inside blood

10 FEBRUARY 2011 | VOLUME 117, NUMBER 6

LYMPHOID NEOPLASIA

Comment on Ju et al, page 1938

JAK blockade and HTLV

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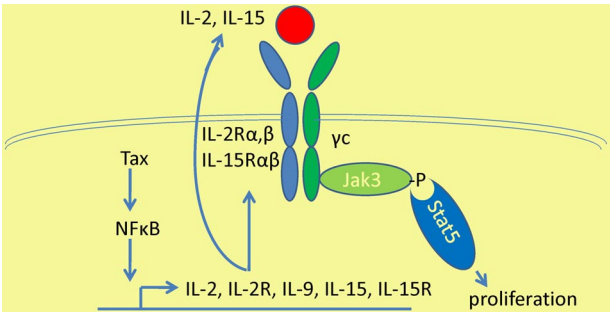
In this issue of *Blood*, Ju and colleagues report that a selective inhibitor of Janus kinase 3 (Jak3) blocks autocrine and paracrine interleukin 2 (IL-2), IL-9, and IL-15 activation, which is important for lymphocyte proliferation induced by human T-cell leukemia virus (HTLV).[1]



Constitutive Jak-Stat signaling in HTLV-1 infection resulting in overexpression of interleukins 2, 9, and 15, interleukin receptors 2 and 15, and activation of Jak3 and Stat5, resulting in lymphocyte proliferation.

DNA sequence analysis predicts 90 protein tyrosine kinases encoded by the human genome, including 32 nonreceptor kinases.[2] One group of nonreceptor kinases are the Janus family kinases: Jak1, Jak2, Jak3, and Tyk2. Whereas, Jak1, Jak2, and Tyk2 are constitutively expressed in mammalian cells, Jak3 is primarily restricted to hematopoietic cells. Hematopoietic cytokines and growth factors use members of the Jak family for signal transduction, and Jaks are important for cell proliferation, survival, development, and differentiation. Loss of Jak function results in immune deficiency, such as a form of severe combined immune deficiency syndrome associated with loss of Jak3. In contrast, activating mutations in Jaks cause malignant transformation.

HTLV type 1 (HTLV-1) is the etiologic agent of adult T-cell leukemia lymphoma (ATLL) and tropical spastic paraparesis (TSP), also termed HTLV-1–associated myelopathy (HAM).[3] The transcriptional activator protein, Tax, promotes virus replication by up-regulating transcriptional activity of CREB/ATF proteins. Tax, which suppresses apoptosis through constitutive activation of the NFκB pathway, is also sufficient for immortalization of $CD4^+$ lymphocytes. Tax also exhibits posttranscriptional effects through inhibition of cell-cycle phase inhibitors, DNA repair factors, DNA damage responses, and chromosome instability checkpoint proteins. Despite its role in initiating transformation, Tax expression is diminished or absent after ATLL is established, and such immortalized cells frequently exhibit growth factor independence.

The Jak-Stat pathway is constitutively activated in HTLV-1–transformed cells.[4] This may occur through constitutive autocrine stimulation of IL-2, IL-15, and IL-2 and IL-15 receptor expression, as a result of Tax-induced NFκB expression (see figure).[5] Alternatively, paracrine stimulation of IL-9 by HTLV-1 Tax could also promote activation of the IL-9 receptor on monocytes, which in turn stimulates proliferation of HTLV-1–infected lymphocytes.[6] The current article by Ju and colleagues demonstrates that inhibition of all 3 receptor-mediated pathways prevents proliferation of HTLV-1–infected lymphocytes more effectively than inhibition of any one of the pathways.[1] Moreover, because the IL-2, IL-9, and IL-15 receptors all share the use of the common γ chain (γc), inhibition of γc-associated Jak3 proved to be as effective as combined inhibition of all 3 pathways. CP690 550 is a selective Jak3 inhibitor, plus it also inhibits mutant forms of Jak2.[2] Clinical studies are under way in patients with rheumatoid arthritis and psoriasis; other studies will also examine the prevention of renal transplant rejection.

The Jak-Stat pathway may also be constitutively activated in transformed cells due to gain-of-function mutations. Although Jak2 mutations are common in myeloproliferative disorders, Jak3 mutations have been reported in only a few patients with solid tumors, and have not been identified in ATLL.[2,7] Alternatively, the Jak-Stat pathway may be activated by loss of suppressor of cytokine signaling (SOCS) proteins, E3 ubiquitin ligases that promote the degradation of Jak proteins. HTLV-1 infection overcomes the effects of interferon-induced Jak-Stat activation by up-regulation of SOCS1.[8]

In light of the limited efficacy of current therapies for ATLL and HAM/TSP, the current preclinical results with Jak3–targeted therapy offer a potential new avenue of treatment for these disorders.

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

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Comment on Castellino et al, page 1806

Sobering realities of surviving Hodgkin Lymphoma

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In this issue of *Blood*, Castellino and colleagues investigate morbidity and mortality in a cohort of long-term survivors of Hodgkin lymphoma (HL) from the Childhood Cancer Survivor Study. They observe frequent and serious late sequelae of therapy occurring even after 20 years of follow-up; their findings highlight the need to consider long-term implications when selecting therapeutic strategies for young patients with curable lymphomas.

The unprecedented advancement and success in the treatment of childhood and adolescent hematologic malignancies over the past decades is tempered by the fact that many survivors develop secondary life-threatening complications. The extent of the spectrum of secondary malignancies and cardiac toxicities has only recently been realized. The predominant culprit of these complications has been radiation therapy.[1-3] Long-term survivors of HL are a group of people who are particularly devastated by late effects of therapy due to a "perfect storm"-type combination of factors: (1) HL is predominantly a disease of adolescents and young adults; (2) high cure rates mean that survivors can live for many decades after therapy; and (3) nodular sclerosis, the most common subtype, preferentially afflicts young women and frequently with mediastinal involvement, which has historically been treated with radiation therapy. Therefore, this interaction of disease characteristics with historical management strategies has led to the extremely high rates of solid tumors—particularly breast cancer—and ischemic heart disease in this population of survivors.

Castellino and colleagues herein report on morbidity and mortality in 2742 survivors of HL from the Childhood Cancer Survivor Study.[4] Although some other groups have specifically investigated HL survivorship, this is the largest available cohort and, thus, is an important and invaluable resource for studying and realizing the late effects of therapy in this population. In addition, this cohort is mature in that all patients were treated before 1986. Despite excellent survival rates in the early years after therapy, the authors observe that beyond 10 years, there is significant excess mortality from secondary malignancies and cardiovascular disease with no plateau despite longer follow-up. Furthermore, at 20 years after initial treatment for HL, the excess death risk from cardiovascular disease rivals that from solid tumors.

As discussed and highlighted by the authors, although women with breast cancer do not appear to have an excess risk of mortality, the scale of breast cancer morbidity in these survivors is remarkable (cumulative incidence at 30 years after diagnosis is 18.3%) and should not be underemphasized. In fact, breast cancer, cardiovascular disease, and thyroid cancer were the principal morbidities identified in this report and as 94% of patients received supra-diaphragmatic radiation, it is probable that radiation therapy was causative in most cases. Although Castellino and colleagues identify a radiation dose > 30 Gy as a risk factor for overall mortality, it is important to realize that lower doses of radiation were linked to morbidity and are not benign in terms of long-term sequelae. In addition, a recent survivorship report evaluated the long-term outcome of pediatric patients with HL who received low-dose radiation and demonstrated that secondary tumors occurred with similar frequency and latency as in studies where HL patients received high-dose radiation.[5]

Although we have made significant advances in the treatment of HL over the past 20 years and have moved on from using high-dose extended-field radiation, much progress remains to be made. The lessons of this report are clear—it is critical to consider the long-term toxicity of treatment when selecting therapy for newly diagnosed patients. Moreover, it is important to continue to develop and evaluate novel targeted therapies that maintain high cure rates while obviating the need for combination radiation and chemotherapy that may cause these unacceptable long-term effects. Immune-based therapies using monoclonal antibodies and tumor-specific T cells are examples of targeted approaches already being evaluated in clinical trials for patients with HL, which offer the promise of tumor-specific killing while sparing bystander organs.[6,7] Hence, a vision for the future of HL therapy could be that targeted therapies are combined and used upfront with carefully selected regimens so that sobering reports such as this one will be tales of the past.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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