**Schleussner et al., *The AP-1 -BATF and -BATF3 module is essential for growth, survival and TH17 / ILC3 skewing of anaplastic large cell lymphoma***

**Supplementary MATERIALS AND METHODS**

***Cell lines and transfections***

For transient transfection assays, K299 cells were electroporated (EP) in OPTI-MEM I using Gene-Pulser II (Bio-Rad) with 50 F and 500 kV. Transfection efficiency was determined by pEGFP-N3 (Clontech Laboratories) co-transfection and FACS analysis. 48 to 72 h after transfection, GFP+ cells were enriched by FACS. For generation of A-Fos-inducible FE-PD cells, cells were electroporated with 500 F and 250 kV. Twenty-four hours after transfection, 110 g/ml Hygromycin B was added. After 21 - 28 days of culture in the presence of Hygromycin B, cells were suitable for functional assays.

***RNA preparation and PCR analyses***

RNA preparation, cDNA synthesis and semi-quantitative RT-PCR analyses were performed as described.[14](#_ENREF_14) Primers are listed in **Supplementary Table 1**.

***Analysis of cell death and proliferation***

Apoptotic cell death was determined by Annexin V-FITC/PI staining (Bender MedSystems). The percentage of viable GFP-positive cells was determined by PI staining and FACS analysis. Proliferation was measured by [3H]-thymidine incorporation, cell number manually using a haemocytometer chamber and trypan blue dye exclusion.

***Preparation of protein extracts, Western blotting (WB), electrophoretic mobility shift assay (EMSA), and co-immunoprecipitation (CoIP) assays.***

Protein preparation, WB, EMSA and CoIPs were performed as described.[14](#_ENREF_14) EMSA oligonucleotides are listed in **Supplementary Table 1**.The following primary antibodies were used for WB analyses: anti-JUNB (sc-46), anti-IRF4 (sc-6059), anti-PARP1 (sc-8007; all Santa Cruz Biotechnology), anti-BATF (#8638S; Cell Signaling), anti-BATF3 (AF7437; R&D Systems), anti-RORC,[1](#_ENREF_1) anti-FLAG M2 (F1804), anti--actin (A5316, both Sigma Aldrich). Antibodies used for supershifts were: anti-FRA2 (sc-604), anti-JUNB (sc-46), anti-BATF (sc-100974), anti-BATF3 (sc-162246), anti-IRF4 (sc-6059; all Santa Cruz), isotype controls (MAB002; R&D Systems; AB-105-c, R&D Systems). CoIP was performed as described[2](#_ENREF_2) using 1,000 g of whole cell protein extract with 2 g of JUNB (sc-5052), BATF (sc-100974) or BATF3 (sc-398902; all Santa Cruz) antibody or the respective isotype control (MAB002). Thereafter, immunoblotting was performed using anti-JUNB (sc-8051), anti-BATF (8638S), anti-BATF3 (AF7437, R&D Systems), anti-BATF3 (sc-398902; Santa Cruz), and anti--actin antibody.

***DNA constructs***

For the generation of expression plasmids, *BATF* was amplified by use of primers *BATF* BamHI s 5´- GCGGATCCGCCGCCATGCCTCACAGCTCCGACAGC and *BATF* XhoI as 5´- CTCCAGTCAGGGCTGGAAGCGCGGGG, *BATF3* by use of primers *BATF3* BamHI s 5´- GCGGATCCGCCGCCACCATGTCGCAAGGGC and *BATF3* XhoI as 5´- CTCCAGTCATCGGGGCAAGCAGC, and cloned *via* BamHI and XhoI into pcDNA3.1(+). *RORC1* was amplified by use of primers *RORC1* EcoRI s 5´- GGAATTCGCCACCATGGACAGGGCCCCACAGAG and *RORC* XhoI as 5´- CTCGAGTCACTTGGACAGCCCCAC; *RORC2* by use of primers *RORC2* EcoRI s 5´- GGAATTCGCCACCATGAGAACACAAATTGAAG and *RORC* XhoI as. Both *RORC* variants were cloned *via* EcoRI and XhoI into pcDNA3.1(+). All constructs were verified by sequencing.

For generation of the lentiviral *BATF* and *BATF3* expression plasmids, the lentiCRISPRv2-EBFP and -EGFP plasmids (see below) were digested with *PacI* and *EcoRI* (eliminating the U6-promotor and sgRNA-scaffold from the plasmid) and re-ligated using the following oligos: oligo1 s 5’-GTTGTAAATGAGCACACAAAAG and as 5’-AATTCTTTTGTGTGCTCATTTACAACAT. Thereafter, the lentiCRISPRv2-EBFP-oligo1 and lentiCRISPRv2-EBFP-oligo1 plasmids were digested with *XbaI* and *BamHI* (eliminating the Cas9 and switching the *XbaI* and *BamHI* sites) and re-ligated using the following oligo: oligo2 s 5’-CTAGCGGATCCGTTGTATCTAGAA, and as 5’-GATCTTCTAGATACAACGGATCCG, for generation of lentiCRISPRv2-EBFP-empty vector and lentiCRISPRv2-EGFP-empty vector. Subsequently, full length human BATF and BATF3 were amplified from pcDNA3-vectors and cloned into lentiCRISPRv2-EBFP and lentiCRISPRv2-EGFP via *AgeI* and *XbaI*. For amplification of *BATF* and *BATF3*, we used the following oligos: *BATF* s 5’-ACACCGGTGCCACCATGGACTACAAGGATGA, and as 5’-ACTCTAGAGGGCTGGAAGCGCGGGGAGCT; *BATF3* s 5’-ACACCGGTGCCGCCACCATGTCGCAA, and as 5’-ACTCTAGATCGGGGCAAGCAGCCGGCCAC.

For the pRTS-1 (ref. [3](#_ENREF_3))-based inducible A-Fos expression vector, *A-Fos* was amplified from a CMV500-based construct[4](#_ENREF_4) by use of primers A-Fos *Xba*I s 5´-GCTCTAGAAAGCTCCACCATGGACTACAAG and A-Fos *Xba*I as 5´- GCTCTAGAGAAGCTTGAATTAATCAGG, ligated into the *Xba*I site of a modified pUC19 (pUC19-Sfi), and mobilized by SfiI digestion for cloning into pRTS-1.

***CRISPR/Cas9-mediated deletion of BATF and BATF3 in ALCL cell lines***

**(A) Cloning strategy for CRISPR/Cas9 mediated BATF- and BATF3-deletion in Figure 2.** **(1) Cloning of guide RNA lentiCRISPR v2-plasmid.**The lentiviral Cas9 containing plasmid lentiCRISPR v2 (ref. [5](#_ENREF_5)) was a gift from F. Zhang (Addgene #52961, Cambridge, MA, USA). The gRNAs for *BATF* and *BATF3* were designed using E-CRISP program version 5.2 ([www.e-crisp.org/E-CRISP/index.html](http://www.e-crisp.org/E-CRISP/index.html)) and targeted the second exon of *BATF* and the first exon of *BATF3*, respectively (for sequences see **Supplementary Table 1**). Cloning of the gRNA into the lentiCRISPR v2 was performed according to Zhang lab protocol.[5](#_ENREF_5),[6](#_ENREF_6) In brief, lentiCRISPR v2 was digested with BsmBI (Fermentas), dephosphorylated and gel-purified. *BATF* and *BATF3* gRNA oligonucleotides were phosphorylated, annealed, and then ligated into lentiCRISPR v2 plasmid. Ligation reactions were transformed into ‘One Shot’ Stbl3 chemically competent cells (Invitrogen). Plasmids were isolated from single colonies and sequenced to validate successful incorporation of the gRNA oligonucleotides. **(2) Lentiviral packaging, transduction and clone isolation.** HEK-293T cells were seeded at a density of 3.5x105 per ml in a 6-well plate and cultured in D10 medium (DMEM; 10% FBS; 1% Penicillin Streptomycin) 24 h prior to transfection. Transfection was performed using Lipofectamine LTX (Invitrogen). Packaging Plus Reagent Mix, containing 190 μl Opti-MEM (Gibco) with 2.5 μl Plus-Reagent (Invitrogen), 820 ng psPAX2 (Addgene), 410 ng pMD2.G (Addgene) and 250 ng guide RNA containing lentiCRISPR v2in a total volume of 200 μl, was incubated at room temperature for 15 minutes, followed by gentle mixing with Lipofectamine Mix, containing 197 μl Opti-MEM with 3 μl Lipofectamine LTX. The complete mixture was incubated for another 15 minutes at room temperature before being added in a drop-wise manner to the cells. After overnight incubation, the transfection medium was changed to 2 ml of D10 medium. The next day, the medium was removed and centrifuged at 1000 g for 5 minutes to pellet cell debris. The viral supernatant was filtered through a 0.45 μm filter (GE Healthcare) and stored at - 80°C until further use for lentiviral transduction.For transduction, ALCL cell lines were seeded in a 6-well plate at a density of 5x105 per well in R10 medium (RPMI 1640; 10% FBS; 1% Penicillin Streptomycin), followed by addition of 400 μl gRNA virus per well and incubation for 3 days. Cells were then supplemented with 1 μg/ml puromycin to select positive clones. After a further 3 days, puromycin was removed by medium change.To isolate clones, limiting dilution was performed using conditioned medium to enrich for cells with *BATF* or *BATF3* deletion. After incubation for 2 weeks, approximately 5 to 10 clones were collected for amplification. The protein expression levels of BATF and BATF3 were assessed by immunoblotting, and clones with absent or low BATF or BATF3 expression were selected for further analyses. To corroborate desired genomic changes, *BATF* and *BATF3* deletion sites were PCR amplified and sequenced (primer sequences are indicated in **Supplementary Table 1**). After clone isolation, cell line identity was verified by satellite repeat fingerprinting. **(3)** **GFP-labeled BATF and BATF3 double knock-outs monitored over time**. Into the lentiGuide-Puro plasmid (Addgene #52963) a GFP sequence was inserted (a kind gift of the laboratory of Dr. Florian Grebien). Constructs were co-transfected into HEK293T cells together with packaging plasmid psPAX2 and envelope plasmid pMD2.G at a molar ratio of 2:1 using Lipofectamine (Invitrogen). After 3 days, supernatants containing the lentivirus were collected and filtered through a 0.45 m cellulose acetate membrane filter (GE healthcare). Following lentiviral transduction of BATF3 KO cells with the GFP-coupled guide-RNA targeting BATF, the percentage of GFP-positive cells was monitored and analyzed every other day using a MoFlo Astrios EQ cell sorter (Beckman Coulter) ten days after transduction. Isolated GFP-positive cells were put in culture and then used for WB analyses.

**(B) *Cloning strategy of lentiviral BATF and BATF3 sgRNA constructs used in Figure 4E.* (1)**The original lentiCRISPR v2 plasmid was obtained from Addgene (Feng Zhang lab, MIT; Addgene plasmid #52961). We replaced the puromycin-resistance of the original lentiCRISPRv2 plasmid with an EGFP- or EBFP fluorescent reporter via Gibson assembly of an EGFP- or EBFP-fragment, a WPRE-fragment (lentiCRISPRv2) and a pSK-fragment (pBlueScript SK(+), Stratagene). The EGFP/EBFP-WPRE construct was then cloned into lentiCRISPRv2 via *BamHI* and *PmeI*. We used the following oligos for amplifying the respective Gibson fragments: pSK sense (s) 5’-GTTTAAACAACATACGAGCCGGAAGCATAAA, antisense (as) 5’-CGACATCTCCGGCTTGTTTCAGCAGAGAGAAGTTTGTTGCGCCGGATCCCCCGGTACCCAATTCGCCCTATAGT; EGFP/EBFP s 5’-CTTCTCTCTGCTGAAACAAGCCGGAGATGTCGAAGAGAATCCTGGACCGATGGTGAGCAAGGGCGAGGA, as 5’-GTCGACTTAACGCGT TTACTTGTACAGCTCGTCCA; WPRE s 5’-GAGCTGTACAAGTAAACGCGTTAAACGCGTTAAGTCGACAATCA, as 5’-TTTATGCTTCCGGCTCGTATGTTGTTTAAACGGGCCCTGCTAGAGATTTTC. After *DpnI* digestion the assembly was carried out as follows: 15 ng/kb of the respective fragments, 800 U Taq ligase, 0.08 U T5 exonuclease and 0.4 U Phusion DNA polymerase were incubated in reaction buffer (0.1 M Tris-HCl pH 7.5, 10 mM MgCl2, 0.2 mM dGTP/dCTP/dATP/dTTP, 10 mM DTT, 1 mM NAD) at 50°C for 1h. sgRNAs were designed using the CrispRGold tool (<http://crisprgold.mdc-berlin.de/>). Oligos were annealed and cloned via *BsmBI* into lentiCRISPRv2-EGFP or -EBFP, respectively. The following double-stranded sgRNAs were used: *sgBATF*\_1 s 5’-CACCGACAGAACGCGGCTCTACGCA, as 5’-AAACTGCGTAGAGCCGCGTTCTGTC; *sgBATF*\_2 s 5’-CACCGGACTCTACCTGTTTGCCAGG, as 5’-AAACCCTGGCAAACAGGTAGAGTCC; *sgBATF*\_3 s 5’-CACCGCCTCTGTCGGCTCTTCTGGG, as 5’-AAACCCCAGAAGAGCCGACAGAGGC; *sgBATF3*\_1 s 5’- CACCGGCGCCGCGACGCTCCTCTGC, as 5’- AAACGCAGAGGAGCGTCGCGGCGCC; *sgBATF3*\_2 s 5’-CACCGCCCGATCTCTCTCCGCAGCA, as 5’- AAACTGCTGCGGAGAGAGATCGGGC; *sgBATF3*\_3 s 5’-CACCGAGCAAGAAAACACCATGCTG, as 5’- AAACCAGCATGGTGTTTTCTTGCTC. **(2) *Lentivirus production and transduction of target cells.*** Production of lentivirus and lentiviral transduction was performed as described[6](#_ENREF_6) with some modifications. In brief, 4x106 HEK293T/17 cells were seeded the day before transfection. For transfection, 10 µg of the respective lentiCRISPRv2 plasmid, 5 µg of the packaging plasmid psPAX2 (Addgene plasmid #12260, a gift of Didier Tron) and 5 µg of the packaging plasmid pCMV-VSV-G (Addgene plasmid #8454, a gift of B. Weinberg) were mixed in sterile water and supplemented with 2.5 mM CaCl2 to a final volume of 500 µl. The DNA-CaCl2-mixture was incubated at room temperature for 5 min before being added to 500 µl of sterile 2xHBS buffer (50 mM HEPES, 280 mM NaCl, 1.5 mM Na2HPO4 pH 7.05). This mixture was again incubated at room temperature for 20 min. In the meantime, the medium on HEK293T/17 dishes was changed to DMEM supplemented with 25 pM chloroquine. Finally, the DNA-CaCl2-HBS mix was added to the cell dishes and incubated at 37°C. After 6 to 8 hours, the medium was changed to standard DMEM. 48 hours after transfection, the viral supernatant was harvested. For transduction, 8x105 cells of the respective cell line were seeded in 2 ml, and 2-3 ml of viral supernatant were added. Centrifugation was carried out with 2,000 g for 90 min at 32°C. The day after transduction, cells were washed with 1xPBS for three times.

***Murine xenograft experiments***

A murine xenograft model was established by injecting 8x105 K299 WT, BATF KO or BATF3 KO cells into both flanks of 7-9 weeks old NSG mice (NCI, Frederick, MD). Xenograft studies were approved by the institutional review board.

***Immunohistochemistry (IHC) and mRNA extraction of primary lymphoma cases***

For IHC analyses, BATF (sc-100974) or BATF3 antibody (sc-162246; both Santa Cruz) were applied 1:200. Bound antibody was visualized by APAAP and FastRed (DAKO). mRNA extraction of frozen lymphoma samples was approved by the Local Ethics Committee of the Charité – Universitätsmedizin Berlin and performed in compliance with the Declaration of Helsinki.

***Processing and analysis of oligonucleotide microarray data; gene set enrichment analysis (GSEA) and principal component (PC) analysis***

For generation of TH17 and ILC3 signatures, microarray data for TH17, ILC3 and TH1 cells were obtained from GEO (accession number GSE78897). Raw signals were processed by Affymetrix Power Tools from Affymetrix using Robust Multiarray Analysis (RMA) for background correction and normalization, Detection Above Background (DABG) for estimation of the significance of detection and the limma R package for pairwise comparison between cell lines.[7](#_ENREF_7) Genes with a *P* value DABG < 0.05 were assumed to be expressed. For each cross-comparison two signatures were defined by the top 100 up- and downregulated differentially expressed genes (adj. *P*-value < 0.05). The TH17 and ILC3 signatures were defined as the top 100 up-regulated genes as compared to TH1.

For microarray analyses of the various cell lines, RNA processing and hybridization to Human Genome U133 Plus 2.0 arrays (Affymetrix) were performed according to the manufacturer´s recommendation. The analysis was supplemented with ILC3 microarray data obtained from GEO (accession number GSE43409 (ILC3) [GSM1062197, GSM1062198, GSM1062205, GSM1062206, GSM1062207]).[8](#_ENREF_8) Raw signals of ILC3 (activated and non-activated), ALCL (ALK–, ALK+) as well as CTL samples were processed by the affy and limma R packages using RMA for normalization.[7](#_ENREF_7),[9](#_ENREF_9) GSEA of ALCL in contrast to CTL was performed by the GSEA software with default settings and “gene\_set” permutations based on the cell type-specific signatures. Results are shown for the TH17 or ILC3 signature as compared to TH1. Principal component (PC) analyses were performed on un-scaled log2 expression values of ALCL and CTL based on the top 100 up- and downregulated genes from TH17 and TH1 or ILC3 and TH1 comparisons, respectively. The ILC3 samples were projected on the above principle components. Microarray data of the various cell lines are available through Gene Expression Omnibus (GSE107951).

***Processing and GSEA of primary ALCL and PTCL oligonucleotide microarray data***

Human primary ALCL and PTCL oligonucleotide microarray data were obtained from GEO (accession numbers GSE65823, GSE6338, GSE19069).[10](#_ENREF_10),[11](#_ENREF_11),[12](#_ENREF_12) RNA quality control was performed applying Affymetrix *MAS5* normalization with APT and verification of the 3´/5´ratio for -actin. Samples with ratios above 10 were removed from further consideration. The threshold undemanding enough to keep a significant number of samples for statistical analysis (14 ALK– ALCL, 20 ALK+ ALCL, 51 PTCL), while being stringent enough to remove critical samples. Raw signals were processed again with APT applying RMA for background correction and normalization. Sample similarity was visualized by genome wide Pearson correlation matrix of log2 expression, with samples clustered by the Euclidean distance and Ward´s minimum variance method. Three major clusters were obtained, two separating PTCL into different groups, comprising mainly PTCLs, and an ALCL cluster, comprising mainly ALCLs. GSEA was performed for each of the PTCL group and all ALCLs, augmented by PTCLs from the ALCL cluster in both comparisons as well as GSEA between both PTCL groups, assigning the PTCLs from the ALCL cluster to the closest PTCL cluster. The GSEA was performed as for the cell lines. Results are shown for the TH17 and ILC3 signatures as compared to TH1.

***Measurement of the secreted amounts of IL-22, IL-17A and IL-17F by ELISA***

ELISA was performed with supernatants of cell lines, for which cell lines were cultured in a density of 3 x 105 cells per ml for 24 – 48 h before collection of supernatants. For IL-22 detection, the DuoSet ELISA kit DY782, for IL-17A the DuoSet ELISA kit DY317, and for IL-17F the DuoSet ELISA kit DY1335B (all from R&D Systems) was used. Optical density was determined at 450 nm (corrected for optical imperfections of the plate measured at 570 nm).

***Measurement of IL-17A and IL-17F in ALK+ ALCL*** ***patient serum/plasma samples***

Patients with ALK+ ALCL registered to the NHL-BFM registry 2012 between 2012 and 2013 were eligible if informed consent was given by the patients and/or legal guardians, and initial plasma was available. The study was approved by the institutional review board (AZ 193-11, AZ 76/12). Serum/plasma taken in remission without infection before the last course of chemotherapy was analyzed as control, if available. Serum of healthy young adults served as an additional control. The median age of the 21 patients was 14 years (range 7.5-19.5 years), and of the 14 adult healthy volunteers was 27 years (range 24-38 years). All blood samples were shipped to the NHL-BFM laboratory within 24 h of collection, and the serum/plasma was stored at - 80°C. Cytometric bead array Flex Sets for IL-17A and IL-17F (BD-Biosciences) were used according to the manufacturer’s instructions. In brief, serum/plasma samples were pre-diluted 1:4 or 1:10. Samples or standards for IL-17A/-F were incubated with a mixture of IL-17A/-F fluorescent capture beads and IL-17A/-F detection antibodies. Each capture bead Flex set is characterized by a distinct fluorescence; the detection-antibodies are conjugated to phycoerythrin (PE). The samples were measured with a FACS Verse flow cytometer and BD FACSuite™ software (BD-Biosciences). The data were analyzed by FCPA Array™ Software Version 3 (BD-Biosciences, Heidelberg 2.0).

***Chromatin immunoprecipitation (ChIP) assays and real-time PCR analyses***

ChIP assays were performed in two biological replicates using antibodies for BATF (Cell Signaling Technology, #8638; ChIP-validated), BATF3 (R&D Systems, #AF7437) and JUNB (Cell Signaling, #3753; ChIP-validated) according to a modified Millipore protocol ([http://www.merckmillipore.com/DE/de/product/ChromatinImmunoprecipitation%28ChIP%](http://www.merckmillipore.com/DE/de/product/Chromatin-Immunoprecipitation%28ChIP%25)29-Array-Kit,MM\_NF-17-295#anchor\_BRO). In brief, cells were fixed using the two-step cross-linking method (2 mM disuccinimidyl glutarate for 30 min followed by 1% formaldehyde for 5 min)[13](#_ENREF_13) and lyzed with 50 mM Tris-HCl, pH 8.0 / 5mM EDTA / 1 % SDS. Thereafter, samples were sonicated with the Bioruptor Plus (Diagenode; 13 cycles, intensity High, sonication 30 s/break 30 s per cycle). Chromatin was pre-cleared with bovine serum albumin (BSA)-saturated Protein A-Sepharose and incubated overnight at 4°C with the specific antibodies (concentration as indicated by the manufacturer for the ChIP-validated antibodies; 27 g/ 1 x 107 cells for BATF3 antibody). Immuno-complexes were collected with BSA-saturated Protein A-Sepharose for 1 h at 4°C. After washing, protein-DNA complexes were eluted using 1 % SDS / 0.1 M NaHCO3. Reversal of the cross-linking, RNAse treatment, proteinase K digestion, and DNA purification by phenol-chloroform extraction were performed according to standard protocols.Quantitative PCR (qPCR) was carried out in triplicates with ChIP-DNA corresponding to 3 x 105 cell equivalents using the CFX96 system and GoTaq® qPCR Master Mix (Promega). Primer sequences are shown in **Supplementary Table 2**. Non-recruiting intergenic regions on chromosome 4 and 12 were amplified as references. A total of 4 ng input DNA was used as a control. For quantification, the normalized expression (ΔΔCq) was calculated by the CFX manager software (Bio-Rad) and the primer efficiencies as indicated in **Supplementary Table 2**.

***Statistics***

Statistical analyses were done in R v2.9.1 (http://www.r-ptoject.org/) and GraphPad Prism Version 5.0. Two-sided Welch´s *t*-test was used to analyze data from proliferation, growth and apoptosis assays. Statistical calculations for IL-17A and IL-17F serum/plasma samples were performed using SPSS (standard version 24, SPSS Inc., Chicago, IL). Cytokine levels were compared between different groups using Kruskal-Wallis tests.

**References for Supplementary Materials and Methods**

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