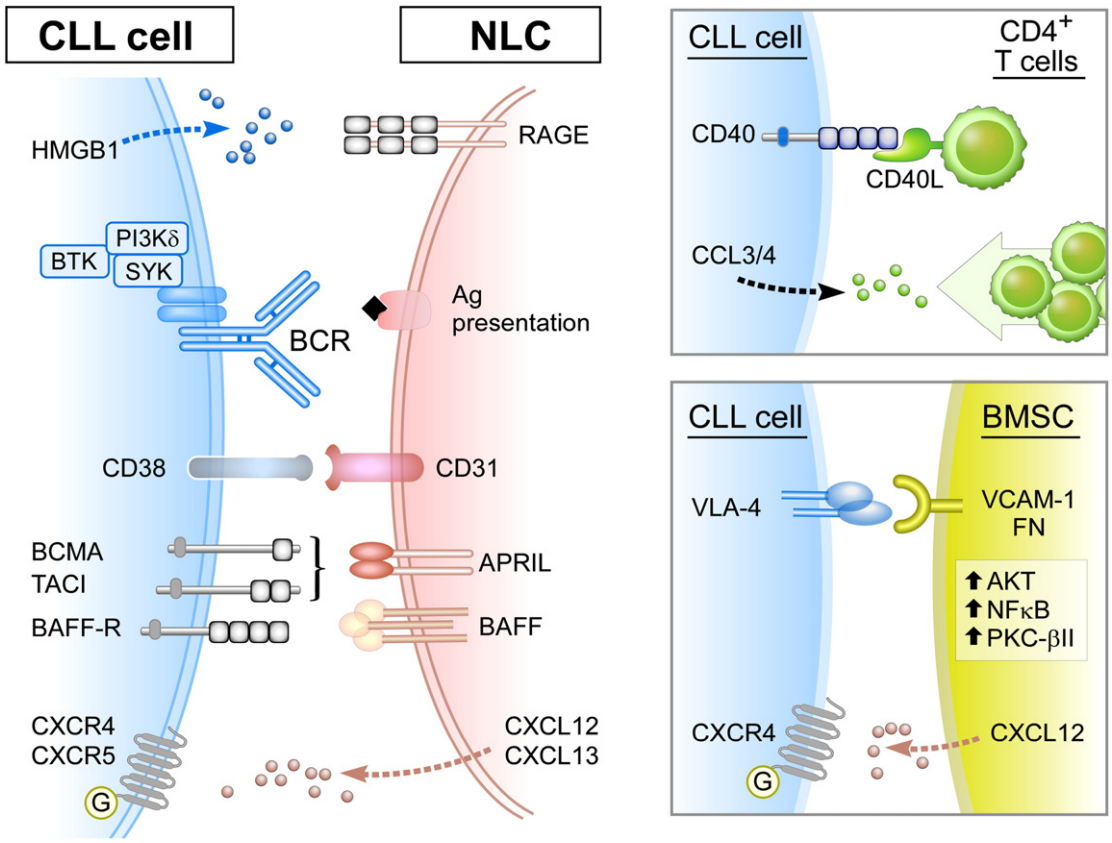

Fig. 1. Contact between CLL cells and nurselike cells (NLC) is established and mantained by chemokine receptors and adhesion molecules expressed on CLL cells and corresponding ligands on NLCs (left panel). HMGB1 released by CLL cells is involved in the differentiation of NLCs through RAGE receptor ligation (Jia et al., 2014). BCR signaling is activated in CLL cells after NLC contact (Burger et al., 2009). CD31 molecule expressed on NLCs interacts with CD38 on the surface of CLL cells (Deaglio et al., 1998). NLCs express TNF family members BAFF and APRIL, providing survival signals to CLL cells via corresponding receptors (BCMA, TACI and BAFF-R) (Nishio et al., 2005). NLCs attract CLL cells via the G protein-coupled chemokine receptors CXCR4 (Burger et al., 1999) and CXCR5 (Burkle et al., 2007), which are expressed at high levels on CLL cells. CLL cells can also be activated by CD40L expressing $CD4^+$ T cells (upper right panel) and these interactions favor survival and expansion (Kitada et al., 1999). BCR stimulation induces CLL cells to secrete CCL3/4 chemokines (Burger et al., 2009), which recruit T cells and monocytes for cognate interactions (Krzysiek et al., 1999). VLA-4 integrins, expressed on the surface of CLL cells, establish cell–cell adhesion contacts through VCAM-1 (Osborn et al., 1989) or fibronectin (FN) (Wayner et al., 1989) expressed on bone marrow stromal cells (BMSCs) (bottom right panel). Interaction between CLL cells and BMSCs, either through direct cell–cell contact or microvesicle release, induces AKT (Ghosh et al., 2010), NFκB and PKC-βII activation in BMSCs (Lutzny et al., 2013). BMSCs predominantly express the chemokine CXCL12 (Bleul et al., 1996), whereas NLCs express both CXCL12 (Burger et al., 2000) and CXCL13 (Burkle et al., 2007).