Overexpression of one of the three MYC genes is a hallmark of many human cancers. They encode transcription factors that regulate expression of a number of genes critical for tumor development. Conditional transgenic mouse models have shown that MYC inhibition slows tumor progression, MYC is an attractive target for therapy and effective pharmacological MYC inhibition has been a long-standing goal in cancer research. Recent publications have shown that selective inhibitors of BET bromodomain and extra-terminal (BET) domain family of proteins, that bind to acetylated lysines on histones, show promise as potent anti-cancer drugs via down-regulation of the MYC oncogene. Here we confirm that two structurally different BET protein inhibitors (BETi), JQ1 (1-proto type) and RVX-2135, inhibit the proliferation and induces apoptosis of lymphoma cells arising in Myc transgenic mice. BETi have been reported to directly inhibit MYC transcription. Surprisingly, in our system BETi inhibition had no effect on MYC transcription, despite inhibiting broad transcriptional effects evidenced by genome wide clustering of down-regulated genes.

Figure 3. BETi does not suppress Myc transcription in Myc induced murine lymphoma cells. A) qRT-PCR analysis of Myc mRNA expression in indicated cell lines treated with different concentrations of BETi. B) Western blot analysis of c-Myc protein levels. C) Western blot analysis of 820 cells treated for 24h with CHIR99021 (Selleck chemicals) in the presence or absence of the indicated concentrations of BETi.

Figure 4. BETi induce broad transcriptional effects affecting several growth promoting gene signatures. A) Supernovitated hierarchical clustering of Illumina beadchip microarray data in J820 and EU239 cells treated with BETi. Shown are the 50 most down and up-regulated genes (fold-change). B) Venn diagram of the genes down-regulated by treatment with JQ1 and EU239 cells with 1 µM JQ1 for 24h. C) QSEA of genes co-regulated (down) by JQ1 in both J820 and EU239 cells.

Figure 5. RVX2135 causes potent therapeutic responses in mouse models of aggressive Myc-induced lymphoma. A) J820 cells were transplanted into syngeneic B6 mice via tail vein injection. Four days after injection, mice were dosed with 75 mg/kg (b.i.d. five days per week) RVX2135 (n=4) or vehicle (n=7). B) A lymphoma arising in a J-Myc mouse (ID12749) was transplanted into recipient B6 mice via tail vein injection, accompanied by treatment with either vehicle or RVX-2135. Four days after injection, mice were dosed with 75 mg/kg b.i.d. RVX2135 (n=8) or vehicle (n=9).

Results

Overexpression of one of the three MYC genes is a hallmark of many human cancers. They encode transcription factors that regulate expression of a number of genes critical for tumor development. Conditional transgenic mouse models have shown that MYC inhibition slows tumor progression, MYC is an attractive target for therapy and effective pharmacological MYC inhibition has been a long-standing goal in cancer research. Recent publications have shown that selective inhibitors of BET bromodomain and extra-terminal (BET) domain family of proteins, that bind to acetylated lysines on histones, show promise as potent anti-cancer drugs via down-regulation of the MYC oncogene. Here we confirm that two structurally different BET protein inhibitors (BETi), JQ1 (1-proto type) and RVX-2135, inhibit the proliferation and induces apoptosis of lymphoma cells arising in Myc transgenic mice. BETi have been reported to directly inhibit MYC transcription. Surprisingly, in our system BETi inhibition had no effect on MYC transcription, despite inhibiting broad transcriptional effects evidenced by genome wide clustering of down-regulated genes.

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