inside blood commentary

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LYMPHOID NEOPLASIA

Comment on Geskin et al, page 2798

IL-13 as a novel growth factor in CTCL

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In this issue of *Blood*, Geskin et al report that interleukin-13 (IL-13) acts as an autocrine growth factor in cutaneous T-cell lymphoma (CTCL) and that simultaneous antibody-based neutralization of IL-13 and IL-4 inhibits in vitro proliferation of CTCL cells.[1]

CTCL is composed of 2 closely related, yet clinically very distinct, subtypes of mycosis fungoides (MF) and erythroderma typically associated with circulating Sézary cells (Sézary syndrome [SS]). Despite extensive investigation, the pathogenesis of CTCL, both MF and erythroderma/SS, remains poorly understood. Consequently, the therapies remain predominantly empirical, and not directly based on pathobiology of the malignant cells. Recent identification in CTCL of point mutations of the *PLCG1* and other cell signaling-related genes[2] may accelerate introduction of targeted therapies in this disorder.

The growing body of mostly circumstantial evidence indicates that cytokine signaling plays a critical role in CTCL.[3–5] Although for most of the disease course, the CTCL cells depend on cytokines for their survival and proliferation, at the late stage they seem to become cytokine independent but continue to display persistent activation of cytokine signaling pathways such as signal transducer and activator of transcription 3 (STAT3) and STAT5, presumably due to genetic alterations within the signaling proteins. Although early on, T helper 1 (Th1)–type cytokines such as IL-2 and IL-15 dominate in MF, Th2 cytokines such as IL-4 gradually begin to prevail relatively soon, due to the loss of the IL-12–responsive STAT4 expression in some cases.[5] There is also evidence of the CTCL cells' Th17 differentiation,[6,7] likely driven, or augmented, by bacterial and fungal infections, frequently seen in the advanced stages of CTCL characterized by marked immunosuppression, seemingly due in part to expression of IL-10.[4] Whereas IL-17 expression has been found in MF lesions,[6] other investigators identified IL-26 as being dominant in the Th17-biased CTCL cells.[7] IL-32 has also been suggested to play a role of an autocrine growth factor in CTCL, in particular in the advanced disease.[8] Surprisingly, IL-32 expression correlated with expression of the Th1 cytokine interferon γ but not the Th2 cytokines. Finally, CTCL cells have been found to produce the pruritus-promoting, inflammatory cytokine IL-31.[9]

The above findings clearly indicate that CTCL lesions contain multiple cytokines and their number, type, and exact composition are dynamic and disease-stage dependent.[4,5] This cytokine diversity is associated with plasticity of the CTCL cells,[4] reflected by their ability to acquire various Th phenotypes, depending on the stimuli provided by the cytokines, antigen-presenting cells, and other factors present in their direct milieu. Consequently, most of the CTCL skin lesions, in particular at the earlier stages of the disease, are expected to contain a large number of various cytokines and phenotypically diverse subpopulations of the CTCL cells.

Recent studies have also implicated IL-13 in pathogenesis of CTCL. This Th2-type cytokine is functionally closely related to IL-4 by sharing a common receptor composed of the IL-4Rα and IL-13Rα1 chains, with both cytokines activating STAT6 as the major cell-signaling transmitter. Guenova et al reported on the strong bias of leukemic Sézary cells as well as nonmalignant cells from the same SS syndrome patients toward the Th2 phenotype, marked by the IL-4 and IL-13 secretion.[10] The CTCL cell-derived, IL-4– and IL-13–containing supernatants promoted conversion of the normal T cells from the Th1 to the Th2 phenotype, and neutralizing antibodies to IL-4 and IL-13 restored the Th1 phenotype. In turn, Wolk et al demonstrated that IL-13 plays a role in the susceptibility of CTCL patients to the bacterial infections by downregulating expression of antibacterial proteins.[7] The current study[1] complements these observations by providing evidence that IL-13 directly stimulates growth of Sézary cells and acts in these cells as an autocrine growth factor. Although IL-13 inhibition by a neutralizing antibody markedly suppressed growth of the Sézary cells, the inhibition was even more profound when an IL-4–neutralizing antibody was also added. Interestingly, the IL-13 expression was seen not only in the leukemic Sézary cells but also at all stages of MF, with the most robust expression at the advanced stages of the disease.

The emerging important role of IL-13 in CTCL[1,7,10] makes this cytokine an attractive target for a therapeutic intervention, in particular if IL-4 is targeted simultaneously. As described by Geskin et al,[1] inhibition of the IL-4 and IL-13 binding to their common receptor by an anti–IL-4Rα monoclonal antibody dupilumab had shown therapeutic efficacy in asthma and atopic dermatitis, 2 Th2-type disorders. Given the availability of

highly potent small-molecule Jak inhibitors, targeting the Jak1 and Tyk2 kinases associated with the IL-4Rα/IL-13Rα1 complex is also a consideration. In principle, STAT6 may also be an attractive target given the relative specificity of its activation by IL-4 and IL-13. However, clinical-grade STAT6 inhibitors are still under development. It could be argued that the selective targeting of IL-13/IL-4–mediated cell activation as a single therapeutic modality should be the most effective in erythroderma/SS and the MF cases with the strongest Th2 bias. It may, however, be insufficient in other cases and its effects may be transient even in the responding patients, unless combined with other therapeutic approaches.

In summary, identification of IL-13 as an important factor in CTCL expands our understanding of the pathogenesis of this complex lymphoproliferative disorder and has potential therapeutic implications.

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MYELOID NEOPLASIA

Comment on Rijal et al, page 2815

INPP4B, a new player in the chemoresistance of AML

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In this issue of *Blood*, Rijal et al have identified the inositol polyphosphate 4-phosphatase II (INPP4B) as a poor prognostic marker in acute myeloid leukemia (AML), driving chemoresistance through a novel gain-of-function mechanism independent of its phosphatase functions.[1]

Although there has been no therapeutic breakthrough for the treatment of AML over the last 20 years, the cytogenetic and molecular characterization of this disease has allowed stratifying of risk groups with very different prognoses in terms of disease-free and overall survival (OS), and has identified relevant therapeutic targets currently under investigation, such as Fms-like tyrosine kinase 3-internal tandem duplication (*FLT3*-ITD), IDH1/2, or epigenetic regulators.[2,3] Furthermore, the analysis of residual disease following chemotherapy also helps to stratify postremission therapy. Thus, do we need another new prognostic marker to manage our patients? The answer is "yes" if this marker predicts early response to chemotherapy (ie, primary induction failure), and more importantly, if this new marker is linked to chemoresistance. Rijal et al investigated the expression profile of several phosphatases involved in the phosphoinositide-3 kinase (PI3K) pathway and found that INPP4B can fill in these 2 requirements.

Class I PI3K that produces the D3-phosphoinositide second messenger phosphatidylinositol 3,4,5-trisphosphate in response to membrane receptor activation plays a critical role in cell proliferation, survival, metabolism, and motility. These lipid kinases and the phosphatases regulating the level of D3-phosphoinositides have been an intense area of research in the field of cancer for the past 2 decades.[4] Most AML display a constitutive activation of the PI3K pathway that contributes to cell proliferation and chemoresistance.[5] Several mechanisms converge to activate the PI3K pathway in AML, including mutated receptor tyrosine kinases (ie, *FLT3*-ITD), growth factors (ie, insulin-like growth factor 1), or microenvironment players (ie, SDF1α/CXCR4 or fibronectin/VLA-4 modules). Much less is known regarding the negative regulators of this pathway. Rijal et al first performed a quantitative gene expression screen of 11 phosphoinositide phosphatases using a mass spectrometry detection system in 22 AML samples and found a reduction of the 5-phosphatase (SH2 domain-containing inositol 5′-phosphatase 2) expression, whereas *INPP4B* and *INPP5B* were significantly overexpressed compared with normal bone marrow (BM) cells. However, high *INPP4B* expression solely emerged as a potential indicator of poor AML survival. Having verified good concordance between *INPP4B* gene expression and protein levels, they assessed INPP4B protein expression in a panel of 205 BM biopsies from patients treated with intensive chemotherapy and eventually allogeneic stem cell transplantation as postremission therapy. They identified 25 patients (12%) with high INPP4B expression and poor outcome both in terms of leukemia-free and OS. There was no significant association between high INPP4B expression and other classical poor risk features (age, secondary AML, leukocytosis, cytogenetic risk, or *FLT3*-ITD). However,