Expounding on the essence of epigenetic and genetic abnormalities in blastic plasmacytoid dendritic cell neoplasms

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Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic malignancy now known to derive from immature plasmacytoid dendritic cells. However, the cell of origin for this entity was unknown a mere two decades ago when it was alternatively speculated to be of natural killer (NK)-cell or monocytic origin. Coupled with recent advancements in genetic technologies, we have been at an inflection point in time for understanding the essence of this disease.[1]

The recent paper by Sapienza *et al.*, in this issue of the Journal, makes a groundbreaking and essential push forward in our understanding of BPDCN.[2] The work is pivotal as: 1) it is the first to focus specifically on understanding epigenetic alterations in BPDCN; 2) it studies a large number of well annotated cases of BPDCN using broad and comprehensive genetic analyses; and 3) it assesses the therapeutic value of targeting BPDCN with epigenetic modifying therapies *in vivo*. However, to understand the importance of the study by Sapienza *et al.*, it is critical to provide an overview of this neoplasm.

Initially described in 1990 as a possible histiocytic or monoblastic leukemia,[3,4] and then later believed to be an NK-cell tumor due to expression of both CD56 and CD4,[5,6] the cellular lineage of BPDCN was debated for more than a decade. Then, in 1999, Lucio *et al.*[7] postulated a dendritic cell origin due to expression of CD123, a sensitive, though not specific, plasmacytoid dendritic cell marker. Further research continued to support the plasmacytoid dendritic cell origin based not only on CD123 expression but also expression of TCL1 and also cellular differentiation assays, all which pointed to plasmacytoid dendritic cells as the normal cellular counterpart for this tumor.[8-10] In the 2008 World Health Organization classification, it was finally introduced as BPDCN and has continued with this designation in the revised 2016 WHO classification. BPDCN demonstrates aggressive behavior, presenting with cutaneous lesions and bone marrow involvement, and, despite a frequent good response to initial therapy, the median survival varies from 10 to 19.8 months.

The genetics and molecular aspects of this entity have also been explored by several groups. An abnormal karyotype is common (>50% of patients) and particular chromosome regions are more frequently targeted in BPDCN based on classic cytogenetic analyses as well as comparative genomic hybridization studies: 4q, 5q, 6q, 9, 12p, 13q,

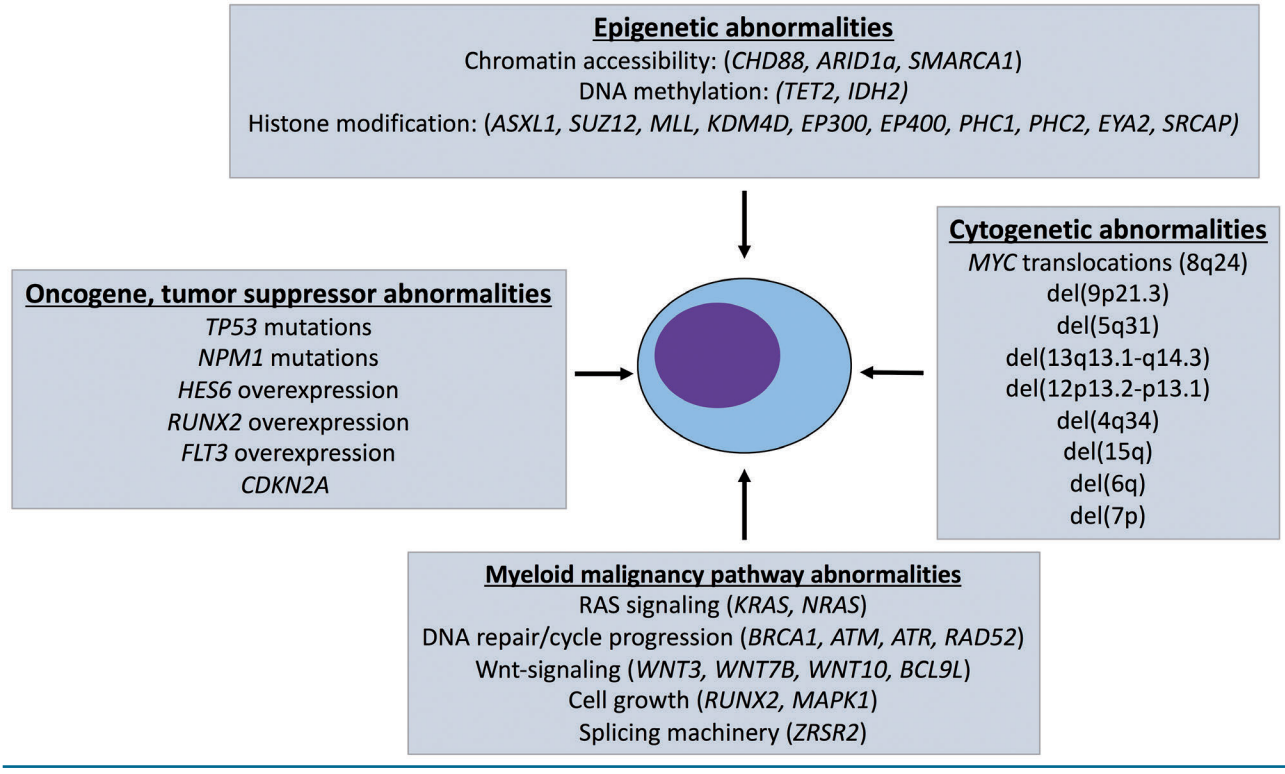

Figure 1. Genetic abnormalities and biological pathways important in blastic plasmacytoid dendritic cell neoplasm.

and 15q (Figure 1).[11-13] Deletion of the 9p21.3 locus is the most recurrent event in BPDCN, found to be associated with a poor outcome when biallelic.[11] More recently, the presence of a recurrent gene rearrangement involving the *MYC* locus, specifically t(6;8)(p21;q24) has been reported in several studies including one by our own group, and has been seen in association with older onset and shorter median survival.[14-16] Whole-exome sequencing (WES) and targeted sequencing studies have identified recurrent mutations involving *TET2*, *ASXL1*, *TP53*, and *NPM1*,[17,18] while separate studies have appointed E-box transcription factor TCF4 as a master regulator of the BPDCN oncogenic program as bromodomain and extra-terminal domain inhibitors (BETis) induced BPDCN apoptosis due to disruption of the TCF4 dependent regulatory network.[19] Finally, aberrant activation of the NF-kB pathway has been identified through gene expression profiling.[20] However, as can be seen, our understanding of the genetic aspects of BPDCN has been somewhat limited.

In the current issue of the Journal, Sapienza *et al.*[2] significantly advance our understanding of BPDCN by analyzing 14 patients, as well as the patient-derived CAL-1 cell line, by WES. This broad and detailed sequencing demonstrated that BPDCN patients were affected by mutations of genes involved in epigenetic regulation, with 25 mutated epigenetic modifier genes including those implicated in DNA methylation (*TET2* and *IDH2*), chromatin accessibility (*ARID1a*, *CHD8*, *SMARCA1*), and histone modification including: methylation (*ASXL1*, *SUZ12*, *MLL*), demethylation (*KDM4D*), acetylation (*EP300*, *EP400*), ubiquitination (*PHC1*, *PHC2*), dephosphorylation (*EYA2*) and exchange (*SRCAP*) (Figure 1). This finding highlights the dysregulation of the epigenetic program in BPDCN as a hallmark of the disease indicating possible therapeutic interventions. In addition, by analyzing the transcriptome of the samples studied by WES, they examined the specific impact of these epigenetic-associated gene mutations. Gene set enrichment analysis additionally revealed two significant deregulation signatures associated with methylation of DNA: one driven by *KDM5B34* histone demethylase and another by the *PRMT5* methyltransferase-associated gene. The authors also detected gene set enrichment of those genes associated with response to decitabine, a DNA demethylating agent. Finally, based on the apparent significance of epigenetics in BPDCN, the authors did what few have done before, and tested *in vivo* the efficacy of four US Food and Drug Administration (FDA)-approved epigenetic drugs (5'-Azacytidine, decitabine, romidepsin and bortezomib) in a mouse xenograft model using the CAL-1 cell line. These drugs were used as single agents or in combination, and when used as a single agent, 5'-Azacytidine and decitabine significantly prolonged mice overall survival, while among all the combinations tested, treatment with 5'-Azacytidine in combination with decitabine achieved the best result in terms of survival. The significance of this study cannot be understated as it links genotype to advancements in epigenetic forms of treatment and fundamental biological processes.

Blastic plasmacytoid dendritic cell neoplasm is a rare disease with an extremely aggressive behavior; the advances here in the genetics and molecular aspects of this entity, as well as the therapeutic approach, are quite revealing and significantly open the door for future clinical trials. This work nicely provides further support for the essence of why development of new epigenetic treatment strategies are a rational approach for this aggressive disease.

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