Casein kinase 1: a new tale of chronic lymphocytic leukemia (CLL) microenvironment

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Comment on: Janovska P, Verner J, Kohoutek J, *et al.* Casein kinase 1 is a therapeutic target in chronic lymphocytic leukemia. Blood 2018;131:1206-18.

The biological history of chronic lymphocytic leukemia (CLL) is strictly related to the ability of leukemic cells to invade and manipulate tissue microenvironments. This evidence is unequivocal by the observation that despite an apparent long life *in vivo*, CLL cells undergo in spontaneous apoptosis *in vitro* during culture in complete medium (1). This can be avoided by culturing CLL cells in presence of a feeder layer represented by stromal cells (2), endothelial cells (3) and macrophage population (also called nurse-like cells) (4). In this perspective, CLL cells recirculate from blood to tissues through transient interactions with endothelium through firm adhesion molecules and chemokines that trigger integrin activation, thus inducing firm adhesion and transendothelial migration into tissues where stromal cells guide lymphocyte homing retention (5). CLL cells infiltrate bone marrow and lymph node compartments, disrupting the physiological architecture of tissues and generating hallmark structures called proliferation centers (6). Inside tissue microenvironments, CLL cells establish a complex crosstalk with surrounding non-transformed cells of stromal and immune compartments manipulating its biological functions. This crosstalk protects CLL cells from spontaneous or drug-induced apoptosis contributing to genetic instability and establishing a protective niche hiding residual CLL cells from conventional drugs (7). In the last years, novel kinase inhibitors of B-cell receptor signaling pathway (BCRi) have been approved for the treatment of CLL patients. These drugs, as ibrutinib and idelalisib, cause rapid resolution of lymphadenopathy and/or organomegaly with redistribution of leukemic cells from tissues into the blood (8).

This peculiar activity suggests that these agents interfere with CLL cell adhesion and other tissue retention signals (9-11). Despite the important benefits of these agents, it's now clear the subsistence of multiple side effects (12). and the existence of intrinsic and extrinsic resistance (13-15). All these observations remark that CLL is still an incurable disease and the new treatments are not still curative, opening the possibility to associate in the clinical practice different therapeutic strategies.

In this study published on *Blood*, Janovska and colleagues (16) introduced a new player in the complex crosstalk between CLL cells and microenvironment. Casein kinase 1δ/ε is a key component in the Wnt/polarity proteins pathway (PCP). Non-canonical Wnt/PCP pathway is significant for communication of CLL cells with accessory cells in tissue microenvironments regulating chemotaxis and transendothelial migration in the chemokine gradient and *in vivo* homing of CLL cells. PCP pathway contributes to CLL pathogenesis mainly via regulation of chemotactic responses to chemokines. Of interest, PCP-high patients group showed worse clinical parameters as treatment-free survival promoting the idea that PCP pathway may contribute to the CLL pathogenesis (17).

Of note, CK1 was overexpressed in CLL cells compared with B cells isolated donors. This data make CK1 a suitable specific therapeutic target in CLL cells. To dissect the role of CK1 in the process of homing and retention of CLL cells inside tissue niches, the authors used specific adenosyl triphosphate-competing CK1 inhibitors. One of this, PF-670462 inhibited both CK1δ and CK1ε isoforms. First, CK1 δ/ε isoforms were involved in CLL cells migration towards CCL19 and CXCL12 chemokines, bone marrow stromal cells and in integrin-mediated adhesion. Inhibition of both isoforms of CK1 by PF-670462 was able to

counteract CLL cells chemotaxis, suggesting the possibility to interfere with CLL cell trafficking using this compound. Moreover, inhibition of CK1 δ/ε isoforms determined a significant reduction of CCL3 and CCL4, that are secreted by CLL cells and recruit accessory cells that in turn can deliver pro-survival signals. These results opened the possibility to combine the inhibition of CK1 with the inhibition of BTK, key player in CLL pathogenesis. Since ibrutinib is able to interfere with CLL chemotaxis, the authors combined PF-670462 with BTK inhibition founding a significant reduction of CLL cells migration towards CCL19 and CXCL12. Lastly, the authors analyzed the synergistic combination of PF-670462 and ibrutinib in a mouse model. The combination showed to be most effective compared with single treatment and it was able to stopped accumulation of leukemic cells in peripheral blood and spleen. In addition, CK1 inhibition slowed down the progression in mice after ibrutinib cessation.

The study of Janovska *et al.* provides new insights in the complexity of CLL cells interaction with microenvironmental accessory cells illustrating the role of a new player. Given the increasing knowledge about the importance of microenvironment in the maintenance of leukemic cells, the possibility to find new appealing target in CLL adds new alternative to the therapeutic targets strategies based on BCR and antiapoptotic signaling inhibition. Moreover, it opens new queries about the possibility to use for example ibrutinib with other pharmacological agents. A key question become if CK1 inhibitors could overcome the resistance to BCRi and how these CK1 inhibitors alone or in combination with BCRi could be used in the clinical practice. From a therapeutic view, a new PI3K delta inhibitor, umbralisib (TGR-1202) possesses also the unique capability to inhibit CK1ε, which distinguishes it from idelalisib. CK1ε is able to activate mRNA translation through phosphorylation of 4E-BP1 orchestrating upstream signals as c-Myc. Umbralisib disrupts the 4E-BP1-c-Myc axis inducing death in lymphoma cells, it is currently in phase 3 clinical trial showing promising good activity and, of importance, differs from the other PI3Kδ inhibitors by a better safety profile (18).

In conclusion, this manuscript inserts a new piece in the complex puzzle of CLL microenvironment: CK1 may play a relevant role as a new therapeutic target in CLL.

Acknowledgments

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Peipei Xu (Department of Hematology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.06.21). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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