Comment on Heine et al, page 1192

Ruxolitinib targets DCs: for better or worse?

Ayalew Tefferi

In this issue of Blood, Heine et al demonstrate the dose-dependent inhibitory effect of ruxolitinib on the generation of dendritic cells (DCs) from monocytes. The drug also inhibited DC activation, tissue migration, and induction of allogeneic or antigen-specific T-cell responses, including in vivo viral clearance.

Human DCs originate from hematopoietic stem cells that give rise to developmentally and functionally distinct DC subsets with the ability to infiltrate lymphatic and other tissues, process and present antigens, and effectively prime T cells toward effector or regulatory responses. Accordingly, DCs can augment or dampen host inflammatory response, and their inhibition might result in increased propensity to infections, compromised immune response to cancer, and dysregulated autoimmunity.

Growth factors (eg, granulocyte-macrophage colony-stimulating factor, Fms-related tyrosine kinase 3 ligand), other cytokines (eg, tumor necrosis factor alpha [TNF-α]), and transcription factors (eg, interferon regulatory factor 8) are essential for DC development and differentiation. DCs themselves are major sources of cytokines, including interleukin-12 (IL-12) and TNF-α. These very same cytokines are aberrantly expressed in myelofibrosis (MF), which is also characterized by constitutive Janus kinase signal transducer and activator of transcription (JAK-STAT) activation. Therefore, DCs are either directly or indirectly involved in the inflammatory process that accompanies MF.

Ruxolitinib inhibition is not specific to mutant JAK2; it also targets wild-type JAK2 and JAK1 equipotently, as well as other kinases. The corresponding signaling pathways that are affected include JAK-STAT, mitogen-activated protein kinase extracellular-regulated kinase 1/2 (MAPK-ERK1/2), and phosphatidylinositol-3 kinase AKT (PI3K-AKT). These pathways are also used for transcriptional induction of DC-relevant cytokines. Therefore, it is not surprising to discover ruxolitinib-associated DC dysfunction; however, the particular observation highlights the risk for adverse off-target effects arising from nonspecific treatment strategies that target multiple cytokines and physiologically important pathways.

Disruption of physiologic JAK-STAT signaling, especially in the context of multi-JAK inhibition, also affects lymphocyte homeostasis. The composite DC-lymphocyte effect might partly explain the ruxolitinib-induced downregulation of interleukin (IL)-6, IL-8, TNF-α, interferon-gamma, IL-1Ra, and other inflammatory cytokines in vivo (see figure). One could argue that such cytokine modulation might be of benefit for inflammation-associated diseases, including MF. However, such a treatment strategy ignores the basic principle of cancer therapy, which is selective suppression of the malignant clone. Instead, it encourages settling for symptom palliation as a treatment end point.

Ruxolitinib therapy in MF conjures limited benefit in terms of reversing bone marrow fibrosis or significantly reducing JAK2 V617F allele burden; its value is mostly limited to relief of constitutional symptoms and reduction in spleen size. Even then, benefit comes at the cost of drug-associated anemia, thrombocytopenia, and cytokine-release syndrome during drug discontinuation. Other JAK inhibitors that are either more selective in targeting JAK2 or less likely to cause anemia are not necessarily spared from similar handicaps (ie, lack of selective anticlonal activity and association with nontrivial drug side effects, including gastrointestinal and neurologic complications). The observation by Heine et al further highlights the need to be vigilant about long-term ill effects.

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<th>Cytokines increased in myelofibrosis</th>
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Cytokines that are aberrantly expressed in MF are known to be developmentally required or secreted by DCs and also targeted by ruxolitinib. G-CSF, granulocyte colony-stimulating factor; HGF, hepatocyte growth factor; INF, interferon; IP-10, interferon-inducible protein 10; MCP-1, monocyte chemoattractant protein 1; MIG, monokine induced by interferon-gamma; MIP-1α, macrophage inflammatory protein 1α; VEGF, vascular endothelial growth factor.
The sequence of events in diffuse large B-cell lymphoma

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In this issue of Blood, Morin et al report their findings on complete genome sequence analysis of primary diffuse large B-cell lymphoma (DLBCL) primary tumors and cell lines and reveal novel somatic point mutations, rearrangements, and fusions.1 Importantly, they also demonstrate the temporal acquisition of mutations, providing insight into the evolution of mutations occurring in DLBCL.

DLBCL is a heterogeneous disease with subtypes defined by distinct molecular signatures and clinical outcomes. Recent studies using massively parallel sequencing have demonstrated that DLBCL molecular subtypes also harbor distinct repertoires of somatic copy number alterations and single nucleotide variants (SNVs).2,3 These studies also highlighted alterations in distinct molecular pathways implicated in disease pathogenesis, including the role of histone modifications in the germinatal center B-cell (GCB) subtype4,5 and B-cell receptor and NF-kB signaling in the activated B-cell (ABC) type. Identification of such pathways opens new avenues for attack to treat more aggressive lymphomas2 and provides new insight into lymphoma pathogenesis.8 It is noteworthy that in the present study, there was little correlation between tumor subtype and the number of genomic rearrangements, as the 5 most highly rearranged cases includes 3 ABC cases and 2 GCB cases. However, the type of mutations that occur differs between GCB and ABC subtypes, and in their manuscript the authors demonstrate somatic mutations affecting each of 3 separate genes (GNAI2, S1PR2, and GNAI3) that cooperate in p-mediated B-cell homing and indicate that these genes are enriched or occur solely in GCB DLBCL.

This manuscript uses whole-genome sequencing (WGS) rather than whole-exome sequencing or RNA-seq. WGS provides the opportunity to determine the pattern, frequency, and location of somatic mutations across the entire tumor genome. It also has the potential to detect regulatory mutations that are not detectable using whole-exome sequencing approaches. The authors show here that mutations do not occur in nonrandom locations but are enriched near transcription start sites. Nonexonic mutations near the transcription start sites of genes are obviously of interest, but in the B-cell malignancies, recurrent promoter mutations are difficult to differentiate from the process of acquired somatic hypermutation (aSHM), as previously reported by this group.9 However, the present study also reveals mutations in new genes of interest and previously undescribed mutations in individual cases, as well as recurrent mutations. The average mutation load determined by WGS in DLBCL is well above the level previously determined using whole-exome sequencing. After correcting for contamination with nontumor cells, the authors report an average of 12,086 somatic mutations, amounting to a frequency genome-wide of 4.21 mutations/megabase and 205.6 (range, 35-400) nonsilent mutations per genome. The pattern of rearrangements and copy number alterations in some of the highly rearranged genomes is consistent with a process of chromothripsis.

WGS also has the advantage of being more sensitive to splice-site mutations. Eleven of the newly detected genes harbored mutation signatures indicative of tumor suppressor function with mutations at splice sites or producing a truncated protein. Mutation hot spots are indicative of potential oncogenes, and these were observed in a subset of the genes detected.

Several of the noted genes have signatures for aSHM, and these hot spots more likely reflect the preference of activation-induced cytidine deaminase for certain sequence motifs rather than evidence of selection. However, the remaining recurrent hotspots inconsistent with aSHM include those with known dominant-acting mutations in lymphoma, including MYD88, CARD11, CD79B, and EZH2, as well as TBL1XR1, MEF2B, FAT4, PKD1, NLRP5, and DSEL, the function of which has not been elucidated.

The cohort of patients studied is relatively small. High-throughput studies usually provide either high coverage and low sample number or lower coverage and more samples. The present study provides 30 times coverage of more than 40 primary, previously untreated DLBCLs and 13 cell lines. There will always be criticism of looking for higher coverage and higher sample numbers, but the number of somatic...
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