showing that Mk-biased CD41^{hi} HSCs are expanded in MPNs, these cell populations appearing to lose their self-renewal potential suggests that still unknown factors, operating at the primitive stem cell level, are required for the phenotypic variability observed across MPNs.

As our understanding of the cellular heterogeneity of the HSC compartment improves, so too will our understanding of how MPN mutant stem cells survive to sustain disease. In turn, hopefully, we can design improved therapeutic strategies that better target MPN clones and those mutated cells at the earliest stages of the hematopoietic hierarchy. This work, taken together with recent clinical studies of IFNs in MPNs, provides a glimpse into MPN stem cell biology with the goal of informing additional therapeutic studies in MPNs and other stem cell–derived hematopoietic malignancies.

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LYMPHOID NEOPLASIA

Comment on Patrussi et al, page 2182

IL-9 in CLL: sensing home and settling down!

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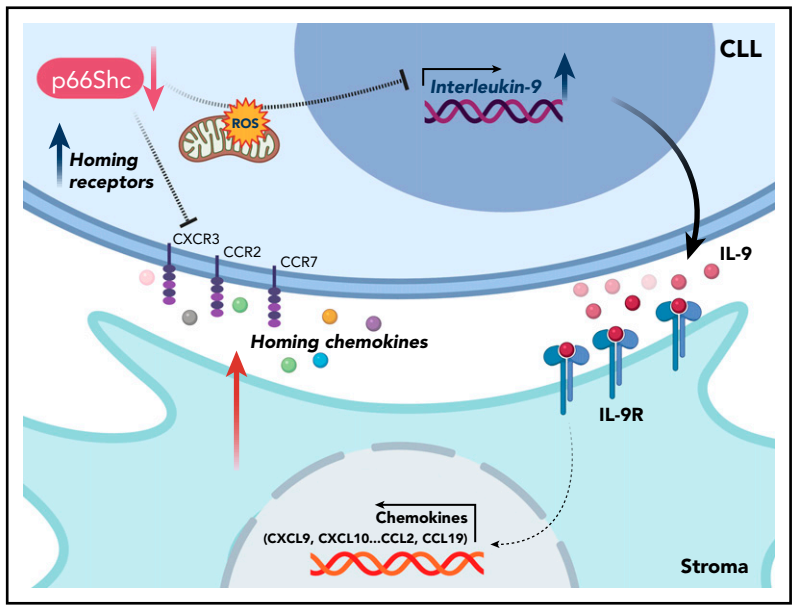
In this issue of *Blood*, Patrussi et al describe a complex, interleukin-9 (IL-9)–dependent, signaling pathway underlying the crosstalk between chronic lymphocytic leukemia (CLL) and stroma cells, highlighting the exquisite dependency of tumor cells on their microenvironment for survival and proliferation.[1]

The CLL microenvironment has ignited substantial scientific curiosity in the past decade and has ultimately revealed new vulnerabilities of tumor cells, which are now therapeutically exploited by B-cell receptor (BCR) inhibitors. Although this



Proposed model of the p66Shc-mediated IL-9 crosstalk between CLL and stroma cells. Low levels of p66Shc in CLL cells simultaneously enhance the expression of homing receptors and permit the transcription of IL-9 in an ROS-dependent manner. CLL-derived and secreted IL-9 binds to IL-9-receptors expressed on stroma cells and drives the expression of homing cytokines, further attracting CLL cells to their niche. Created with BioRender.com.

approach has proven to be highly successful in the clinic, acquired resistance and drug intolerance indicate that alternative therapeutic approaches are still needed.

Following the authors' previous observations that CLL B cells with decreased expression of p66Shc display enhanced infiltration of nodal and extranodal tissues and associates with disease aggressiveness,[2] they now identify IL-9 as a main conduit linking p66Shc levels to cell-homing. P66Shc was previously identified as an adaptor protein, which contributes to the disease pathogenesis by modulating reactive oxygen species (ROS) levels and apoptosis thresholds.[3] In a set of elegant experiments, the authors demonstrate that through its ROS-generating function low levels of p66Shc lead to enhanced secretion of IL-9 by CLL cells. Operating as a sensor to identify stroma cells in their immediate microenvironment, engagement of the IL-9 receptor on stroma cells subsequently induces the transcription and secretion of numerous chemokines (CXCL9, CXCL10, CXCL11, CXCL13, CCL2, and CCL19), which ultimately facilitate the recruitment of tumor cells to these stroma niche cells (see figure). Importantly, this molecular crosstalk between tumor and stroma cells, identified through in vitro coculture and in vivo mouse experiments, has clinical implications. The authors describe high levels of IL-9 associated with low p66Shc levels, *IGHV* unmutated CLL, enhanced nodal disease and liver infiltration, and shorter overall survival, indicating that the proposed mechanisms can confidently be extrapolated to patients. Whether the assessment of IL-9 plasma levels in patients is prognostically meaningful as an independent marker, as discussed by the authors, remains to be evaluated prospectively.

A key finding described in this paper is the identification of CLL-derived IL-9 as a niche-remodeling cytokine, generating a promigratory environment for tumor cells. Although IL-9 is known to be predominantly produced by T-cell subsets and mast cells,[4] secretion by CLL cells must be considered aberrant because normal B cells have not been shown to constitutively produce IL-9, possibly through its inhibition by fully maintained p66Shc activity.[2] Furthermore, although effects of IL-9 have extensively been studied in T and mast cells, a contribution of IL-9 signaling to tumor-induced remodeling of mesenchymal stromal cells has not yet been appreciated. The authors have further demonstrated that antagonizing IL-9 with a neutralizing antibody impairs homing and disease progression in the Eμ-TCL1 mouse model, adding to the body of evidence that stroma-derived factors are essential for disease progression. It can be speculated that additional direct effects of IL-9 antagonism on the skewed T-cell compartment in CLL could have also contributed to the observed antileukemic effects. Collectively, the authors' experiments further illustrate how targeting CLL-stroma interactions is a meaningful way to treat CLL, and potentially other lymphoma as well.

An important distinction to be made when considering the targeting of CLL-stroma interactions is the spatial distribution of the target, as this is likely to impact on the development of drug resistance. This is also true for IL-9 and its receptor, as transgenic mice engineered to constitutively produce IL-9 showed an expansion of IL-9 receptor-positive B1 cells,[5] suggesting that autocrine mechanisms may also contribute to the therapeutic effects mediated by anti–IL-9 treatment. Previous attempts to interfere with CLL-stroma interactions have repeatedly identified essential kinases known to mediate BCR signaling (eg, LYN, BTK, PKC-β) in tumor B cells, but also have been found to be expressed in cells of the microenvironment.[6,7] Because the tumor microenvironment is not under selective pressure to evolve, nor is there evidence of genomic instability in these cells, acquired drug resistance to stroma therapies is likely to be significantly delayed or absent for drugs directly targeting stroma cells, as opposed to targeting of proteins expressed within the tumor cell. Therefore, it seems reasonable to assume that targeting of IL-9 signaling, which involves downstream phosphorylation of JAK1/3,[8] may also be achievable with JAK inhibitors and may constitute an alternative method to block the effects of IL-9 on stroma cells.

Finally, it remains to be demonstrated to what extent targeting of the p66Shc-IL-9–chemokine axis is clinically beneficial. Because stroma cells are known to also contribute to environment-mediated drug resistance of malignant B cells, their direct targeting can synergize with coadministered drugs as recently demonstrated for PKC inhibitors.[9] Similarly, anti–IL-9 treatments may therefore also enhance the efficacy of other drugs. The success of BCL2 inhibitors in combination with BTK inhibitors already provides clinical proof that similar approaches are meaningful and deserve further experimental and clinical explorations. The proposed transcellular signaling pathway identified by Patrussi et al provides many new insights into how to target CLL-mediated activation of stroma cells and is likely to further enrich our armory of CLL drugs in the future.

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