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BET inhibitors impair leukemic stem cell function only in defined oncogenic subgroups of acute myeloid leukaemias

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ABSTRACT

Bromodomain and Extra-Terminal inhibitors (BETi) such as OTX015 are active in Acute Myeloid Leukaemias (AML). Their activity on Leukemic Stem Cells (LSCs) is less documented. We interrogated the anti-LSC activity of OTX015 in a niche-like long-term culture in 26 primary AML samples and validated our findings in vivo. OTX015 impaired LSCs in AMLs harbouring Core Binding Factor or KMT2A gene fusions, NPM1 or chromatin/spliceosome genes mutations, but not in those with aneuploidy/TP53 mutations. In four patients, we dissected the transcriptomic footprint of Bet inhibition on LSCs versus blasts. Our results can instruct future clinical trials of BETi in AML.

Bromodomain and Extra-Terminal (BET) proteins including BRD4 regulate gene expression notably through enhancer-dependent control of transcriptional elongation. In most cellular systems, the MYC transcriptional program is dependent on BET proteins [1]. Following the discovery that murine Mll-Af9 Acute Myeloid Leukaemia (AML) cells are dependent on Brd4 expression [2], and the development of chemical inhibitors of Bet protein binding to acetylated lysines (BETi), the pre-clinical activity of BETi in AML has been extensively investigated in cell lines, syngeneic mouse models, primary patient cells, and patient-derived xenografts (PDX). AML is a heterogeneous group of diseases comprising distinct oncogenic entities [3]. Beyond MLL/KMT2A-rearranged AMLs, several oncogenic groups of AMLs, including NPM1 mutations, IDH2 mutations, Core-Binding Factor (CBF) translocations, EVI1/MECOM-rearrangements and monosomy 7 have been considered BET-dependent based on murine models, human cell lines and studies on primary patients samples [4–8]. The latter included short-term assays and treatment of established patients-derived xenografts (PDX). Treatment failure in AML is often caused by the persistence of Leukemic Stem Cells (LSCs). LSCs are best interrogated by in vivo PDX assays, but ex vivo long-term culture assays have been developed as proxies for faster interrogation of drug activity in AML subtypes with limited xenotransplantation potential in immunocompromised mice [9]. Growing body of studies documenting the activity of BETi in AML reported intriguing results regarding the activity of BETi in LSCs. For instance, a study performed in an Mll-Af9-driven mouse model of AML showed that chronic BETi exposure tends to select LSCs [10], whereas other studies performed with primary patient samples with AML revealed that immunophenotypically-defined LSCs are sensitive to short-term exposure to BETi [11]. These conflicting observations prompted us to examine how primary patient samples from various AML subtypes respond to long-term exposure to BETi. We thus interrogated a cohort of 26 primary AML samples grouped according to the robust oncogenetic classification of Papaemmanuil et al. [3] (Supplementary Table 1). Primary AML cells were treated with sustained and clinically-relevant doses of the BETi OTX015 (now MK-8626) in a niche-like ex vivo LSC assay derived from Griessinger et al. [9]. Thawed primary bone marrow mononucleated cells (BMNCs) were plated on a MS-5 feeder, cultured in serum-replete medium with cytokines (SCF, TPO, IL-3, FLT3-L, IL-6, G-CSF, GM-CSF and EPO) in 3% O_2 to mimic physiologic oxygen bone marrow tension. OTX015 200 nM or vehicle (DMSO) was added initially and at every weekly semi-refreshing of medium. After a 3-week exposure, residual $mSca1^-/hCD45^+$ leukemic cells were sorted and plated in methylcellulose in the presence of serum and cytokines in 20% O_2. Colonies were numbered after 14 days, and the colony output was normalized to the number of leukemic cells initially seeded prior to OTX015 exposure to derive the proportion of Leukemic Long-Term Culture Initiating Cells (L-LTC-IC) among BMNCs (Fig. 1**A**, detailed methods in Supplementary Material). In vehicle-treated cells, the median frequency of L-LTC-IC was 1.1×10^{-4} cells (range 1.3×10^{-5} to 2.1×10^{-3}), without significant correlation to European LeukaemiaNet (ELN) risk group (Supplementary Fig. 1). In 17 patients, OTX015 exposure significantly reduced L-LTC-IC output (Fig. 1**B**). Notably, OTX015 impaired L-LTC-IC in 3/3 patients with t(8;21) or inv(16) Core Binding Factor (CBF) AML, 4/5 patients with NPM1 mutation, regardless of the FLT3 genotype, in 6/6 patients with chromatin/spliceosome genes (including 5 with MLL/KMT2A partial tandem duplications [MLL-PTD]), and in 3/3 patients with MLL/KMT2A fusions. Conversely, OTX015 had no activity on L-LTC-ICs in 5 of 6 patients with aneuploidy or TP53 mutations, in 2/2 patients with inv(3) leading to EVI1/MECOM rearrangement, and in UPN6 harbouring a WT1 mutation and $FLT3^{ITD}$ as sole identified driver lesions. To validate in vivo the findings from our ex vivo colony-based LSC assay, we transplanted equal amounts of leukemic cells from UPN 8 (LSCs sensitive to OTX015) and UPN 7 (LSCs resistant to OTX015) treated ex vivo by OTX015 200 nM for three weeks into sublethally-irradiated recipient NSG-S mice and monitored chimerism and survival (Fig. 1**A**). OTX015-exposed cells from UPN 8 showed delayed engraftment in the peripheral blood (Fig. 1**C**) and prolonged survival (Fig. 1**D**). Only one mouse from the OTX015 group displayed significant (> 15%) engraftment 23 weeks from transplant. Exome sequencing of BMNCs at sacrifice in this mouse showed similar representation of the NPM1 and IDH2 driver lesions compared to BMNCs from a recipient mouse from the vehicle group with comparable disease kinetics (Supplementary Fig. 2), without acquisition of novel mutations, suggesting epigenetic reprogramming of a subset of cells

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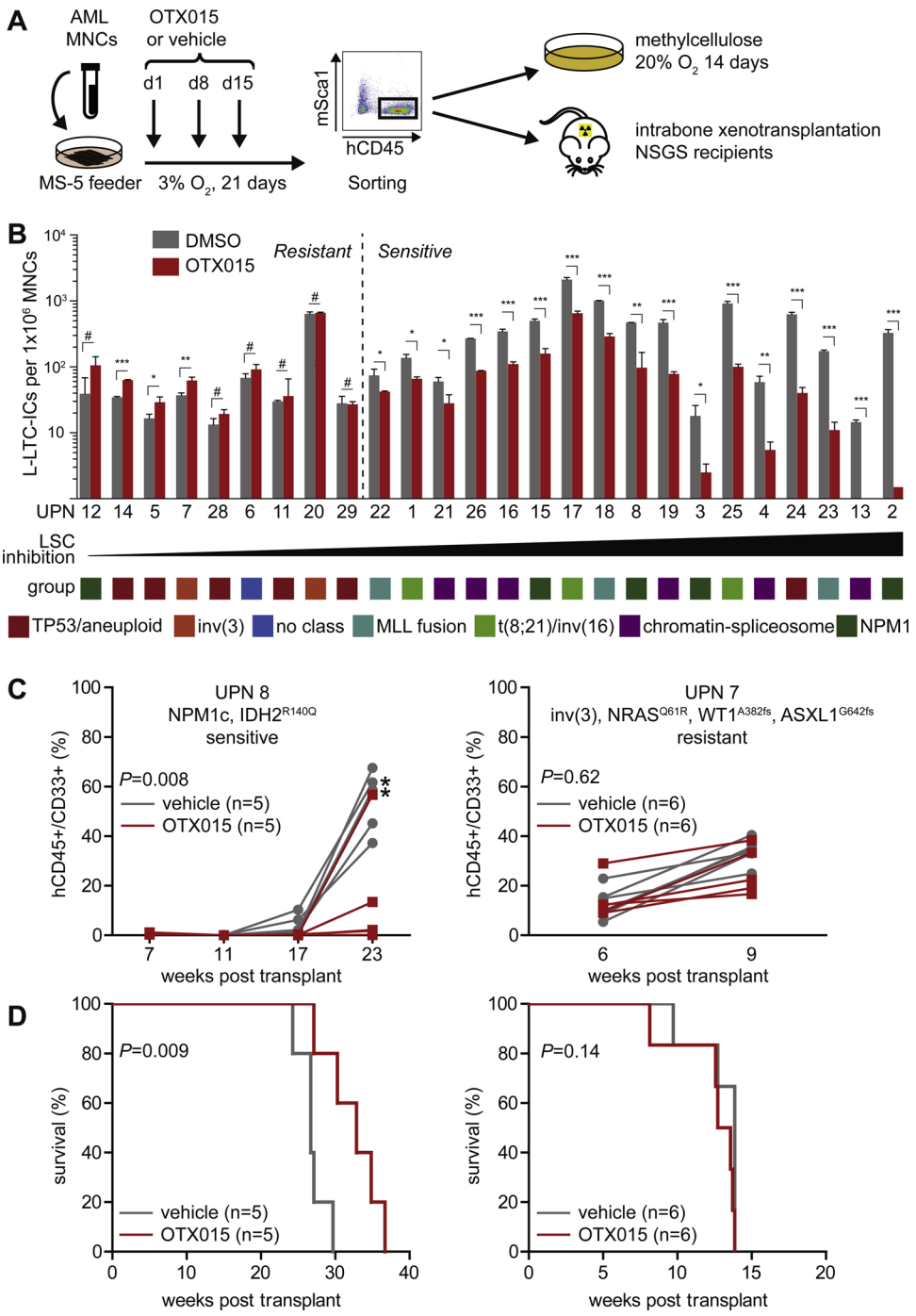

Fig. 1. Interrogation of OTX015 activity on Leukaemic Stem Cell activity ex vivo. A. Schematics of the experimental work-flow for L-LTC-IC assays with OTX015 and validation in patient-derived xenografts (PDX). **B.** Results of the L-LTC-IC assay with OTX015 or vehicle (DMSO). Frequency of L-LTC-IC (mean and standard deviation) after exposure to OTX015 200 nM (red) or vehicle (DMSO 0.1%, grey) in 26 primary AML samples classified according to their oncogenic group (defined according to ref. 3). Samples are ranked from left to right according to the highest to the lowest ratio of L-TC-IC with OTX015 relative to vehicle, indicating increasing sensitivity of LSCs to BET inhibition. Student t test: # non-significant, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. **C.** Kinetics of engraftment of primary cells from UPN 8 (left panel) and 7 (right panel) treated ex vivo with OTX015 (red) or vehicle (grey) and transplanted into irradiated recipient NSGS mice. P values from 2-way ANOVA accounting for time and drug. **D.** Survival of recipient mice after engraftment. P values from log-rank tests (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

during ex vivo OTX015 exposure [12]. Conversely, OTX015 treatment did not alter leukemic progression upon transplantation in UPN 7 (Fig. 1**C** and **D**). Collectively, these results showed that the niche-like ex vivo assay provides a validated proxy of LSC function and response to BETi in PDX mouse models, and that sustained Bet inhibition impairs more strikingly LSC activity in defined AML sub-groups, including NPM1c, CBF, and chromatin/splicing groups than in complex-karyotype and inv(3) subgroups.

Because oncogenic groups dictate the sensitivity of LSCs to BETi, it is difficult to delineate a specific transcriptional program that may define sensitivity of LSCs to BETi irrespective of oncogenetic subclasses. We thus compared the transcriptomic changes induced by BETi in LSCs versus blasts isolated from three MLL-PTD-positive patients (UPN 16, 21, and 26) from the chromatin-spliceosome group of AML, whose LSCs were sensitive to OTX015, using genome-wide transcriptional profiling. $SSC^{low}/CD45^{dim}$ blasts were sorted into $CD34^{+}/CD38^{-}$, $CD34^{+}/CD38^{+}$, and $CD34^{-}$ fractions (Supplementary Fig. 3) and exposed to OTX015 200 nM or vehicle for 72 h in niche-like conditions before gene expression profiling. Post-treatment sorting of phenotypically defined populations was not feasible due to low cell numbers. In parallel, the L-LTC-IC assay was applied to each cell fraction without drug exposure, to determine their relative enrichment in L-LTC-ICs (Fig. 2**A**). Fractions with L-LTC-IC frequency $> 1 \times 10^{-5}$ were considered as LSCs, those with fewer than 1×10^{-5} L-LTC-ICs as blasts (Fig. 2**B**). In vehicle-treated cells, the MYC transcriptional program was upregulated in LSCs compared to blasts, while inflammatory response genes were upregulated in blasts (Fig. 2**C**). Transcriptomic changes persisting 72 h after OTX015 exposure were modest, with an important overlap between

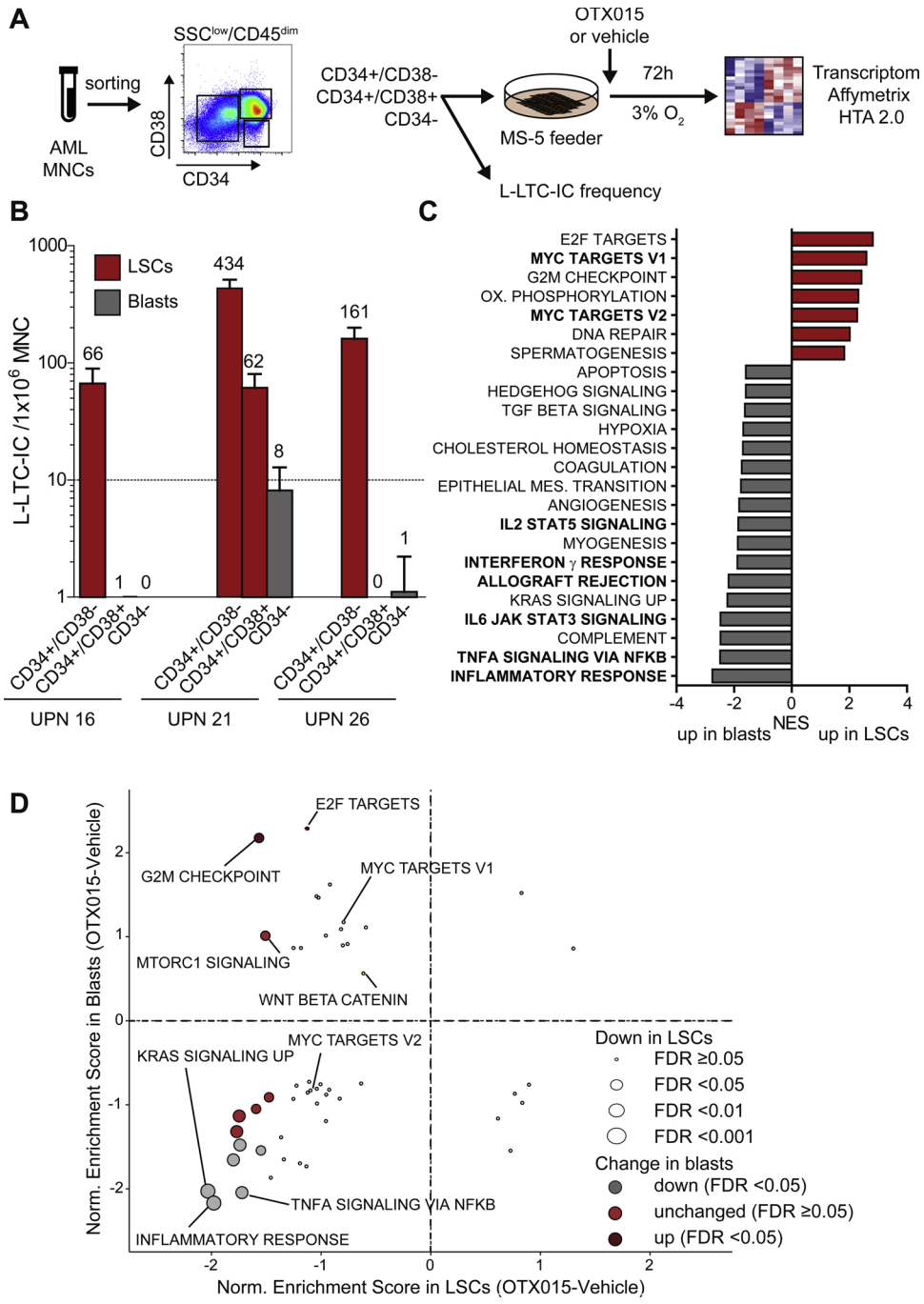

Fig. 2. Transcriptomic changes upon sustained OTX015 exposure in blasts and LSCs. **A.** Schematics of the experimental work-flow for functional annotation of sorted leukemic fractions and gene expression profiling after 72 -h OTX015 ex vivo exposure in three AML samples from the chromatin group all harbouring MLL^{PTD}. **B.** L-LTC-IC frequency in each fraction. Fractions with $> 1 \times 10^{-5}$ L-LTC-IC frequency were considered as LSC-enriched. **C.** Gene Set Enrichment Analysis (GSEA) of MSigDB Hallmark genesets differentially expressed in LSCs versus blasts in the vehicle (DMSO) condition with a FDR q-value ≤0.01. **D.** Scatter plot representation of GSEA of Hallmark genesets in OTX015 versus vehicle conditions in LSCs (x axis) and Blasts (y axis). Contrasts were generated as DMSO-OTX015, and results are displayed as -Normalized Enrichment Scores (-NES) so that negative values represent genesets whose expression is repressed by OTX015 relative to vehicle. The size of dots indicates the FDR q-value of pathways downregulated in the LSC fraction, and among those significantly downregulated (FDR q-value < 0.05), fill colours indicate the change in the Blast fraction.

blasts and LSCs, and mostly led to transcriptional repression of hallmark pathways (Fig. 2**D**). Interestingly, downregulation of the MYC-driven program was not significant in both fractions, while a sustained repression of inflammatory gene expression programs was visible in both LSCs and blasts. Our analysis also uncovered LSC-specific downregulated pathways upon sustained BET inhibition. These included G2/M transition pathway genes, which were significantly upregulated in blasts, and other pathways, such as MTORC1 signaling, which was downregulated LSCs without significant changes in blasts. Conversely, E2F target genes were downregulated in LSCs but upregulated in blasts (Fig. 2**D**, Supplementary Fig. 4 and Supplementary Table 2). These observations, in keeping with previous findings on the epigenetic plasticity of the MYC transcriptional program in murine AML models [12], raise the intriguing possibility that BET inhibitors exert anti-leukemic properties in a subset of AMLs by inhibiting a pro-leukaemogenic inflammatory program. Indeed, leukaemias with MLL/KMT2A rearrangements have been shown to rely on NFK-B signalling for survival and LSC capacity [13]. BET inhibitors emerge as a relevant drug class to target cancer-promoting inflammatory programs [14]. Further studies are required to determine whether inhibition of a BET-dependent inflammatory program is also relevant to other subsets of AML, and whether in some tumours, a specific epigenetic profile of cancer stem cells may endow these cells with a specific vulnerability to BET inhibition irrespective of the activity of BET inhibitors on the bulk of the tumour. BET inhibition has recently been reported to stimulate the self-renewal of normal hematopoietic stem cells [15]. Clinical trials will be required to determine whether BET inhibition can be a relevant strategy to eliminate residual LSCs, for instance in a maintenance setting after intensive chemotherapy, in selected oncogenic subgroups of AML.

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Declaration of Competing Interest

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AM, LR, JPa, AAli and JB performed in vitro experiments. JPe and AAlb performed transcriptomics experiments. MD performed statistical analyses. MP, LH, SQ and EC performed genomic annotations of samples. CG, ER, LA, TB, JS and HD provided patients samples. RI designed and analyzed the experiments. AP and RI interpreted the data and drafted the manuscript. All authors approved the final version of the manuscript. We thank Saint-Louis Hospital's Tumour Biobank (Daniela Geromin, Carole Albuquerque) for managing patient biological samples, the Flow Cytometry and Next-Generation Sequencing facilities from Institut Universitaire d'Hématologie at Hôpital Saint-Louis (Sophie Duchez, Christelle Doliger, Julien Pelé and Niclas Setterblad) and Eric Solary for providing MS-5 cells.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.leukres.2019.106269.

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