SUPPLEMENTAL METHODS

Plasmids, reporter assays and lentiviral infections. 293T cells were transiently transfected by calcium-phosphate precipitation method and luciferase reporter assays were performed as previously described [1,2]. Each transfection was performed in duplicates and luciferase activities were measured 48hr post-transfection using the Dual-Luciferase Reporter Assay Kit (Promega) according to the manufacturer's instructions. The BCL6 reporter construct was previously reported [3]. PGM2L1 reporter construct was obtained by sub-cloning the promoter region (-762/+80) into pGL3b vector (Promega). PGM2L1-mutant 1, 2 and 3 were generated using the Quick Change site-directed mutagenesis kit (Stratagene).

qChIP assay and data analysis. DNA fragments enriched by Chromatin Immunoprecipitation (ChIP) were analyzed for expression of individual targets including BCL6 (positive control) and beta-actin (negative control) using primers reported in Table S1 and SYBR Green PCR Master Mix (Applied Biosystems) as recommended by the manufacturer. ΔCt were calculated for anti-BCL6 and control IgG immunoprecipitated DNA fragments relative to their input DNA and then used to calculate the $\Delta\Delta$Ct. Fold changes ($2^{-\Delta\Delta Ct}$) observed in BCL6 vs control IgG immunoprecipitated DNA were corrected using beta-actin as negative control and reported as relative fold enrichment. QPCR reactions were performed in triplicates and each experiment was repeated at least twice.

ChIP-on-chip data analysis. ChIP-on-chip Significance Analysis (CSA) is detailed in [4]. Briefly, probe p-values were derived from three replicate experiments and combined for each 500-base promoter segment using a Gamma cumulative distribution function. Each promoter was associated with the highest 500-base BCL6-localization segment, and the false discovery rate as a function of gene rank, was computed using the Benjamini Hochberg procedure.

DNA binding motifs discovery. Pattern enrichment was measured using classification relative error rate [5], an average of the proportion of bound regions that do not contain sites matching the pattern (false negative predictions) and the proportion of unbound regions that contain sites for the pattern (false positive predictions). Motif discovery and enrichment was performed using CSA-identified highest binding-likelihood regions in promoters with FDR below 0.0001 (bound) relative to these regions in promoters with FDR greater than 0.5 (unbound). *De novo* motifs were identified using DME [6], and *de novo* motif discovery was followed by module discovery using motif anchoring [7]. Functional depth cutoffs were set after conditioning on CpG-island overlap; cutoffs for sites overlapping and not overlapping CpG-islands include M0: (0.770, 0.774), M2: (0.755, 0.899), and M00424: (0.778, 0.783). Potential BCL6 co-factors were inferred by identifying enriched TRANSFAC motifs [8] and enrichment p-values were calculated using permutation testing [5].

Gene expression profiling, differential expression and inferred networks. Gene expression profiles were generated as previously reported [9] using the HG-U133Plus2.0 GeneChip® platform (Affymetrix) for naïve (5), memory (5) and GC B cells (10) isolated from human tonsils and for B cell tumors including chronic lymphocytic leukemia (8), FL (38), DLBCL (42) and the HG-U95A GeneChip® platform (Affymetrix) for Ramos cells infected with control siRNA (4) or siRNA targeting BCL6 (4). GC-downregulated genes were identified using fold-change criteria and p-value thresholds determined using a non-parametric U test. These were automatically preset to identify differentially expressed gene sets at or below 0.05 false discovery rates. Down regulated genes satisfied one of the following criteria: i) low expression in centroblasts relative to naïve B cells and/or memory B cells; ii) comparable (not significantly low or high) expression in naïve, centroblasts and memory B cells that is low relative to expression in at least one B cell tumor type. The BCL6 network was inferred by applying ARACNe to GEP from normal B cells (20), FL (38) and lymphoblastoid cell lines (5). ARACNe was run with bootstrapping, at a p-value<0.0001 threshold before correction for multiple testing. Transcription factors whose ARACNe-inferred hubs were enriched in genes with BCL6-bound promoters were identified using a binomial distribution and FWER-corrected p-value. Gene set enrichment in Ramos BCL6 siRNA experiments was calculated using GSEA [10] with t-test based p-values for weighting statistics.

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