# JAK/STAT blockade reverses the malignant phenotype of Hodgkin and Reed–Sternberg cells

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## SUPPLEMENTARY INFORMATION

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**Supplemental Table 1. Clinical data.**

| **cHL subtype** | | | **CSF3R-positive** | **CSF3R-negative** | **p** |
|---|---|---|---|---|---|
| | NS | 57 | 46 | 6 | |
| | MC | 28 | 24 | 4 | |
| | LR | 7 | 7 | 0 | |
| | NC | 12 | 4 | 1 | |
| Stage | | | | | n.s. |
| | I-III | 75 | 65 | 11 | |
| | IV | 30 | 26 | 4 | |
| Age | | | | | 0.027 |
| | 45 | 72 | 66 | 6 | |
| | >45 | 31 | 23 | 8 | |
| Gender | | | | | n.s. |
| | Male | 45 | 35 | 8 | |
| | Female | 60 | 54 | 6 | |
| IPS | | | | | n.s. |
| | 3 | 32 | | | |
| | >3 | 71 | | | |
| Relapse | | | | | |
| | Yes | 28 | 24 | 3 | n.s. |
| | No | 75 | 64 | 11 | |
| Outcome | | | | | n.s. |
| | F | 91 | 78 | 13 | |
| | U | 27 | 24 | 3 | |
| **Total** | | **105** | **89** | **16** | |

**Supplemental Table 2. All gene sets.**

| SOURCE | DATABASE | DESCRIPTION |
|---|---|---|
| BioCarta | BIOCARTA_BCELLSURVIVAL_PATHWAY | B-cell Survival Pathway |
| | BIOCARTA_BCR_PATHWAY | BCR Signaling Pathway |
| | BIOCARTA_BLYMPHOCYTE_PATHWAY | B Lymphocyte Cell Surface Molecules |
| | BIOCARTA_CACAM_PATHWAY | Ca++/ Calmodulin-dependent Protein Kinase Activation |
| | BIOCARTA_CASPASE_PATHWAY | Caspase Cascade in Apoptosis |
| | BIOCARTA_CD40_PATHWAY | CD40L Signaling Pathway |
| | BIOCARTA_CDC25_PATHWAY | cdc25 and chk1 Regulatory Pathway in response to DNA damage |
| | BIOCARTA_CELLCYCLE_PATHWAY | Cyclins and Cell Cycle Regulation |
| | BIOCARTA_CYTOKINE_PATHWAY | Cytokine Network |
| | BIOCARTA_FCER1_PATHWAY | Fc Epsilon Receptor I Signaling in Mast Cells |
| | BIOCARTA_G1_PATHWAY | Cell Cycle: G1/S Checkpoint |
| | BIOCARTA_G2_PATHWAY | Cell Cycle: G2/M Checkpoint |
| | BIOCARTA_GATA3_PATHWAY | GATA3 participate in activating the Th2 cytokine genes expression |
| | BIOCARTA_GRANULOCYTES_PATHWAY | Adhesion and Diapedesis of Granulocytes |
| | BIOCARTA_IFNA_PATHWAY | IFN alpha signaling pathway |
| | BIOCARTA_IFNG_PATHWAY | IFN gamma signaling pathway |
| | BIOCARTA_IL10_PATHWAY | IL-10 Anti-inflammatory Signaling Pathway |
| | BIOCARTA_IL12_PATHWAY | IL12 and Stat4-Dependent Signaling Pathway in Th1 Development |
| | BIOCARTA_IL17_PATHWAY | IL 17 Signaling Pathway |
| | BIOCARTA_IL2_PATHWAY | IL 2 signaling pathway |
| | BIOCARTA_IL22BP_PATHWAY | IL22 Soluble Receptor Signaling Pathway |
| | BIOCARTA_IL2RB_PATHWAY | IL-2 Receptor Beta Chain in T-cell Activation |
| | BIOCARTA_IL3_PATHWAY | IL 3 signaling pathway |
| | BIOCARTA_IL4_PATHWAY | IL 4 signaling pathway |
| | BIOCARTA_IL5_PATHWAY | IL 5 Signaling Pathway |
| | BIOCARTA_IL6_PATHWAY | IL 6 signaling pathway |
| | BIOCARTA_IL7_PATHWAY | IL-7 Signal Transduction |
| | BIOCARTA_INFLAM_PATHWAY | Cytokines and Inflammatory Response |
| | BIOCARTA_LYM_PATHWAY | Adhesion and Diapedesis of Lymphocytes |
| | BIOCARTA_LYMPHOCYTE_PATHWAY | Adhesion Molecules on Lymphocyte |
| | BIOCARTA_MCM_PATHWAY | CDK Regulation of DNA Replication |
| | BIOCARTA_MHC_PATHWAY | Antigen Processing and Presentation |
| | BIOCARTA_NFKB_PATHWAY | NF-kB Signaling Pathway |
| | BIOCARTA_STAT3_PATHWAY | Stat3 Signaling Pathway |

| | | |
|---|---|---|
| | BIOCARTA_STRESS_PATHWAY | TNF/Stress-Related Signaling |
| | BIOCARTA_TCR_PATHWAY | T-cell Receptor Signaling Pathway |
| | BIOCARTA_TCYTOTOXIC_PATHWAY | T Cytotoxic Cell Surface Molecules |
| | BIOCARTA_TGFB_PATHWAY | TGF beta signaling pathway |
| | BIOCARTA_TH1TH2_PATHWAY | Th1/Th2 Differentiation |
| | BIOCARTA_THELPER_PATHWAY | T Helper Cell Surface Molecules |
| | BIOCARTA_TNFR1_PATHWAY | TNFR1 Signaling Pathway |
| | BIOCARTA_TNFR2_PATHWAY | TNFR2 Signaling Pathway |
| MSigDB Team | DIRMEIER_LMP1_RESPONSE_EARLY | Clusters 1 and 2: genes upregulated in B2264-19/3 cells (primary B lymphocytes) within 30-60 min of activation of LMP1 (oncogene encoded by Epstein–Barr virus, EBV) |
| | DIRMEIER_LMP1_RESPONSE_LATE_DN | Cluster 4: genes downregulated in B2264-19/3 cells (primary B lymphocytes) within 60-180 min of activation of LMP1 (oncogene encoded by Epstein–Barr virus, EBV) |
| | DIRMEIER_LMP1_RESPONSE_LATE_UP | Cluster 3: genes upregulated in B2264-19/3 cells (primary B lymphocytes) within 60-180 min after activation of LMP1 (oncogene encoded by Epstein–Barr virus, EBV) |
| | HADDAD_T_LYMPHOCYTE_AND_NK_PROGENITOR_DN | Genes downregulated in hematopoietic progenitor cells (HPC) of T lymphocyte and NK (natural killer) lineage |
| | HADDAD_T_LYMPHOCYTE_AND_NK_PROGENITOR_UP | Genes upregulated in hematopoietic progenitor cells (HPC) of T lymphocyte and NK (natural killer) lineage |
| | HALLMARK_INFLAMMATORY_RESPONSE | Genes defining inflammatory response |
| | JAIN_NFKB_SIGNALING | Genes abnormally regulated in response to CD40L and IL4 [GeneID=959;3565] stimulation of B lymphocytes from patients with a hypomorphic mutation of IKBKG [GeneID=8517] |
| | KLEIN_TARGETS_OF_BCR_ABL1_FUSION | Genes changed in pre-B lymphoblastic leukemia cells with BCR-ABL1 fusion [GeneID=613, 25] *vs.* normal pre-B lymphocytes |
| | WHITFIELD_CELL_CYCLE_LITERATURE | A list of known cell-cycle-regulated genes that was compiled from the literature by the authors |
| | ZHAN_EARLY_DIFFERENTIATION_GENES_DN | B lymphocyte early differentiation genes (EDG): top genes down-regulated in tonsil B lymphocytes (TBC) compared to the tonsil plasma cells (TPC) |
| | ZHAN_EARLY_DIFFERENTIATION_GENES_UP | B lymphocyte early differentiation genes (EDG): top genes up-regulated in tonsil B lymphocytes (TBC) compared to the tonsil plasma cells (TPC) |
| | ZHAN_LATE_DIFFERENTIATION_GENES_DN | B lymphocyte late differentiation genes (LDG): top genes down-regulated in plasma cells from tonsils (TPC) compared to those from bone marrow (BPC) |

| | | |
|---|---|---|
| | ZHAN_LATE_DIFFERENTIATION_GENES_UP | B lymphocyte late differentiation genes (LDG): top genes upregulated in plasma cells from tonsils (TPC) compared to those from bone marrow (BPC) |
| Kyoto Encyclopedia of Genes and Genomes | KEGG_APOPTOSIS | Apoptosis |
| | KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY | B-cell receptor signaling pathway |
| | KEGG_CALCIUM_SIGNALING_PATHWAY | Calcium signaling pathway |
| | KEGG_CELL_CYCLE | KEGG cell cycle |
| | KEGG_CHEMOKINE_SIGNALING_PATHWAY | Chemokine signaling pathway |
| | KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION | Cytokine–cytokine receptor interaction |
| | KEGG_FC_EPSILON_RI_SIGNALING_PATHWAY | Fc epsilon RI signaling pathway |
| | KEGG_FC_GAMMA_R_MEDIATED_PHAGOCYTOSIS | Fc gamma R-mediated phagocytosis |
| | KEGG_JAK_STAT_SIGNALING_PATHWAY | JAK/STAT signaling pathway |
| | KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY | Natural killer cell mediated cytotoxicity |
| | KEGG_TGF_BETA_SIGNALING_PATHWAY | TGF-beta signaling pathway |
| Broad Institute | MODULE_122> Adhesion molecules | Adhesion molecules |
| | MODULE_169 | MODULE_169_Immune response |
| | MODULE_170 | MODULE_170_Immune response |
| | MODULE_223 | Immune (defense) response |
| | MODULE_263 | Chemotaxis (chemokines) |
| | MODULE_291 | B-cell malignancies expression clusters |
| | MODULE_33 | Immune / stress response genes |
| | MODULE_345 | Immune response and Ag processing and presentation |
| | MODULE_358 | MODULE_358_B lymphoma expression clusters |
| | MODULE_361 | MODULE_361_B lymphoma expression clusters |
| | MODULE_362 | Angiogenesis |
| | MODULE_456 | MODULE_456_B lymphoma expression clusters |
| | MODULE_521 | T-cell proliferation genes |
| | MODULE_522 | Immune response genes |
| | MODULE_54 | Cell cycle (expression cluster) |
| | MODULE_545 | IL-1 signaling |
| | MODULE_56 | Cell cycle (KEGG, GenMapp) |
| | MODULE_75 | Immune response |
| | MODULE_76 | Inflammatory response |
| | MODULE_84 | Immune (humoral) and inflammatory response |
| Reactome | REACTOME_ACTIVATION_OF_CASPASES_THROUGH_APOPTOSOME_MEDIATED_CLEAVAGE | Activation of caspases through apoptosome-mediated cleavage |

| | | |
|---|---|---|
| | REACTOME_ACTIVATION_OF_NF_KAPPAB_IN_B_CELLS | Activation of NF-kappaB in B-cells |
| | REACTOME_ACTIVATION_OF_RAS_IN_B_CELLS | Activation of RAS in B-cells |
| | REACTOME_ADAPTIVE_IMMUNE_SYSTEM | Adaptive Immune System |
| | REACTOME_ANTIGEN_ACTIVATES_B_CELL_RECEPTOR_BCR_LEADING_TO_GENERATION_OF_SECOND_MESSENGERS | Antigen activates B-cell Receptor (BCR) leading to generation of second messengers |
| | REACTOME_ANTIGEN_PRESENTATION_FOLDING_ASSEMBLY_AND_PEPTIDE_LOADING_OF_CLASS_I_MHC | Antigen Presentation: Folding, assembly and peptide loading of class I MHC |
| | REACTOME_CA_DEPENDENT_EVENTS | Ca-dependent events |
| | REACTOME_CA2_ACTIVATED_K_CHANNELS | Ca2+ activated K+ channels |
| | REACTOME_CA2_PATHWAY | Ca2+ pathway |
| | REACTOME_CALCINEURIN_ACTIVATES_NFAT | Calcineurin activates NFAT |
| | REACTOME_CD22_MEDIATED_BCR_REGULATION | CD22 mediated BCR regulation |
| | REACTOME_CD28_CO_STIMULATION | CD28 co-stimulation |
| | REACTOME_CD28_DEPENDENT_PI3K_AKT_SIGNALING | CD28 dependent PI3K/Akt signaling |
| | REACTOME_CD28_DEPENDENT_VAV1_PATHWAY | CD28 dependent Vav1 pathway |
| | REACTOME_CELL_CYCLE | Reactome Cell Cycle |
| | REACTOME_CELL_CYCLE_CHECKPOINTS | Cell Cycle Checkpoints |
| | REACTOME_CELL_CYCLE_MITOTIC | Cell Cycle, Mitotic |
| | REACTOME_CHEMOKINE_RECEPTORS_BIND_CHEMOKINES | Chemokine receptors bind chemokines |
| | REACTOME_CLASS_I_MHC_MEDIATED_ANTIGEN_PROCESSING_PRESENTATION | Class I MHC mediated antigen processing & presentation |
| | REACTOME_CYTOKINE_SIGNALING_IN_IMMUNE_SYSTEM | Cytokine Signaling in Immune system |
| | REACTOME_DOWNREGULATION_OF_TGF_BETA_RECEPTOR_SIGNALING | Downregulation of TGF-beta receptor signaling |
| | REACTOME_DOWNSTREAM_SIGNALING_EVENTS_OF_B_CELL_RECEPTOR_BCR_ | Downstream signaling events of B-cell Receptor (BCR) |
| | REACTOME_DOWNSTREAM_TCR_SIGNALING | Downstream TCR signaling |
| | REACTOME_FC_EPSILON_RECEPTOR_FCERI_SIGNALING | Fc epsilon receptor (FCERI) signaling |
| | REACTOME_G1_S_DNA_DAMAGE_CHECKPOINTS | G1/S DNA Damage Checkpoints |
| | REACTOME_G1_S_SPECIFIC_TRANSCRIPTION | G1/S-Specific Transcription |

| | | |
|---|---|---|
| | REACTOME_G2_M_CHECKPOINTS | G2/M Checkpoints |
| | REACTOME_G2_M_DNA_DAMAGE_CHECKPOINT | G2/M DNA damage checkpoint |
| | REACTOME_G2_M_DNA_REPLICATION_CHECKPOINT | G2/M DNA replication checkpoint |
| | REACTOME_G2_PHASE | G2 Phase |
| | REACTOME_IL_6_TYPE_CYTOKINE_RECEPTOR_LIGAND_INTERACTIONS | IL-6-type cytokine receptor ligand interactions |
| | REACTOME_IMMUNE_SYSTEM | Genes involved in Immune System |
| | REACTOME_IMMUNOREGULATORY_INTERACTIONS_BETWEEN_A_LYMPHOID_AND_A_NON_LYMPHOID_CELL | Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell |
| | REACTOME_INNATE_IMMUNE_SYSTEM | Innate Immune System |
| | REACTOME_INTERFERON_GAMMA_SIGNALING | Interferon gamma signaling |
| | REACTOME_INTERFERON_SIGNALING | Interferon Signaling |
| | REACTOME_INTERLEUKIN_10_SIGNALING | Interleukin-10 signaling |
| | REACTOME_INTERLEUKIN_4_AND_INTERLEUKIN_13_SIGNALING | Interleukin-4 and Interleukin-13 signaling |
| | REACTOME_INTERLEUKIN_6_FAMILY_SIGNALING | Interleukin-6 family signaling |
| | REACTOME_MHC_CLASS_II_ANTIGEN_PRESENTATION | MHC class II antigen presentation |
| | REACTOME_RUNX1_REGULATES_TRANSCRIPTION_OF_GENES_INVOLVED_IN_BCR_SIGNALING | RUNX1 regulates transcription of genes involved in BCR signaling |
| | REACTOME_SIGNALING_BY_RECEPTOR_TYROSINE_KINASES | Signaling by Receptor Tyrosine Kinases |
| | REACTOME_SIGNALING_BY_THE_B_CELL_RECEPTOR_BCR_ | Signaling by the B-cell Receptor (BCR) |
| | REACTOME_STAT5_ACTIVATION | STAT5 Activation |
| | REACTOME_TCR_SIGNALING | TCR signaling |
| | REACTOME_TNF_RECEPTOR_SUPERFAMILY_TNFSF_MEMBERS_MEDIATING_NON_CANONICAL_NF_KB_PATHWAY | TNF receptor superfamily (TNFSF) members mediating non-canonical NF-kB pathway |
| | REACTOME_TNF_SIGNALING | TNF signaling |
| | REACTOME_TNFR1_INDUCED_NFKAPPAB_SIGNALING_PATHWAY | TNFR1-induced NFkappaB signaling pathway |
| | REACTOME_TNFR1_INDUCED_PROAPOPTOTIC_SIGNALING | TNFR1-induced proapoptotic signaling |

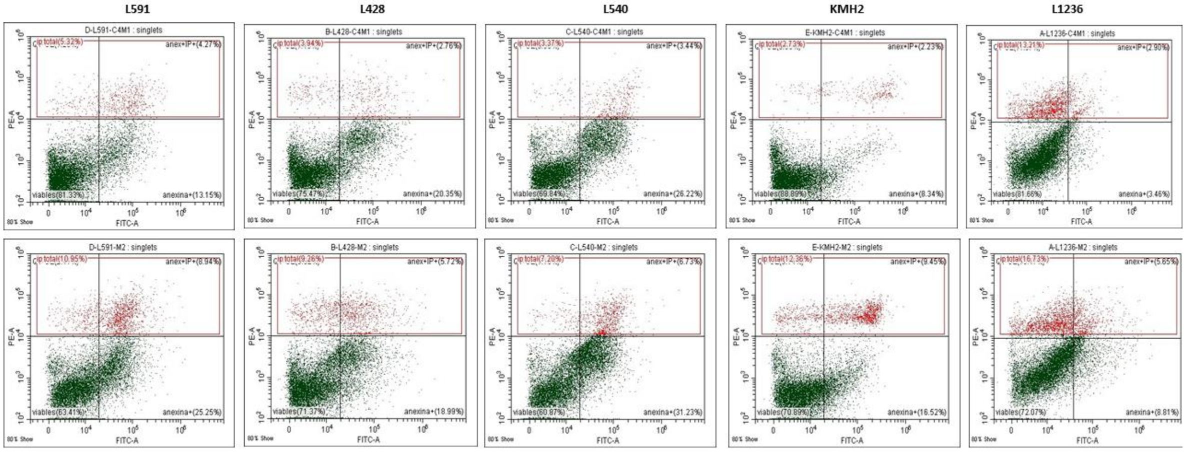
**Supplemental Table 3. Significant TcGSA gene sets**

| Description | p | Public database gene set name | Contributor |
|---|---|---|---|
| **Immune response** | 3.218E-34 | MODULE_75 | Broad Institute |
| **Cytokine-cytokine receptor interaction** | 3.364E-30 | KEGG_CYTOKINE_CYTOKINE_RECEPTOR_ INTERACTION | Kyoto Encyclopedia of Genes and Genomes |
| **Immunoregulatory interactions between a lymphoid and a non-lymphoid cell** | 5.837E-18 | REACTOME_IMMUNOREGULATORY_INTERACTIONS_ BETWEEN_A_LYMPHOID_AND_A_NON_LYMPHOID_CELL | Reactome |
| **Calcium signaling pathway** | 9.750E-16 | KEGG_CALCIUM_SIGNALING_PATHWAY | Kyoto Encyclopedia of Genes and Genomes |
| **JAK/STAT signaling pathway** | 2.653E-12 | KEGG_JAK_STAT_SIGNALING_PATHWAY | Kyoto Encyclopedia of Genes and Genomes |
| **Adhesion molecules** | 2.653E-12 | MODULE_122 | Broad Institute |
| **Chemotaxis (chemokines)** | 5.797E-12 | MODULE_263 | Broad Institute |
| **Immune / stress response genes** | 1.355E-11 | MODULE_33 | Broad Institute |
| **IL 17 signaling pathway** | 5.111E-10 | BIOCARTA_IL17_PATHWAY | BioCarta |
| **Inflammatory response** | 1.561E-08 | MODULE_76 | Broad Institute |
| **Cell cycle, mitotic** | 1.646E-08 | REACTOME_CELL_CYCLE_MITOTIC | Reactome |
| **Immune (defense) response** | 4.210E-08 | MODULE_223 | Broad Institute |
| **Chemokine receptors bind chemokines** | 2.031E-06 | REACTOME_CHEMOKINE_RECEPTORS_BIND_ CHEMOKINES | Reactome |
| **Immune response** | 3.929E-06 | MODULE_170 | Broad Institute |
| **Genes defining inflammatory response** | 7.035E-06 | HALLMARK_INFLAMMATORY_RESPONSE | MSigDB Team |
| **Signaling by receptor tyrosine kinases** | 2.356E-05 | REACTOME_SIGNALING_BY_RECEPTOR_ TYROSINE_KINASES | Reactome |
| **Cell cycle: G2/M checkpoint** | 7.081E-05 | BIOCARTA_G2_PATHWAY | BioCarta |
| **Cytokine network** | 1.708E-04 | BIOCARTA_CYTOKINE_PATHWAY | BioCarta |
| **T-cell proliferation genes** | 2.637E-04 | MODULE_521 | Broad Institute |
| **Chemokine signaling pathway** | 3.707E-04 | KEGG_CHEMOKINE_SIGNALING_PATHWAY | Kyoto Encyclopedia of Genes and Genomes |
| **TNF signaling** | 8.846E-04 | REACTOME_TNF_SIGNALING | Reactome |
| **Natural killer cell mediated cytotoxicity** | 1.295E-03 | KEGG_NATURAL_KILLER_CELL_MEDIATED_ CYTOTOXICITY | Kyoto Encyclopedia of Genes and Genomes |
| **Cell cycle checkpoints** | 2.703E-03 | REACTOME_CELL_CYCLE_CHECKPOINTS | Reactome |
| **Class I MHC-mediated antigen processing and presentation** | 5.412E-03 | REACTOME_CLASS_I_MHC_MEDIATED_ ANTIGEN_PROCESSING_PRESENTATION | Reactome |
| **B-cell malignancies expression clusters** | 8.306E-03 | MODULE_291 | Broad Institute |
| **Signaling by the B-cell receptor (BCR)** | 9.270E-03 | REACTOME_SIGNALING_BY_THE_ B_CELL_RECEPTOR_BCR_ | Reactome |
| **IL-6-type cytokine receptor ligand interactions** | 1.220E-02 | REACTOME_IL_6_TYPE_CYTOKINE_ RECEPTOR_LIGAND_INTERACTIONS | Reactome |
| **Downstream signaling events of B-cell receptor (BCR)** | 1.327E-02 | REACTOME_DOWNSTREAM_SIGNALING_ EVENTS_OF_B_CELL_RECEPTOR_BCR_ | Reactome |
| **IL-1 signaling.** | 1.715E-02 | MODULE_545 | Broad Institute |
| **Interleukin-10 signaling** | 2.798E-02 | REACTOME_INTERLEUKIN_10_SIGNALING | Reactome |

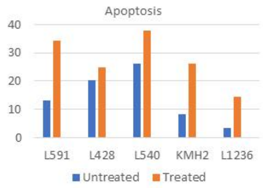
| | | | |
|---|---|---|---|
| **Interleukin-4 and Interleukin-13 signaling** | 3.227E-02 | REACTOME_INTERLEUKIN_4_AND_INTERLEUKIN_13_SIGNALING | Reactome |
| **MHC pathway. Antigen processing and presentation** | 3.230E-02 | BIOCARTA_MHC_PATHWAY | BioCarta |
| **Fc epsilon receptor (FCERI) signaling** | 3.322E-02 | REACTOME_FC_EPSILON_RECEPTOR_FCERI_SIGNALING | Reactome |
| **Genes downregulated in primary B lymphocytes after activation of LMP1** | 3.590E-02 | DIRMEIER_LMP1_RESPONSE_LATE_DN | MSigDB Team |
| **Downregulation of TGF-beta receptor signaling** | 3.590E-02 | REACTOME_DOWNREGULATION_OF_TGF_BETA_RECEPTOR_SIGNALING | Reactome |
| **Interleukin-6 family signaling** | 3.590E-02 | REACTOME_INTERLEUKIN_6_FAMILY_SIGNALING | Reactome |
| **Genes downregulated in hematopoietic progenitor cells (HPCs) of T lymphocyte and NK (natural killer) lineage** | 4.015E-02 | HADDAD_T_LYMPHOCYTE_AND_NK_PROGENITOR_DN | MSigDB Team |

**Supplemental Figure 1.** Apoptosis (A) and cell-cycle analyses (B) Percentage of apoptotic cells (% annexin V+) and G2/M fraction before (top panels) and after ruxolitinib treatment (bottom panels) (two-way ANOVA: *** p <0.001).

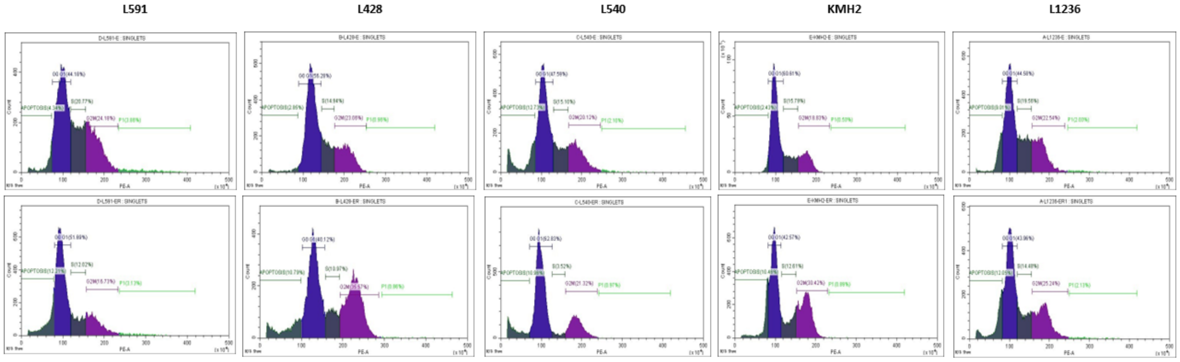
A)



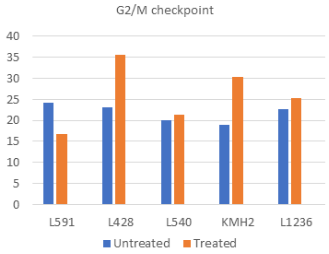
| CELL LINE | APOPTOSIS | | | | | |
|---|---|---|---|---|---|---|
| | Untreated | | TOTAL | Treated | | TOTAL |
| L591 | 4.27 | 13.15 | 17.42 | 8.94 | 25.25 | 34.19 |
| L428 | 2.76 | 20.35 | 23.11 | 5.72 | 18.99 | 24.71 |
| L540 | 3.44 | 26.22 | 29.66 | 6.73 | 31.23 | 37.96 |
| KMH2 | 2.23 | 8.34 | 10.57 | 9.45 | 16.52 | 25.97 |
| L1236 | 2.9 | 3.46 | 6.36 | 5.65 | 8.81 | 14.46 |



B)

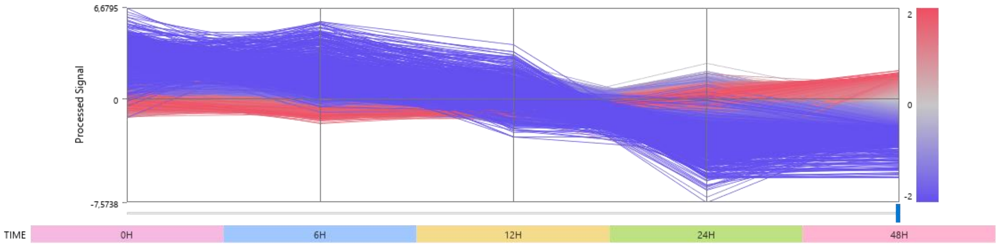


| CELL LINE | G2/M chechpoint | |
|---|---|---|
| | Untreated | Treated |
| L591 | 24.18 | 16.73 |
| L428 | 23.06 | 35.57 |
| L540 | 20.12 | 21.32 |
| KMH2 | 18.83 | 30.42 |
| L1236 | 22.54 | 25.24 |

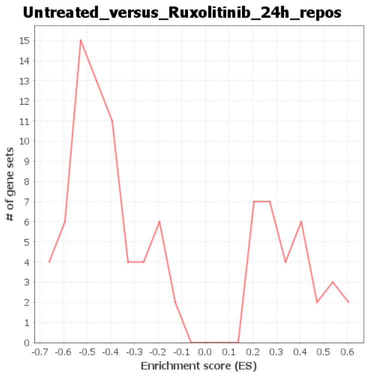


**Supplemental Figure 2.** A) Unsupervised analyses of whole transcriptome changes during the time-course experiments reveal massive transcriptional changes, affecting more than 18% of the transcriptome (average 5360 genes more than three-fold upregulated or downregulated, range 2460-7198 genes). B) GSEA, global enrichment score (ES) histogram confirms that most of the changes involved gene downregulation.

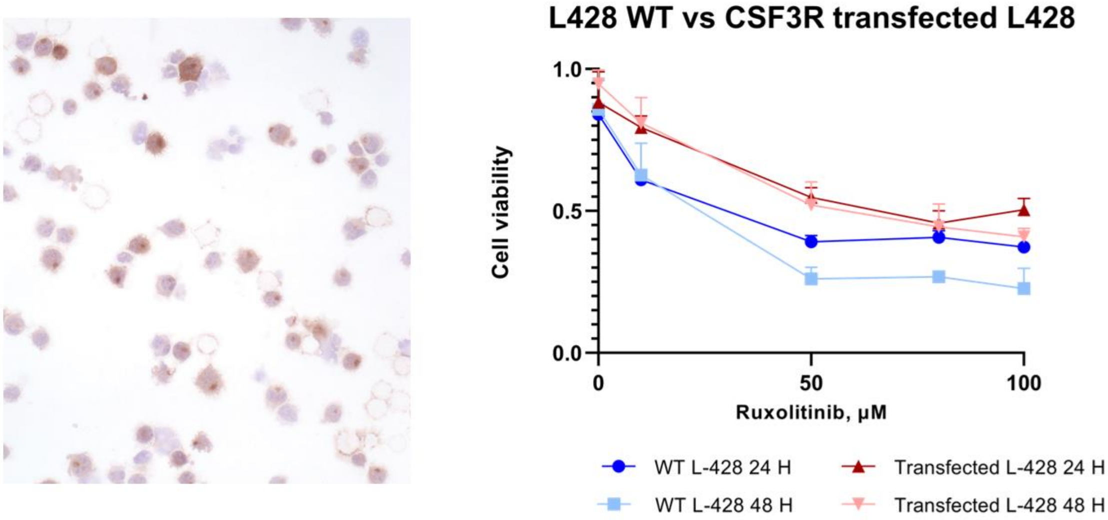
A)



B)



**Supplemental Figure 3.** L-428 transfection experiments using PCMV6-hCSF3R-Myc-DDK-tagged vector. Left: transfection efficiency is evaluated using IHC with anti-Myc mAb (CNIO). Right: viability assays confirming lower ruxolitinib-induced toxicity in L-428-trasfected cells.



**Supplemental Figure 4.** GSEA analyses of L-428 and L-1236 cell lines treated with 5-Aza-dC/decitabine (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE86068) [38] (top panel), compared with ruxolitinib (bottom panel), showing completely different modulation of pathways. The y-axis represents the enrichment score (ES), comparing phenotypes untreated and after 24 h of treatment. The bars correspond to gene sets upregulated in untreated cells (gene sets with a nominal value of $p < 0.05$ are marked with an asterisk).