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Review

How the microenvironment wires the natural history of chronic lymphocytic leukemia

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ABSTRACT

The investigation on the mechanisms that govern the development and progression of cancer is constantly swaying between "seed" and "soil". Chronic lymphocytic leukemia (CLL) makes no exception. Its natural history, including response to treatment and drug resistance, is determined both by causal and influential genes and by the relationships that leukemic cells entertain with their supportive microenvironments. Therefore dissecting the role of microenvironment may provide new strategies of diagnosis and treatment. CLL, though phenotypically homogeneous, is clinically heterogeneous and despite major therapeutic advances remains incurable. Conceivably the host of new non-genotoxic drugs that operate at the forefront between tumor cells and their milieu will modify the present therapeutic perspective by re-shaping the tumor cell/microenvironment cross talk.

1. CLL key events occur in tissues

CLL key events occur mainly in peripheral lymphoid organs and in the bone marrow (BM) where conducive microenvironments are established and maintained through a dynamic, interactive co-evolution of tumor and normal bystander cells [1] (Fig. 1). CLL microenvironments share the general properties of cancer microenvironment: new vessels provide nutrients, growth factors are produced locally and leukemic cells are protected from immune elimination. The main actors of CLL cell/microenvironment co-evolution are yet incompletely defined populations of stromal, endothelial and immune cells. Pseudofollicular proliferation centers (PC) scattered in infiltrated tissues are the source of most cellular generation in CLL, a highly dynamic process that spawns a daily birth rate of around 1–2% [2,3]. The progeny that escapes apoptosis accumulate in tissues and may then flow into the peripheral blood (PB). Circulating clonal cells may re-enter the tissues to start a new other rounds of proliferation.

Leukemic cells infiltrating different tissues are exposed to different microenvironmental conditions. One example is the hypoxic gradient in the BM, another example is the striking heterogeneity of bystander cells in peripheral lymphoid organs with the compartmentalization in B and T cell areas. These differences influence the emergence and evolution of tissue-related intraclonal heterogeneity and dictate the importance of investigating which rules govern the traffic of leukemic cells and their homing to specific tissue microenvironmental niches.

2. CLL conducive microenvironments

The complex cross talk between CLL cells and their microenvironments are largely dependent upon a functional leukemic B-cell receptor (BCR) that allows antigen (Ag) interaction [4]. A debate is ongoing on the nature of the stimulating Ags, whether they are exogenous Ags provided by pathogenic bacteria [5] or fungi [6] or self Ags presented by apoptotic cells [7]. An intriguing possibility is that surface monoclonal immunoglobulins (Ig) themselves may somehow autonomously act as triggering Ags [8]. Irrespective of the nature and source of Ag stimulation, the outcome is a stimulation of the BCR-triggered pathway [9]. The evident therapeutic relevance of this observation is reinforced by the *in vivo* finding that CLL cells in infiltrated tissues have signs of BCR-induced activation [10]. *In vitro* CLL cells from different patients differ significantly in their capacity to signal through the BCR: some (most expressing unmutated IgVH genes) carry more competent BCRs and others (usually showing mutated IgVH genes) appear to be unresponsive [11].

Differences in signal transduction may be ascribed to the nature of the Ag and/or to the receptor affinity. It is reasonable to postulate that in responsive cases an on going antigenic stimulation might promote CLL survival and possibly also growth, while in

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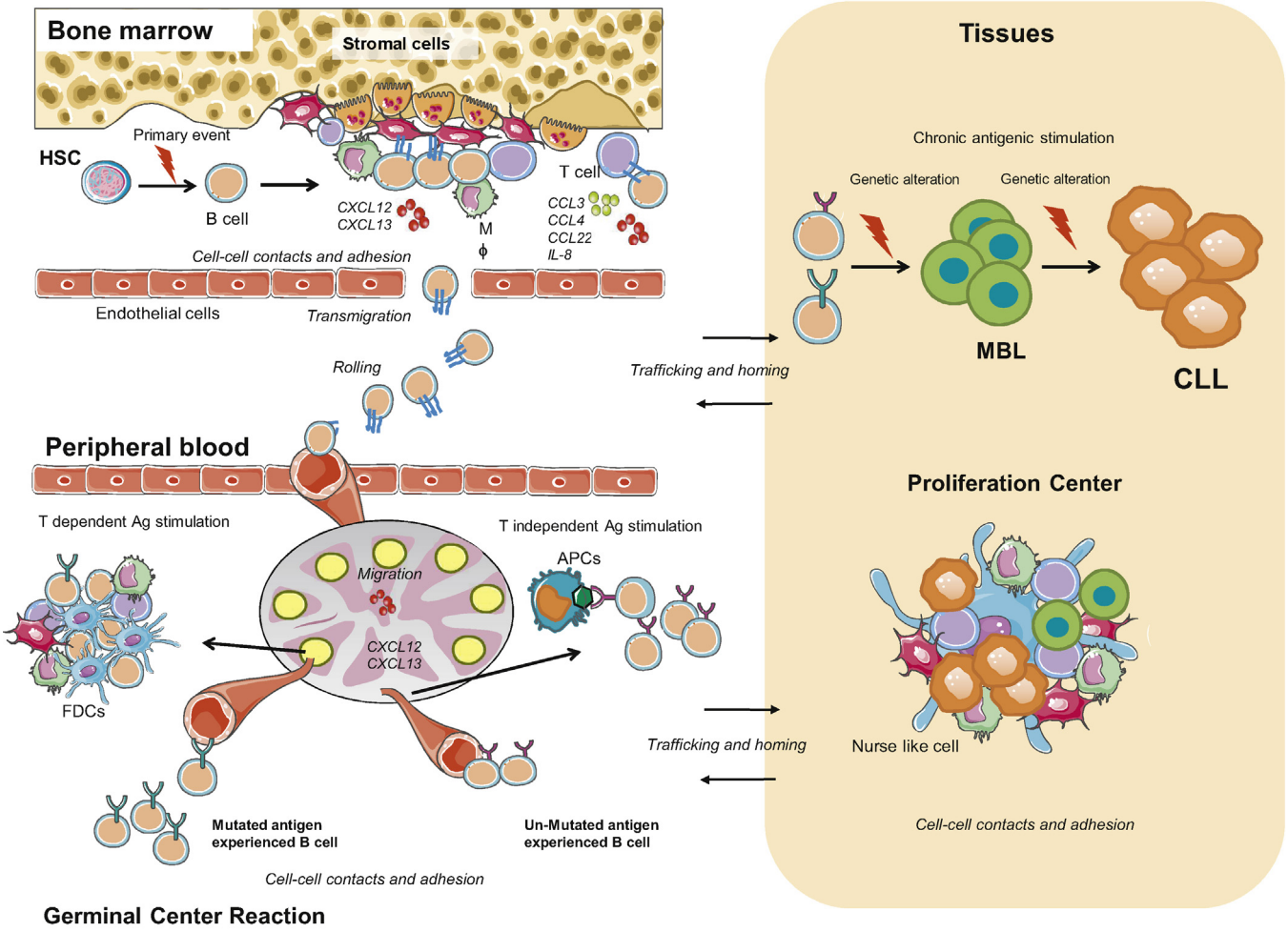

Fig. 1. Schematic model of CLL development, trafficking and homing. Yet undetected genetic alterations possibly occur already at the stage of HSC and predispose B cells to the CLL onset. Circulating monoclonal CD5+ B cells are attracted by different stimuli, interact with the cellular elements of the microenvironment and transmigrate into the lymph nodes and bone marrow. T-dependent or T-independent immune response, persistent microenvironmental interactions and accumulating genetic aberrations ultimately contribute to the progression of MBL into overt CLL. Figure was produced using Servier Medical Art: www.servier.com.

unresponsive cases a continuous antigenic binding might lead to receptor desensitization and cell anergy [12,13]. It is however unknown where the stimulatory Ags are located and why the proliferation occurs essentially in areas that take the form of PC. This leads also to consider that in every patient all leukemic cells carry the same monoclonal BCR, hence have the same potential reactivity, while only a very limited proportion enter the cell cycle. The implication is that either the relevant Ags are only intermittently present or that Ag stimulation is important in triggering the initial clonal expansion but less so in maintaining the malignancy. These possibilities would be especially true in case of foreign Ag, difficult to explain if Ags are presented by apoptotic cells, even more unlikely if surface monoclonal Ig provide an autonomous signal. An alternatively hypothesis is that Ag stimulation might continuously tickle individual cells and lead them to the decisional crossroad between apoptosis and proliferation, the outcome of such decision being influenced by the microenvironment organization that leads to the formation of PC. This hypothesis would be easily understandable if BCR stimulation is triggered by leukemic monoclonal surface Ig themselves. Admittedly a reductionist hypothesis is more easily experimentally testable, still it is more than conceivable that different Ags may be operating and explains the complexity and heterogeneity of disease evolution in different patients.

Within this general context several other potential abnormalities have to be taken into account. As an example a critical aspect of CLL clonal expansion is the incapacity of leukemic cells to differentiate into Ab-producing cells able to somehow neutralize the stimulating Ag. The implication is that the triggering Ag perpetuates an unabated reaction. Another potential abnormality is an alteration of the signal transduction system that following BCR stimulation leads to the cytoskeleton modification that are needed for cell proliferation and trafficking [14,15].

Several other key molecules act at the forefront between CLL B cells and their microenvironments including CD40 [16], Toll-like receptors (TLR) [17], BAFF and April [18] receptors. The individual pathogenetic weight of each molecule is unclear as it is unknown to what extent they cooperate with the BCR stimulation in different patients. Evidence is increasing that membrane-associated as well as endosomal TLRs have a role in CLL development and progression [19,20]. It has been reported that TLR signaling pathways in the lymph node microenvironment could contribute to NF-κB activation, expression of costimulatory molecules and regulation of survival of CLL cells [21]. Furthermore different subgroups of CLL cases (with different BCR molecular features) have distinct expression profiles of TLR signaling molecules [22]. Also, at least in a proportion of patients, *in vitro* CLL cell sensitivity to fludarabine may be modulated by the stimulation of TLR, likely mimicking