J Hematol Thrombo Dis 2017, 5:5(Suppl)
DOI: 10.4172/2329-8790-C1-006

AP1 transcriptional regulation drives therapeutic response in oncogenic-kinase driven leukemia

Mohammad Azam
University of Cincinnati, USA

Protein kinases are frequently activated in a variety of human cancers and represent attractive drug targets. In this regard, chronic myeloid leukemia (CML) represents an important paradigm, as the success of imatinib in treating CML patients provided proof of concept for targeted anti-kinase therapy and paved the way for the development of tyrosine kinase inhibitor (TKI) therapy for several solid tumor types. Despite the impressive response to TKI therapy in the clinic, it is not curative because a small population of cancer cells are insensitive to treatment; manifesting as minimal residual disease (MRD)1. The cells responsible for MRD in CML are referred to leukemia-initiating cells (LICs), whereas those responsible for MRD in solid tumors are referred to as cancer stem cells (CSCs). In ~50-60 % of CML patients, continuous drug treatment is needed to prevent MRD cells from reinstating the disease. MRD cells serve as a reservoir of cells that can develop TKI resistance by acquiring mutations or by activating alternative survival mechanisms. Even the most potent kinase inhibitors are ineffective against LICs that are present in MRD. Recent studies have revealed that growth factor signaling mediates resistance to TKI therapy in both leukemia and solid organ tumors2-4, but, it remains to be determined if intrinsic resistance conferred by a diverse set of growth factors utilizes distinct or shared molecular pathways. We hypothesized that the critical genes mediating TKI resistance might be modulated by both BCR/ABL and growth factor signaling. To gain insight into intrinsic TKI resistance, in leukemic stem cells, we performed whole-genome expression profiling from BCR/ABL transformed cells (+/- growth factor). As envisioned, both growth factor signaling and oncogenic signaling converges to induce the expression of c-Fos and Dusp1 that causes resistance to TKI. Interestingly, genetic studies in mice revealed that the deletion of Dusp1 and c-Fos is synthetic lethal to BCR-ABL expression. Mice deleted for both genes are resistant to BCR-ABL-induced leukemogenesis suggesting that these genes constitute non-oncogene dependence to leukemic transformation. Chemical inhibition of c-Fos and Dusp1 suppressed BCR-ABL-induced leukemia and cured mice of established CML disease. Chemical inhibition of *c-Fos, Dusp*1 and BCR-ABL eradicated leukemic stem cells and MRD in multiple in vivo models, and primary patient xenotransplants. Interestingly, deletion of c-Fos and Dusp1 is synthetic lethal to B-ALL development. In other words, unlike in CML, deletion of c-Fos and Dusp1 is sufficient to eradicate B-ALL. Overall, our preliminary data suggests that expression levels of c-Fos and Dusp1 determine the threshold of TKI efficacy (Fig. 1), such that lower levels confer sensitivity; while higher levels drive resistance in both leukemia and solid organ cancers (Kesarwani et. al. nature medicine, 2017). Thus, growth-factor-induced expression of c-Fos and Dusp1 confers intrinsic resistance in to TKI therapy cancer stem cells in a wide-ranging set of tumors; it may represent a unifying Achilles heel of kinase-driven cancers.

Mohammad.Azam@cchmc.org