

Transcription Therapy in Hematological Malignancies

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Transcription therapy refers to therapeutic manipulation of gene expression in malignant cells. To date, this is the most successful therapeutic strategy in acute leukemia and is poised to become one of the major treatment modalities for cancer patients in the "post chemotherapy era". Aberrant transcriptional control of gene expression (by mutations or deregulation of transcription factors) is a fundamental process in hematological malignancies. Transcription factors are protein that bind to specific genes resulting inactivation or repression of their expression. Mutations in transcription factors cause abnormal gene expression patterns, resulting in a survival or proliferative advantage and defects in differentiation in affected cells or tissues.

In the past five years, molecular studies of transcriptional mechanisms of action as well as high throughput functional genomic studies of oncogenic transcriptional programs have completely changed our perspectives on these disease. For example, from the mechanistic standpoint, the discovery of a common pathway of transcriptional repression through recruitment of histone deacetylases led to intensive development of drugs to block these enzymes, many of which are now in clinical trials. From the functional genomic standpoint, studies of diffuse large B cell lymphomas (DLBCL), show that this disease actually consists of at least two separate entities: activated B cell" and "germinal B cell" DLBCLs, which are distinct in their clinical behavior and can be individually and specifically targeted by novel experimental drugs. Awareness of the critical importance of transcriptional mechanisms in the pathogenesis of

hematologic malignancies requires a re-evaluation of how these diseases are classified and treated. Thus, older systems such as the FAB and the Working formulation do not adequately reflect the biology of these tumors. The most recent WHO classification of leukemias and lymphomas only partially acknowledges this by defining certain disease subsets according to mutated transcription factors. However, prospective and retrospective studies of transcription patterns indicate that these schemes are still inadequate. It is not surprising therefore that transcriptional based molecular classification and transcriptional molecular therapeutics are becoming a centerpiece of hematology research. In fact, a number of transcription therapy modalities are now at the biochemical, translational or clinical stage of testing. Among these, the histone deacetylase inhibitor drugs (HDIs), and DNA methyltransferase inhibitor drugs (MTIs) have been validated in several model systems and are under study in a large number of clinical trials. This is a high priority for the (US) National Cancer Institute which is involved in accelerating and facilitating such studies.

The second major category of biological processes altered in hematological malignancies involves signal transduction. This was recently highlighted by the finding that mutations of the Flt3 receptor tyrosine kinase are the most common genetic alteration in acute myeloid leukemia. Interestingly, most transcription factor mutations are insufficient on their own to cause leukemia. Likewise, Flt3 mutations also do not cause malignant transformation. However, when both (Flt 3 + transcription factor) mutations occur in

the same cell, malignant transformation occurs, consistent with the observed coexistence of a transcriptional hit and a signaling hit in most leukemias. Flt3 tyrosine kinase inhibitors are currently in clinical trials in patients with acute leukemias and other hematologic malignancies, it is likely that transcription therapy and signal transduction therapy will need to be combined in future therapeutic trials for maximal efficacy.

In my laboratory we study the basic mechanisms through which oncogenic transcription factors mediate aberrant transcriptional control of the genome. We focus principally on a family of transcriptional repressors that includes proteins such as Bcl-6 – which is the most commonly involved oncoprotein in B-cell lymphomas, and PLZF – which causes the retinoid refractory variant of APL when fused to the retinoic acid receptor alpha. Through a combination of structural biology, biochemical and biological as-

says we discovered separate mechanisms of action for these two proteins. We designed transcription therapy drugs to block these mechanisms and have found that these drugs selectively kill DLBCL cells that are Bcl-6 dependent. To more precisely define the biology and predict the optimal treatment of hematological malignancies we took advantage of information provided by the human genome project to design and produce a special type of microarray containing up to 35,000 gene promoter regions. We expect these reagents to facilitate more accurate clinical classification than current methods, and to design therapeutic strategies tailored to individual patients. We believe that such approaches will one day be the standard of care for cancer patients.

We will discuss recent developments in experimental transcriptional therapeutics of leukemias and lymphomas and the current state of clinical trials designed to test these agents.