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Editorial

The JAK-STAT Pathway and Hematological Malignancy: Beyond Stats

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The Janus kinase-signal transducers and activators of transcription (JAK-STAT) is an evolutionarily conserved signaling pathway that mediates cellular responses to dozens of cytokines and growth factors [1]. These responses, including proliferation, differentiation, migration, and apoptosis, are essential for the development and homeostasis of hematopoietic cells. The disruption of the normal homeostatic process arising from aberrant JAK-STAT activation leads to oncogenic consequences. Genetic lesions that cause constitutively active JAK-STAT signaling have been demonstrated in many chronic and acute hematologic malignancies [2]. Somatic JAK2 V617F mutations and other mutant alleles have been identified in most patients with myeloproliferative neoplasms (MPNs) [3]. IL-6 or IL-10/STAT3 signaling is required for the survival of activated B-cell like subtype of diffuse large B-cell lymphoma (ABC DLBCL) [4]. The auto-secretion of IL6 or IL10 in these cancer cells is due to oncogenic MYD88 L265P mutations, which are present in about a third of patients [5]. We and others have demonstrated that the chromosome 9p24 region that JAK2 resides is amplified in 30-50% of primary mediastinal and Hodgkin lymphoma [6]. The amplification results in increased expression of JAK2, whose activation is dependent on autocrine IL-13 cytokine stimulation.

The knowledge of the JAK-STAT pathway underlying the pathogenesis of hematologic malignancies is limited, even though the pathway has been intensively studied for the last two decades. The JAK-STAT cascade begins with the binding of an extracellular ligand to its receptor. The receptor engagement leads to activation of an intracellular JAK, which then phosphorylates the downstream substrate STAT. The activated STATs form a dimer and enter the nucleus to bind to specific enhancer sequences in target genes. While this canonical pathway seems simple and direct, a new JAK activity that influences the global transcriptional state has been discovered by a *Drosophila* genetic study [7]. Loss- and gain-of-function analyses have revealed that the *Drosophila* JAK homologue increases tumor formation through modification of chromatin structure. *Drosophila* JAK homologue prevents heterochromatin formation to globally up-regulate gene expression, as evidenced by reduced methylation of histone H3 lysine 9 (H3K9me), a suppressive histone mark. A recent elegant study has extended this finding and discovered underlying molecular mechanisms [8]. In MPN cells, the mutant JAK2 isoform is present in the nucleus and acts as a kinase for histone H3 to phosphorylate tyrosine 41 (H3Y41). H3Y41 phosphorylation displaces the inhibitory heterochromatin protein HP1 from chromatin and initiates gene transactivation. The genes induced for expression through this mechanism include important proto-oncogenes, such as LMO2. No STAT motif on the LMO2 promoter regions indicates that its expression is independent of the canonical STAT pathway. The studies have demonstrated the conserved non-canonical pathway for JAKs.

The major research interest in my laboratory is to dissect the role of this non-canonical JAK signaling pathway in B cell lymphoma. Our recent study has established a JAK2 signaling model for the pathogenesis of primary mediastinal and Hodgkin lymphoma [6,9]. Despite distinct histology entities, these two lymphomas share common biological and molecular features, including JAK2 amplification. The oncogenic role of JAK2 in these lymphoma cells has emerged from an RNA interference library screen. JAK2 and the co-amplified JMJD2C, a gene encoding histone demethylase, are required for cancer cell survival and proliferation. Interestingly, these two genes cooperatively regulate gene expression to promote tumor growth. The molecular mechanism of this synergism is histone modifications with H3K9 demethylation by JMJD2C and H3Y41 phosphorylation by JAK2. These coordinated chromatin modifications release HP1 suppression and consequently lead to opening up chromatin structure for gene transcription. Genome-wide mapping of phosphorylated H3Y41 has demonstrated that nuclear JAK2 up-regulates expression of about 2,000 genes in the cancer cells. These include well-described oncogenes like MYC and NF-KB pathway genes, such as IRF4 and CD40. Strikingly, JAK2 auto-regulates its expression through forming a positive feedback loop with itself, JMJD2C, or the integral component of IL-13 receptor IL-4R, respectively. The cancer cells acquire multi-layers of the positive forward regulation to prevent their apoptotic cell death. Furthermore, JAK2 can induce expression of the other two co-amplified genes PD-L1 and PD-L2, both of which encode ligands for inhibitory PD-1 receptor on T cells [10]. Expression of PD-L1 and PD-L2 may allow these malignant cells to escape immune surveillance in the aggressive T-cell rich microenvironment. Thus, the scale of gene expression through the non-canonical JAK2 pathway is more than previously thought. The study

provides a new insight into the pathogenesis of JAK2-dependent lymphomas.

The discovery of the non-canonical JAK-STAT pathway opens a new area of hematologic research. With the advent of genomic technologies, the information on JAK-dependent modulation of the cancer epigenome will be enriched in the coming years. A better understanding of the signaling mechanism of tumorigenesis will facilitate identification of new drug targets in hematologic malignancies. Successful treatment of MLNs with JAK2 inhibitors provides such an example. We just started a long journey to explore this important oncogenic mechanism. Many questions remain. Some of these questions are: 1. What is a relationship between this pathway and the canonical pathway? 2. Do other JAK family members have a similar function to regulate gene expression? 3. Does JAK2 target other histone proteins? 4. Does this pathway cooperate with other signaling pathways to promote cell survival and proliferation? We anticipate that addressing these questions will no doubt advance our knowledge of the mechanisms of the JAK-STAT pathway in tumorigenesis and may help in the development of therapeutic agents to selectively modulate JAK activity to treat JAK-dependent hematologic malignancies.

REFERENCES

1. Stark GR, Darnell JE Jr. The JAK-STAT pathway at twenty. Immunity. 2012; 36: 503-14.
2. Chen E, Staudt LM, Green AR. Janus kinase deregulation in leukemia and lymphoma. Immunity. 2012; 36: 529-41.
3. O'Shea JJ, Holland SM, Staudt LM. JAKs and STATs in immunity, immunodeficiency, and cancer. N Engl J Med. 2013; 368: 161-70.
4. Lam LT, Wright G, Davis RE, Lenz G, Farinha P, Dang L, et al. Cooperative signaling through the signal transducer and activator of transcription 3 and nuclear factor-{kappa}B pathways in subtypes of diffuse large B-cell lymphoma. Blood. 2008; 111: 3701-13.
5. Ngo VN, Young RM, Schmitz R, Jhavar S, Xiao W, Lim KH, et al. Oncogenically active MYD88 mutations in human lymphoma. Nature. 2011; 470: 115-9.
6. Rui L, Emre NC, Kruhlak MJ, Chung HJ, Steidl C, Slack G, et al. Cooperative epigenetic modulation by cancer amplicon genes. Cancer Cell. 2010; 18: 590-605.
7. Shi S, Calhoun HC, Xia F, Li J, Le L, Li WX. JAK signaling globally counteracts heterochromatic gene silencing. Nat Genet. 2006; 38: 1071-6.
8. Dawson MA, Bannister AJ, Göttgens B, Foster SD, Bartke T, Green AR, et al. JAK2 phosphorylates histone H3Y41 and excludes HP1alpha from chromatin. Nature. 2009; 461: 819-22.
9. Rui L, Schmitz R, Ceribelli M, Staudt LM. Malignant pirates of the immune system. Nat Immunol. 2011; 12: 933-40.
10. Steidl C, Shah SP, Woolcock BW, Rui L, Kawahara M, Farinha P, et al. MHC class II transactivator CIITA is a recurrent gene fusion partner in lymphoid cancers. Nature. 2011; 471: 377-81.

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