Interleukin-6 in CLL: accelerator or brake?

Rosa Lapalombella  THE OHIO STATE UNIVERSITY

In this issue of Blood, Li et al provide insight into the interactions between immunoreceptor signals in a human cancer microenvironment presenting a novel mechanism by which microenvironment-produced interleukin (IL)-6 acts as a tumor suppressor in chronic lymphocytic leukemia (CLL) by inhibiting toll-like receptor (TLR) signaling.1

TLRs belong to the pattern recognition receptor family. TLRs are present on a variety of immune cells and are considered major players in innate and adaptive immunity.2 A novel oncogenic role of TLRs in hematologic malignancies, especially in CLL,3 has been recently proposed where it is believed that cell damage and clonal turnover that take place during tumor progression lead to the release of naked nuclear material. This repeated, low level, T-cell–independent activation of TLR7 on CLL cells may result in enhanced tumor growth.3

TLR7 has been shown to be present and functional on both normal and malignant B cells.3 Several publications have reported on the effects of TLR7 stimulation on CLL cells, with contradictory results in terms of cell proliferation and apoptosis.4 Simultaneous treatment of CLL cells with IL-2 and TLR7 agonists has been proposed as a model to study the proliferative CLL compartment in vitro.5

Their results suggest that although TLR7 stimulation on isolated CLL cells induces rapid proliferation, the presence of spleen-derived stromal cells overrides TLR7 stimulation inducing a “state of tolerance” to TLR7 agonists (see figure). This is characterized by robust activation of STAT3, downregulation of TNF-α, and a decreased rate of proliferation. Because CLL cells did not adhere to stromal cells, the authors hypothesized that a stromal cell–secreted factor was responsible, and they confirmed this by showing that the use of stromal conditioned media in the absence of stromal cells led to similar results. Since STAT3 had been already shown to modulate TLR7 stimulation activates the nuclear factor-κB, c-Jun N-terminal kinase, and p38 pathways, increases the expression of costimulatory molecules on leukemic cells (eg, CD25 and CD86), increases release of inflammatory cytokines (eg, tumor necrosis factor [TNF]-α, IL-6, and IL-10), and induces rapid cell proliferation.5 Additionally, TLR7-stimulated CLL cells acquire sensitivity to cytotoxic agents (eg, vincristine) and killing by cytotoxic T lymphocytes in vitro.3

Despite its importance in tumor biology, the regulation of TLR signaling in a tumor microenvironment remains poorly understood. Results from a phase 1/2 study of the TLR7 agonist 852A in CLL patients showed only modest clinical efficacy after systemic delivery, especially in light of its potent activity in vitro and in vivo against cutaneous CLL.6 This suggested the presence of impaired TLR7 signaling in proliferation centers (PCs) in vivo. To date, all the studies on the functional effects of TLR-agonists on CLL cells used nonproliferating circulating tumor cells. There has not been adequate analysis of the effects of TLR agonists on CLL cells in the PCs in bone marrow and lymphoid organs.3,5 Li et al1 hypothesized that the diverse interactions within the PC microenvironment of the lymphoid organs vs the blood may produce altered responses to TLR agonists. Furthermore, they postulate that a better understanding of TLR7 signaling in the CLL microenvironment will clarify the mechanisms by which TLRs promote tumor progression and allow the development of novel therapeutic strategies.

To address this, the authors developed human stromal cell lines from leukemic spleens to model PCs, and used them to study the significance of TLR7 signaling in this context.

Their results suggest that although TLR7 stimulation on isolated CLL cells induces rapid proliferation, the presence of spleen-derived stromal cells overrides TLR7 stimulation inducing a “state of tolerance” to TLR7 agonists (see figure). This is characterized by robust activation of STAT3, downregulation of TNF-α, and a decreased rate of proliferation. Because CLL cells did not adhere to stromal cells, the authors hypothesized that a stromal cell–secreted factor was responsible, and they confirmed this by showing that the use of stromal conditioned media in the absence of stromal cells led to similar results. Since STAT3 had been already shown to modulate
TLR responses, the authors used an antibody array customized to measure STAT3-activating factors. Results showed that IL-6 was the main cytokine produced by the spleen-derived stromal cells, and that it was capable of tolerizing CLL cells to TLR7 agonists in a dose-dependent manner. Additionally, IL-6 receptor-blocking antibodies or Janus kinase inhibitors were able to block IL-6–induced CLL tolerization. Of note, IL-6 was previously shown to inhibit proliferation of CLL cells in response to TNF-α, although a mechanism for that was not provided. The downregulation of TLR7 and TNF-α mRNAs associated with TLR7 tolerization led the authors to hypothesize that IL-6 was inhibiting TLR7 signaling through an miR/RNA network. By performing in silico analyses of the 3′ untranslated regions of TNF-α and TLR7, the authors identified seed sequences for miR-17 and miR-19a, and showed that IL-6 stimulation induced upregulation of these miRs. Overexpression of miR-17 and miR-19a was able to tolerize CLL cells directly, whereas miR-17 and miR-19a antagoniRs restored TLR7 signaling.

IL-6 has been shown to exhibit context-dependent immunoregulatory properties. Chronic IL-6 signaling has been linked to tumorigenesis in numerous human cancers by stimulating tumor cell proliferation, metastatic dissemination, and tumor evasion of immune surveillance. However, a tumor growth–opposing role has recently been proposed in which IL-6 provides proliferative signals to leukocyte populations and mobilizes antitumor T-cell immune responses. Consistent with this context-dependent effect of IL-6, the authors show that in the absence of exogenous TLR signaling, IL-6 enhances short-term engraftment of CLL in vivo, whereas in the presence of TLR7 agonists, IL-6 acts as a tumor suppressor by slowing leukemia progression.

Overall, this study represents a useful step forward in our understanding of CLL biology and reiterates the pivotal role of the microenvironment in nurturing CLL cells. By identifying IL-6 and TLR7 signaling in the CLL spleen microenvironment (and, notably, using human spleen-derived stromal cells to do this), Li et al have added to our relatively limited knowledge of the roles of these factors in CLL. Here, the authors provide evidence for the immunosuppressive capacity of IL-6, introducing the idea that therapeutically disrupting IL-6 signaling might have context-dependent implications. As is typically the case in research, more work will be needed to resolve certain questions, such as why IL-6 treatment causes reduced CLL cell numbers in mice and how it enhances sensitivity of TLR7-activated CLL cells to cytotoxic agents. In particular, focused examination of the IL-6 context dependency reported here may help to reconcile the complex and sometimes contradictory reports regarding IL-6 in CLL; for example, the cause and importance of IL-6 secretion by CLL cells themselves, as well as the observation that high serum levels of IL-6 correlate with more aggressive disease. Hopefully, the data provided by Li et al move us closer to being able to manipulate the CLL microenvironment to the benefit of our patients.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

© 2015 by The American Society of Hematology

LYMPHOID NEOPLASIA

Comment on Hagner et al, page 779

Evolution: IMiDs to PPMs, revolution in DLBCL?

Grzegorz S. Nowakowski Mayo Clinic

In this issue of Blood, Hagner et al provide preclinical evidence that CC-122 might be active in both major molecular subtypes of diffuse large B-cell lymphoma (DLBCL). The development and evolution of immunomodulatory drugs (IMiDs) is one of the most fascinating drug development stories in cancer medicine. This history began with their use as an antiemetic drug used in pregnancy and was abruptly halted because of the association with severe birth defects. Their use as an antiemetic drug continued to evolve with demonstrated activity in multiple myeloma. Novel properties make CC-122 potentially active in a subtype of DLBCL in which its predecessor, lenalidomide, has limited activity. There are 2 subtypes of DLBCL: activated B-cell–like (ABC) and germinal center B-cell–like (GCB) subtypes. The former is characterized by tonic B-cell receptor...
Interleukin-6 in CLL: accelerator or brake?

Rosa Lapalombella