LymphomaHub

CLL/SLL, MCL

PI3Kδ blockade with idelalisib or duvelisib enhances AID-mediated genomic instability in normal, Chronic Lymphocytic Leukemia, and Mantle Cell Lymphoma cells

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On the 23rd February 2017, Mara Compagno, Qi Wang, and Chiara Pighi (Children's Hospital Boston and Harvard Medical School, Boston, Massachusetts) *et al.* published a Research Letter in Nature, reporting their results on how idelalisib, duvelisib, and ibrutinib affect Activation-Induced Cytidine Deaminase (AID) expression.

Key Highlights:

Idelalisib and duvelisib

- In Class Switch Recombination (CSR)-activated mouse B-cells, as well as MEC1 (CLL), Mino and JeKo-1 (MCL) cell lines, PI3Kδ blockade reduced proliferation and enhanced *AID* mRNA levels
- Due to enhanced AID expression, PI3Kδ blockade increased CSR to IgG_1 in activated mouse B-cells as well as in germinal center B-cells *in vivo*; effects were significant at doses ranging from 0.1μl–1μl (equivalent to plasma concentration observed in patients)
- In activated mouse B-cells, PI3Kδ blockade increased the formation of translocation junctions between *c-myc* and AID on-target sites in the *IGH* locus or AID off-target sites in the genome
- In MEC1 and JeKo-1 cell lines, translocation to the *IGH* locus and AID off-targets was increased
- In activated mouse B-cells, the median fold change in translocation frequency:
  - For AID on-target and off-target sites with idelalisib = 2.0 and 2.6
  - For AID on-target and off-target sites with duvelisib = 4.3 and 4.7
- On-target and off-target translocation at junctions were nearly completely stopped in AID-deficient B-cells, indicating that the increased genomic instability induced by PI3Kδ blockade is AID-dependent
- PI3Kδ blockade increased both AID-dependent chromosomal translocation formation and somatic hypermutation in activated mouse B-cells
- PI3Kδ blockade appeared to enhance tumor formation and AID-mediated genomic instability *in vivo* in mice, and enhanced AID-mediated genomic instability in MEC1 and JeKo-1 cell lines

Ibrutinib

- In CSR-activated mouse B-cells, ibrutinib reduced proliferation, enhanced *AID* mRNA and protein levels, and increased CSR
- Ibrutinib increased translocation to *IGH* and AID off-target sites, although weaker than PI3Kδ inhibitors, and increased the frequency of plasma cell tumor formation in pristane-treated mice

- In human B-cells, ibrutinib reduced cell proliferation, and significantly enhanced AID expression, as well as the frequency of translocation junctions to AID on-target and off-target sites

The authors reported that PI3Kδ blockade enhances AID-mediated genomic instability in normal and malignant B-cells. They hypothesize that the increase in AID levels during treatment with PI3Kδ inhibitors could result in secondary oncogenic mutations or translocations in patients with B-cell malignancies. Moreover, increased AID expression "could accelerate resistance to targeted therapy through an increased mutational rate."

It was also found that ibrutinib seemed to have more limited effects, which the authors attribute to its indirect mechanism of inhibition of the PI3K pathway.

In addition, the authors suggest that long-term monitoring for clonal evolution over time in patients on PI3Kδ inhibitors should be carried out; especially as "mutational signatures consistent with AID activity can be tracked in the evolution of CLL clones" and high AID expression is a poor prognostic factor in CLL.

The authors concluded that their findings suggest that genome-wide translocation assays should be carried out more regularly to "identify the genotoxic effects of drugs that were previously considered to be non-damaging to DNA."

Abstract:

Activation-induced cytidine deaminase (AID) is a B-cell-specific enzyme that targets immunoglobulin genes to initiate class switch recombination and somatic hypermutation. In addition, through off-target activity, AID has a much broader effect on genomic instability by initiating oncogenic chromosomal translocations and mutations involved in the development and progression of lymphoma. AID expression is tightly regulated in B cells and its overexpression leads to enhanced genomic instability and lymphoma formation. The phosphatidylinositol 3-kinase δ (PI3Kδ) pathway regulates AID by suppressing its expression in B cells. Drugs for leukaemia or lymphoma therapy such as idelalisib, duvelisib and ibrutinib block PI3Kδ activity directly or indirectly, potentially affecting AID expression and, consequently, genomic stability in B cells. Here we show that treatment of primary mouse B cells with idelalisib or duvelisib, and to a lesser extent ibrutinib, enhanced the expression of AID and increased somatic hypermutation and chromosomal translocation frequency to the Igh locus and to several AID off-target sites. Both of these effects were completely abrogated in AID-deficient B cells. PI3Kδ inhibitors or ibrutinib increased the formation of AID-dependent tumours in pristane-treated mice. Consistently, PI3Kδ inhibitors enhanced AID expression and translocation frequency to IGH and AID off-target sites in human chronic lymphocytic leukaemia and mantle cell lymphoma cell lines, and patients treated with idelalisib, but not ibrutinib, showed increased somatic hypermutation in AID off-targets. In summary, we show that PI3Kδ or Bruton's tyrosine kinase inhibitors increase genomic instability in normal and neoplastic B cells by an AID-dependent mechanism. This effect should be carefully considered, as such inhibitors can be administered to patients for years.

Reference:

1. Compagno M., Wang Q., Pighi C., *et al.* Phosphatidylinositol 3-kinase δ blockade increases genomic instability in B cells. Nature. 2017 Feb 23;542(7642):489-493. DOI: 10.1038/nature21406. Epub 2017 Feb 15.