Supplementary Information

Ullrich et al., The IL-15 cytokine system provides growth and survival signals in Hodgkin lymphoma and enhances the inflammatory phenotype of HRS cells

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Cytokine and cytokine receptor expression in Hodgkin and non-Hodgkin B cell lines.

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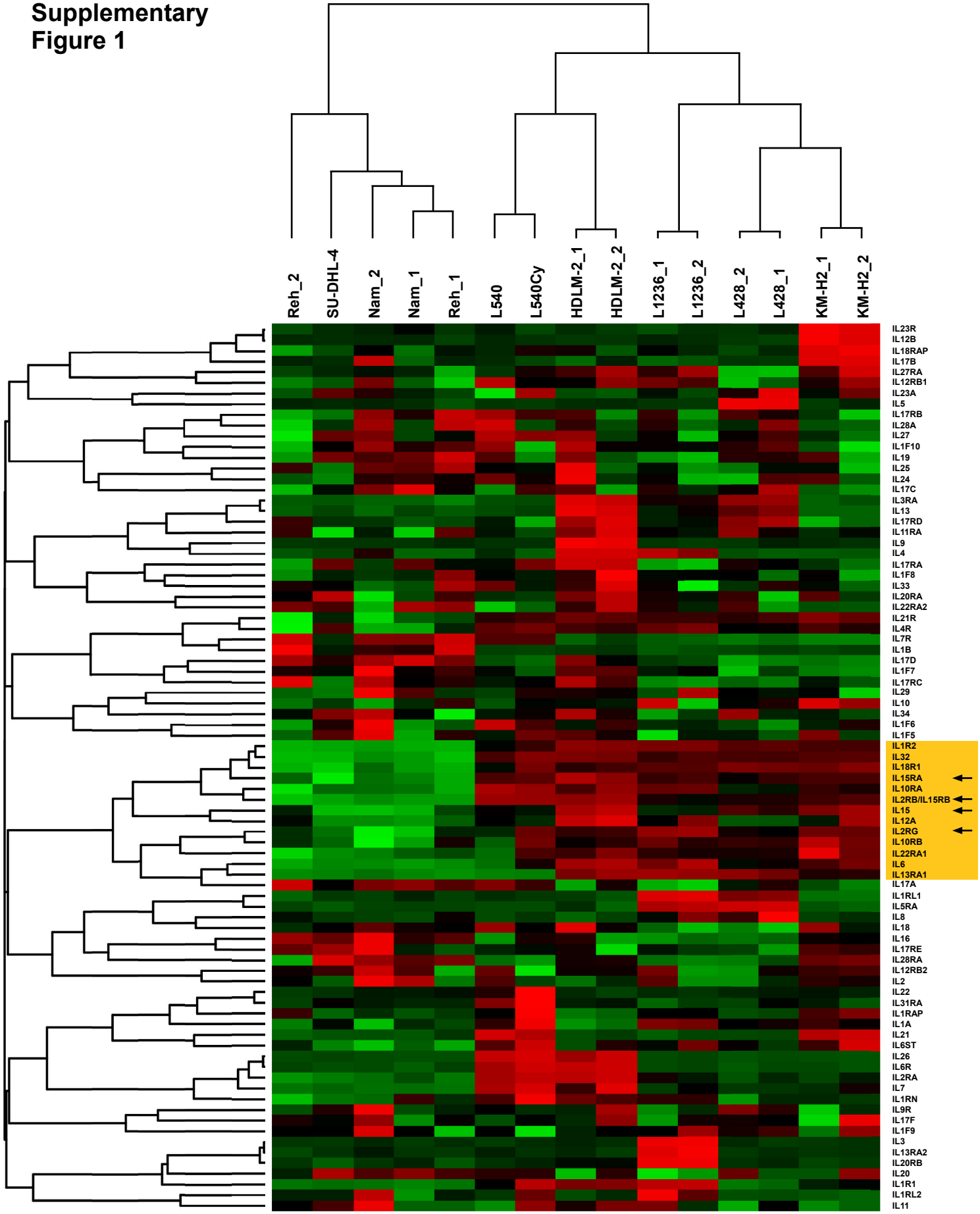
Supplementary Materials and Methods

Supplementary Figure 1



Cytokine and cytokine receptor expression in Hodgkin and non-Hodgkin B cell lines. Gene expression profiles of HRS (L428, L1236, KM-H2, HDLM-2, L540, L540Cy), B-NHL (Namalwa, SUDHL-4) and B acute lymphoblastic leukemia (Reh) cells were generated using Affymetrix U133 Plus 2.0 oligonucleotide microarrays. Gene entries coding for members of the interleukin and interleukin receptor family were selected and used as input gene list for hierarchical clustering and heat map visualization. The color code indicates relative up- (red) or down-regulation (green) of the respective gene across all samples. A core set of cytokine and cytokine receptors genes up-regulated in HRS cell lines is highlighted (yellow box) and the position of the probe sets for IL-15, IL-15Rα, IL-2Rβ/IL-15Rβ and IL-2Rγ (common γ chain) is indicated by arrows.

Supplementary Table 1

HL case #	IL-15 staining in HRS cells
1	partially positive
2	partially positive
3	positive
4	positive
5	partially positive
6	partially positive
7	positive
8	partially positive

Summary of IL-15 immunostaining in classical Hodgkin lymphoma cases. Immunohistochemistry for IL-15 was performed on fresh frozen samples of reactive tonsils (control) and primary HL tissue (n = 8 cases; technical details are described in Supplementary Materials and Methods). Positive/partially positive indicates staining for IL-15 in HRS tumor cells. In addition, in all cases positive staining was observed in cells of the tumor microenvironment (monocytic/dendritic morphology and endothelial cells).

Supplementary Table 2

Ilumina ID	Gene Symbol	log_2FC 4 hr	log_2FC 10 hr	log_2FC 24 hr	p-value adj 4 hr	p-value adj 10hr	p-value adj 24 hr
6650474	TPTE2	1,64	2,22	2,35	0,0008	0	0
130021	IL2RA	1,90	2,21	2,23	0	0	0
770746	ETV5	1,47	1,64	1,57	0,0011	0,0001	0,0002
6590682	CCL3	0,12	0,62	1,52	0,9824	0,4362	0
2810010	CCL3L3	0,10	0,78	1,46	0,9921	0,5108	0,0017
4040576	IL6	0,96	1,13	1,43	0,1329	0,0108	0,0002
840678	ENPP2	0,63	1,09	1,25	0,8151	0,0047	0,0003
2030687	C3orf59	1,02	0,99	1,15	0,0125	0,0108	0,0010
2120167	IL9	1,03	0,98	1,15	0,5132	0,4204	0,1683
60138	CTH	0,19	0,61	1,02	0,9583	0,4358	0,0017
1980524	GBP4	0,69	1,11	1,00	0,8265	0,0216	0,0809
5090408	LRIG1	0,44	0,60	0,93	0,9397	0,7223	0,7168
2900603	IL12B	0,36	0,33	0,93	0,9330	0,7970	0,0809
6220474	RBM10	0,13	0,50	0,93	0,9854	0,7149	0,3601
870202	TNFSF10	0,81	0,96	0,92	0,2752	0,0264	0,0565
610270	ELL2	1,04	1,17	0,89	0,3085	0,0654	0,5353
3990661	FAM177A1	0,46	0,71	0,86	0,9330	0,6100	0,6325
4890195	COPS2	0,63	0,55	0,86	0,8265	0,6122	0,1755
870338	EGR1	0,13	0,68	0,85	0,9808	0,4362	0,1523
5890121	NRG4	0,13	0,53	0,85	0,9768	0,4770	0,0157
2710575	CD69	0,25	0,52	0,83	0,9533	0,6295	0,1979
1980672	IL1A	0,29	0,41	0,82	0,9545	0,7742	0,6203
6220288	PRDM1	0,62	0,50	0,82	0,8265	0,6295	0,1755
3520196	LIG4	0,54	0,28	0,81	0,9330	0,8482	0,4108
6580008	C15orf27	0,31	0,65	0,80	0,9354	0,4602	0,2154
4490520	GPR183	0,94	1,08	0,79	0,0898	0,0096	0,2433
5700220	DAPK1	0,37	0,68	0,79	0,9330	0,2803	0,0809
6900209	ADAM19	0,45	0,77	0,79	0,9330	0,5385	0,7124
4560193	CD44	0,42	0,83	0,78	0,9330	0,1188	0,1979
1190202	SELT	0,30	0,55	0,77	0,9431	0,6472	0,5356
6510377	TNFRSF12A	0,19	0,12	0,76	0,9680	0,9562	0,4677
7050711	LYST	0,56	0,63	0,76	0,9330	0,6295	0,7168
1410446	LRSAM1	0,32	0,33	0,75	0,9354	0,7762	0,3598
2650564	RARRES3	-0,27	-0,37	-0,75	0,9680	0,8598	0,8431
2370601	CCDC94	-0,19	-0,14	-0,77	0,9854	0,9718	0,8876
3830220	UBASH3A	-0,89	-0,63	-0,77	0,7855	0,6665	0,7168
360047	GAS1	-0,34	-0,35	-0,81	0,9384	0,8042	0,4677
5090750	FOXC1	-0,53	-0,59	-0,84	0,9273	0,5741	0,1744
1300228	CUEDC1	-0,73	-0,57	-0,89	0,8265	0,6308	0,2923
6130079	RPL7A	-0,45	-0,56	-0,92	0,9384	0,7412	0,7168
1240192	CSNK1G2	-0,43	-0,64	-0,93	0,9330	0,4362	0,0282
3190703	OTOR	-0,36	-0,52	-0,98	0,9330	0,6382	0,0535
6280458	BCL6	-1,70	-1,97	-1,62	0	0	0

IL-15-regulated genes in KM-H2 HRS cells. To identify IL-15-dependent genes, KM-H2 HRS cells were stimulated with rhIL-15 or PBS control and harvested at 0, 4, 10 and 24 hours. Gene expression profiles were determined for IL-15-treated and PBS-treated control cells using Illumina HumanHT-12 v4 BeadChips. Listed are all genes that demonstrated a log_2 fold change (log_2FC) of at least 0.75 at 24 hours after IL-15 stimulation (33 genes up-regulated, upper part of the table; 10 genes down-regulated, lower part of the table); in addition, the corresponding log_2FC values for 4 and 10 hours are provided to illustrate the kinetics of their induction. Note that *CCND2* (encoding cyclin D2) is not included in this list since its log_2FC is 0.69 at 24 hours after rhIL-15 treatment; however, the log_2FC values for 4 and 10 hours are 0.66 and 0.98, respectively, and differential expression could be corroborated by quantitative PCR as shown in Figure 2d.

Supplementary Table 3

DAVID functional annotation clustering of IL-15-regulated genes in KM-H2 HRS cells. IL-15-dependent gene expression changes in KM-H2 cells were determined by gene expression profiling using Illumina HumanHT-12 v4 BeadChips as described in detail in Supplementary Materials and Methods. Genes that demonstrated a $\log_2$ fold change of at least 0.75 at 24 hours after IL-15 stimulation were used as input for functional annotation clustering (see Supplementary Table 2 for the complete gene list). With the DAVID functional annotation clustering tool similar annotation terms that show an association with the input gene list, are grouped into clusters each reflecting distinct biological processes (e.g., clusters comprising annotation terms related to regulation of apoptosis, regulation of cell proliferation or immune response mechanisms). Shown are annotation clusters 1 through 15 ranked by enrichment score. “Category” and “Term” show the annotation category (Gene Ontology, GO; KEGG Pathway, BIOCARTA, SP_PIR_Keywords, UP_SEQ_Feature) and the accession number and/or name of the respective term. IL-15-regulated genes from our gene list that are associated with a specific annotation term are listed under “Genes”, the number of genes associated with this term under “Count”.

Annotation Cluster 1 **Enrichment Score: 3.4775**

Category	Term	Count	P-value	Genes	Benjamini
GOTERM_BP_FAT	GO:0042981~regulation of apoptosis	12	3,20E-06	TNFSF10, IL6, IL2RA, CD44, LYST, BCL6, FOXC1, LIG4, IL12B, GAS1, IL1A, DAPK1	9,49E-04
GOTERM_BP_FAT	GO:0043067~regulation of programmed cell death	12	3,52E-06	TNFSF10, IL6, IL2RA, CD44, LYST, BCL6, FOXC1, LIG4, IL12B, GAS1, IL1A, DAPK1	7,84E-04
GOTERM_BP_FAT	GO:0010941~regulation of cell death	12	3,65E-06	TNFSF10, IL6, IL2RA, CD44, LYST, BCL6, FOXC1, LIG4, IL12B, GAS1, IL1A, DAPK1	6,50E-04
GOTERM_BP_FAT	GO:0012501~programmed cell death	8	7,52E-04	TNFSF10, IL6, IL2RA, TNFRSF12A, LIG4, GAS1, IL1A, DAPK1	0,0330
GOTERM_BP_FAT	GO:0008219~cell death	8	0,0020	TNFSF10, IL6, IL2RA, TNFRSF12A, LIG4, GAS1, IL1A, DAPK1	0,0582
GOTERM_BP_FAT	GO:0016265~death	8	0,0020	TNFSF10, IL6, IL2RA, TNFRSF12A, LIG4, GAS1, IL1A, DAPK1	0,0534
GOTERM_BP_FAT	GO:0006915~apoptosis	7	0,0038	TNFSF10, IL6, IL2RA, TNFRSF12A, LIG4, IL1A, DAPK1	0,0791
GOTERM_BP_FAT	GO:0051094~positive regulation of developmental process	5	0,0053	IL6, IL2RA, TNFRSF12A, LIG4, IL1A	0,1005
GOTERM_BP_FAT	GO:0045597~positive regulation of cell differentiation	4	0,0204	IL6, IL2RA, TNFRSF12A, LIG4	0,2596

Annotation Cluster 2 **Enrichment Score: 3.2884**

Category	Term	Count	P-value	Genes	Benjamini
GOTERM_BP_FAT	GO:0042981~regulation of apoptosis	12	3,20E-06	TNFSF10, IL6, IL2RA, CD44, LYST, BCL6, FOXC1, LIG4, IL12B, GAS1, IL1A, DAPK1	9,49E-04
GOTERM_BP_FAT	GO:0043067~regulation of programmed cell death	12	3,52E-06	TNFSF10, IL6, IL2RA, CD44, LYST, BCL6, FOXC1, LIG4, IL12B, GAS1, IL1A, DAPK1	7,84E-04
GOTERM_BP_FAT	GO:0010941~regulation of cell death	12	3,65E-06	TNFSF10, IL6, IL2RA, CD44, LYST, BCL6, FOXC1, LIG4, IL12B, GAS1, IL1A, DAPK1	6,50E-04
GOTERM_BP_FAT	GO:0043065~positive regulation of apoptosis	7	7,19E-04	TNFSF10, IL2RA, CD44, LYST, BCL6, IL12B, DAPK1	0,0370
GOTERM_BP_FAT	GO:0043068~positive regulation of programmed cell death	7	7,46E-04	TNFSF10, IL2RA, CD44, LYST, BCL6, IL12B, DAPK1	0,0344
GOTERM_BP_FAT	GO:0010942~positive regulation of cell death	7	7,64E-04	TNFSF10, IL2RA, CD44, LYST, BCL6, IL12B, DAPK1	0,0305

GOTERM_BP_FAT	GO:0006915~apoptosis	7	0,0038	TNFSF10, IL6, IL2RA, TNFRSF12A, LIG4, IL1A, DAPK1	0,0791
GOTERM_BP_FAT	GO:0006917~induction of apoptosis	3	0,1989	TNFSF10, LYST, DAPK1	0,8559
GOTERM_BP_FAT	GO:0012502~induction of programmed cell death	3	0,1999	TNFSF10, LYST, DAPK1	0,8547

Annotation Cluster 3 **Enrichment Score: 2.7201**

Category	Term	Count	P-value	Genes	Benjamini
GOTERM_BP_FAT	GO:0006955~immune response	13	3,45E-08	GPR183, CCL3, IL6, IL2RA, ENPP2, IL9, LIG4, TNFSF10, LYST, CCL3L3, IL12B, GBP4, IL1A	3,07E-05
KEGG_PATHWAY	hsa04060:Cytokine-cytokine receptor interaction	9	1,22E-06	TNFSF10, CCL3, IL6, IL2RA, TNFRSF12A, CCL3L3, IL9, IL12B, IL1A	3,78E-05
SP_PIR_KEYWORDS	cytokine	7	3,06E-06	TNFSF10, CCL3, IL6, CCL3L3, IL9, IL12B, IL1A	4,07E-04
GOTERM_MF_FAT	GO:0005125~cytokine activity	7	5,38E-06	TNFSF10, CCL3, IL6, CCL3L3, IL9, IL12B, IL1A	6,45E-04
GOTERM_BP_FAT	GO:0001817~regulation of cytokine production	6	9,50E-05	IL6, IL9, BCL6, UBASH3A, IL12B, IL1A	0,0105
BIOCARTA	h_erythPathway:Erythrocyte Differentiation Pathway	4	9,58E-05	CCL3, IL6, IL9, IL1A	0,0029
GOTERM_BP_FAT	GO:0006954~inflammatory response	7	1,52E-04	CCL3, IL6, IL2RA, CD44, CCL3L3, IL9, IL1A	0,0134
SP_PIR_KEYWORDS	lymphokine	3	4,50E-04	IL6, IL9, IL1A	0,0295
GOTERM_BP_FAT	GO:0006952~defense response	8	7,45E-04	CCL3, IL6, IL2RA, CD44, LYST, CCL3L3, IL9, IL1A	0,0362
GOTERM_BP_FAT	GO:0042035~regulation of cytokine biosynthetic process	4	9,08E-04	IL6, IL9, IL12B, IL1A	0,0346
GOTERM_BP_FAT	GO:0009611~response to wounding	7	0,0020	CCL3, IL6, IL2RA, CD44, CCL3L3, IL9, IL1A	0,0560
KEGG_PATHWAY	hsa04640:Hematopoietic cell lineage	4	0,0033	IL6, IL2RA, CD44, IL1A	0,0492
GOTERM_CC_FAT	GO:0005576~extracellular region	12	0,0053	LRSAM1, TNFSF10, CCL3, IL6, NRG4, CD44, ENPP2, CCL3L3, IL9, IL12B, OTOR, IL1A	0,3211
GOTERM_CC_FAT	GO:0005615~extracellular space	7	0,0060	TNFSF10, CCL3, IL6, CCL3L3, IL9, IL12B, IL1A	0,1973
GOTERM_MF_FAT	GO:0008083~growth factor activity	4	0,0063	IL6, NRG4, IL9, IL12B	0,3173
GOTERM_BP_FAT	GO:0042108~positive regulation of cytokine biosynthetic process	3	0,0068	IL9, IL12B, IL1A	0,1170
GOTERM_CC_FAT	GO:0044421~extracellular region part	8	0,0078	TNFSF10, CCL3, IL6, CD44, CCL3L3, IL9, IL12B, IL1A	0,1730
BIOCARTA	h_cytokinePathway:Cytokine Network	3	0,0097	IL6, IL9, IL1A	0,1355
KEGG_PATHWAY	hsa04630:Jak-STAT signaling pathway	4	0,0163	IL6, IL2RA, IL9, IL12B	0,1195
GOTERM_BP_FAT	GO:0010604~positive regulation of macromolecule metabolic process	7	0,0210	EGR1, IL6, IL9, FOXC1, PRDM1, IL12B, IL1A	0,2588
GOTERM_BP_FAT	GO:0001819~positive regulation of cytokine production	3	0,0226	IL6, IL12B, IL1A	0,2729
GOTERM_BP_FAT	GO:0010557~positive regulation of macromolecule biosynthetic process	6	0,0251	EGR1, IL6, IL9, FOXC1, IL12B, IL1A	0,2871
SP_PIR_KEYWORDS	Secreted	9	0,0297	CCL3, IL6, NRG4, ENPP2, CCL3L3, IL9, IL12B, OTOR, IL1A	0,4878
GOTERM_BP_FAT	GO:0031328~positive regulation of cellular biosynthetic process	6	0,0301	EGR1, IL6, IL9, FOXC1, IL12B, IL1A	0,3224
GOTERM_BP_FAT	GO:0009891~positive regulation of biosynthetic process	6	0,0316	EGR1, IL6, IL9, FOXC1, IL12B, IL1A	0,3319
GOTERM_BP_FAT	GO:0042592~homeostatic process	6	0,0411	CCL3, IL6, IL2RA, BCL6, SELT, IL1A	0,4009
KEGG_PATHWAY	hsa04620:Toll-like receptor signaling pathway	3	0,0494	CCL3, IL6, IL12B	0,2694
GOTERM_BP_FAT	GO:0051240~positive regulation of multicellular organismal process	3	0,1304	IL6, IL12B, IL1A	0,7453
GOTERM_BP_FAT	GO:0007267~cell-cell signaling	3	0,4621	TNFSF10, CCL3, IL6	0,9907

Annotation Cluster 4 **Enrichment Score: 2.6077**

Category	Term	Count	P-value	Genes	Benjamini
GOTERM_BP_FAT	GO:0008285~negative regulation of cell proliferation	9	2,95E-06	RARRES3, CTH, IL6, IL2RA, CCL3L3, BCL6, IL12B, GAS1, IL1A	0,0013
GOTERM_BP_FAT	GO:0042127~regulation of cell proliferation	11	1,97E-05	RARRES3, CTH, IL6, IL2RA, CCL3L3, IL9, BCL6, LIG4, IL12B, GAS1, IL1A	0,0029
GOTERM_BP_FAT	GO:0001817~regulation of cytokine production	6	9,50E-05	IL6, IL9, BCL6, UBASH3A, IL12B, IL1A	0,0105
GOTERM_BP_FAT	GO:0050671~positive regulation of lymphocyte proliferation	4	3,80E-04	IL6, IL2RA, BCL6, IL12B	0,0278
GOTERM_BP_FAT	GO:0070665~positive regulation of leukocyte proliferation	4	4,01E-04	IL6, IL2RA, BCL6, IL12B	0,0271

GOTERM_BP_FAT	GO:0032946~positive regulation of mononuclear cell proliferation	4	4,01E-04	IL6, IL2RA, BCL6, IL12B	0,0271
GOTERM_BP_FAT	GO:0008284~positive regulation of cell proliferation	7	5,96E-04	IL6, IL2RA, IL9, BCL6, LIG4, IL12B, GAS1	0,0372
GOTERM_BP_FAT	GO:0001775~cell activation	6	7,62E-04	EGR1, GPR183, IL6, BCL6, LIG4, IL12B	0,0318
GOTERM_BP_FAT	GO:0050670~regulation of lymphocyte proliferation	4	0,0013	IL6, IL2RA, BCL6, IL12B	0,0442
GOTERM_BP_FAT	GO:0070663~regulation of leukocyte proliferation	4	0,0013	IL6, IL2RA, BCL6, IL12B	0,0440
GOTERM_BP_FAT	GO:0032944~regulation of mononuclear cell proliferation	4	0,0013	IL6, IL2RA, BCL6, IL12B	0,0440
GOTERM_BP_FAT	GO:0051251~positive regulation of lymphocyte activation	4	0,0020	IL6, IL2RA, BCL6, IL12B	0,0573
GOTERM_BP_FAT	GO:0002696~positive regulation of leukocyte activation	4	0,0026	IL6, IL2RA, BCL6, IL12B	0,0614
GOTERM_BP_FAT	GO:0050867~positive regulation of cell activation	4	0,0029	IL6, IL2RA, BCL6, IL12B	0,0678
GOTERM_BP_FAT	GO:0050863~regulation of T cell activation	4	0,0034	IL6, IL2RA, BCL6, IL12B	0,0726
GOTERM_BP_FAT	GO:0042102~positive regulation of T cell proliferation	3	0,0045	IL6, IL2RA, IL12B	0,0901
GOTERM_BP_FAT	GO:0051249~regulation of lymphocyte activation	4	0,0065	IL6, IL2RA, BCL6, IL12B	0,1142
GOTERM_BP_FAT	GO:0002694~regulation of leukocyte activation	4	0,0089	IL6, IL2RA, BCL6, IL12B	0,1449
GOTERM_BP_FAT	GO:0050865~regulation of cell activation	4	0,0103	IL6, IL2RA, BCL6, IL12B	0,1626
GOTERM_BP_FAT	GO:0042129~regulation of T cell proliferation	3	0,0112	IL6, IL2RA, IL12B	0,1722
GOTERM_BP_FAT	GO:0050727~regulation of inflammatory response	3	0,0161	IL6, IL2RA, BCL6	0,2237
KEGG_PATHWAY	hsa04630:Jak-STAT signaling pathway	4	0,0163	IL6, IL2RA, IL9, IL12B	0,1195
GOTERM_BP_FAT	GO:0050870~positive regulation of T cell activation	3	0,0165	IL6, IL2RA, IL12B	0,2252
GOTERM_BP_FAT	GO:0002684~positive regulation of immune system process	4	0,0228	IL6, IL2RA, BCL6, IL12B	0,2711
GOTERM_BP_FAT	GO:0048872~homeostasis of number of cells	3	0,0275	IL6, IL2RA, BCL6	0,3064
GOTERM_BP_FAT	GO:0002697~regulation of immune effector process	3	0,0280	IL6, BCL6, IL12B	0,3074
GOTERM_BP_FAT	GO:0042592~homeostatic process	6	0,0411	CCL3, IL6, IL2RA, BCL6, SELT, IL1A	0,4009
GOTERM_BP_FAT	GO:0032101~regulation of response to external stimulus	3	0,0608	IL6, IL2RA, BCL6	0,4942

Annotation Cluster 5 **Enrichment Score: 2.5852**

Category	Term	Count	P-value	Genes	Benjamini
GOTERM_BP_FAT	GO:0006928~cell motion	9	2,20E-05	CCL3, IL6, CD44, ENPP2, TNFRSF12A, LYST, FOXC1, IL12B, GAS1	0,0028
GOTERM_BP_FAT	GO:0016477~cell migration	6	6,70E-04	IL6, CD44, TNFRSF12A, LYST, FOXC1, IL12B	0,0390
GOTERM_BP_FAT	GO:0048870~cell motility	6	0,0011	IL6, CD44, TNFRSF12A, LYST, FOXC1, IL12B	0,0394
GOTERM_BP_FAT	GO:0051674~localization of cell	6	0,0011	IL6, CD44, TNFRSF12A, LYST, FOXC1, IL12B	0,0394
GOTERM_BP_FAT	GO:0001568~blood vessel development	3	0,1313	CD44, TNFRSF12A, FOXC1	0,7440
GOTERM_BP_FAT	GO:0001944~vasculature development	3	0,1365	CD44, TNFRSF12A, FOXC1	0,7549

Annotation Cluster 6 **Enrichment Score: 2.5451**

Category	Term	Count	P-value	Genes	Benjamini
GOTERM_BP_FAT	GO:0042330~taxis	5	7,08E-04	CCL3, IL6, ENPP2, LYST, CCL3L3	0,0387
GOTERM_BP_FAT	GO:0006935~chemotaxis	5	7,08E-04	CCL3, IL6, ENPP2, LYST, CCL3L3	0,0387
GOTERM_BP_FAT	GO:0007626~locomotory behavior	5	0,0050	CCL3, IL6, ENPP2, LYST, CCL3L3	0,0965
GOTERM_BP_FAT	GO:0007610~behavior	6	0,0065	EGR1, CCL3, IL6, ENPP2, LYST, CCL3L3	0,1155
SP_PIR_KEYWORDS	chemotaxis	3	0,0116	CCL3, ENPP2, CCL3L3	0,3223

Annotation Cluster 7 **Enrichment Score: 2.5368**

Category	Term	Count	P-value	Genes	Benjamini
GOTERM_BP_FAT	GO:0030098~lymphocyte differentiation	5	1,38E-04	EGR1, GPR183, BCL6, LIG4, IL12B	0,0136
GOTERM_BP_FAT	GO:0002521~leukocyte differentiation	5	3,49E-04	EGR1, GPR183, BCL6, LIG4, IL12B	0,0279
GOTERM_BP_FAT	GO:0001775~cell activation	6	7,62E-04	EGR1, GPR183, IL6, BCL6, LIG4, IL12B	0,0318
GOTERM_BP_FAT	GO:0046649~lymphocyte activation	5	0,0016	EGR1, GPR183, BCL6, LIG4, IL12B	0,0508
GOTERM_BP_FAT	GO:0030097~hemopoiesis	5	0,0031	EGR1, GPR183, BCL6, LIG4, IL12B	0,0701
GOTERM_BP_FAT	GO:0045321~leukocyte activation	5	0,0033	EGR1, GPR183, BCL6, LIG4, IL12B	0,0735
GOTERM_BP_FAT	GO:0048534~hemopoietic or lymphoid organ development	5	0,0044	EGR1, GPR183, BCL6, LIG4, IL12B	0,0888
GOTERM_BP_FAT	GO:0002520~immune system development	5	0,0054	EGR1, GPR183, BCL6, LIG4, IL12B	0,0996
GOTERM_BP_FAT	GO:0030217~T cell differentiation	3	0,0122	EGR1, LIG4, IL12B	0,1808
GOTERM_BP_FAT	GO:0042113~B cell activation	3	0,0165	GPR183, BCL6, LIG4	0,2252
GOTERM_BP_FAT	GO:0042110~T cell activation	3	0,0420	EGR1, LIG4, IL12B	0,4036

Annotation Cluster 8 **Enrichment Score: 1.8904**

Category	Term	Count	P-value	Genes	Benjamini
GOTERM_BP_FAT	GO:0045930~negative regulation of mitotic cell cycle	3	0,0015	BCL6, FOXC1, GAS1	0,0470
GOTERM_BP_FAT	GO:0007346~regulation of mitotic cell cycle	4	0,0070	BCL6, FOXC1, GAS1, IL1A	0,1178
GOTERM_BP_FAT	GO:0045786~negative regulation of cell cycle	3	0,0186	BCL6, FOXC1, GAS1	0,2466
GOTERM_BP_FAT	GO:0010564~regulation of cell cycle process	3	0,0350	BCL6, GAS1, IL1A	0,3568
GOTERM_BP_FAT	GO:0051726~regulation of cell cycle	4	0,0531	BCL6, FOXC1, GAS1, IL1A	0,4640

Annotation Cluster 9 **Enrichment Score: 1.4849**

Category	Term	Count	P-value	Genes	Benjamini
GOTERM_BP_FAT	GO:0043066~negative regulation of apoptosis	6	0,0020	IL6, BCL6, FOXC1, LIG4, IL1A, DAPK1	0,0543
GOTERM_BP_FAT	GO:0043069~negative regulation of programmed cell death	6	0,0021	IL6, BCL6, FOXC1, LIG4, IL1A, DAPK1	0,0544
GOTERM_BP_FAT	GO:0060548~negative regulation of cell death	6	0,0022	IL6, BCL6, FOXC1, LIG4, IL1A, DAPK1	0,0535
GOTERM_BP_FAT	GO:0007346~regulation of mitotic cell cycle	4	0,0070	BCL6, FOXC1, GAS1, IL1A	0,1178
GOTERM_BP_FAT	GO:0051726~regulation of cell cycle	4	0,0531	BCL6, FOXC1, GAS1, IL1A	0,4640
GOTERM_BP_FAT	GO:0006916~anti-apoptosis	3	0,0984	FOXC1, IL1A, DAPK1	0,6625
GOTERM_CC_FAT	GO:0005694~chromosome	3	0,3152	BCL6, FOXC1, LIG4	0,9369
GOTERM_CC_FAT	GO:0043228~non-membrane-bounded organelle	7	0,6374	COPS2, LYST, BCL6, FOXC1, RPL7A, LIG4, DAPK1	0,9950
GOTERM_CC_FAT	GO:0043232~intracellular non-membrane-bounded organelle	7	0,6374	COPS2, LYST, BCL6, FOXC1, RPL7A, LIG4, DAPK1	0,9950

Annotation Cluster 10 **Enrichment Score: 1.4077**

Category	Term	Count	P-value	Genes	Benjamini
GOTERM_BP_FAT	GO:0040008~regulation of growth	5	0,0112	CTH, CD44, TNFRSF12A, BCL6, FOXC1	0,1701
GOTERM_BP_FAT	GO:0001558~regulation of cell growth	4	0,0136	CTH, CD44, TNFRSF12A, BCL6	0,1957
GOTERM_BP_FAT	GO:0008361~regulation of cell size	3	0,0992	CTH, TNFRSF12A, BCL6	0,6613
GOTERM_BP_FAT	GO:0032535~regulation of cellular component size	3	0,1544	CTH, TNFRSF12A, BCL6	0,7789

Annotation Cluster 11 **Enrichment Score: 0.9648**

Category	Term	Count	P-value	Genes	Benjamini
GOTERM_BP_FAT	GO:0043009~chordate embryonic development	4	0,0527	FOXC1, PRDM1, LIG4, GAS1	0,4658
GOTERM_BP_FAT	GO:0009792~embryonic development ending in birth or egg hatching	4	0,0539	FOXC1, PRDM1, LIG4, GAS1	0,4648
GOTERM_BP_FAT	GO:0001701~in utero embryonic development	3	0,0759	FOXC1, PRDM1, LIG4	0,5714
GOTERM_MF_FAT	GO:0003677~DNA binding	6	0,6409	EGR1, BCL6, FOXC1, PRDM1, LIG4, ETV5	0,9999

Annotation Cluster 12 **Enrichment Score: 0.8509**

Category	Term	Count	P-value	Genes	Benjamini
GOTERM_CC_FAT	GO:0031226~intrinsic to plasma membrane	7	0,0762	GPR183, TNFSF10, IL6, CD44, ENPP2, CD69, GAS1	0,6187
GOTERM_BP_FAT	GO:0009967~positive regulation of signal transduction	3	0,1764	TNFSF10, IL6, GAS1	0,8226
GOTERM_BP_FAT	GO:0010647~positive regulation of cell communication	3	0,2084	TNFSF10, IL6, GAS1	0,8650

Annotation Cluster 13 **Enrichment Score: 0.8374**

Category	Term	Count	P-value	Genes	Benjamini
UP_SEQ_FEATURE	disulfide bond	14	0,0055	GPR183, CCL3, NRG4, IL6, IL2RA, ENPP2, TNFRSF12A, LRIG1, OTOR, CD44, CD69, CCL3L3, ADAM19, IL12B	0,6321
SP_PIR_KEYWORDS	disulfide bond	14	0,0075	GPR183, CCL3, NRG4, IL6, IL2RA, ENPP2, TNFRSF12A, LRIG1, OTOR, CD44, CD69, CCL3L3, ADAM19, IL12B	0,2836
SP_PIR_KEYWORDS	signal	14	0,0198	CCL3, IL6, IL2RA, ENPP2, TNFRSF12A, IL9, LRIG1, GAS1, OTOR, SELT, CD44, CCL3L3, ADAM19, IL12B	0,4125
UP_SEQ_FEATURE	signal peptide	14	0,0202	CCL3, IL6, IL2RA, ENPP2, TNFRSF12A, IL9, LRIG1, GAS1, OTOR, SELT, CD44, CCL3L3, ADAM19, IL12B	0,8408
GOTERM_CC_FAT	GO:0009986~cell surface	4	0,0549	IL2RA, CD44, TNFRSF12A, CD69	0,6430
GOTERM_CC_FAT	GO:0009897~external side of plasma membrane	3	0,0674	IL2RA, CD44, CD69	0,6392
GOTERM_CC_FAT	GO:0031226~intrinsic to plasma membrane	7	0,0762	GPR183, TNFSF10, IL6, CD44, ENPP2, CD69, GAS1	0,6187
GOTERM_CC_FAT	GO:0044459~plasma membrane part	9	0,1621	GPR183, TNFSF10, IL6, IL2RA, CD44, ENPP2, CD69, LIG4, GAS1	0,8419
SP_PIR_KEYWORDS	transmembrane protein	4	0,1668	GPR183, IL2RA, CD44, CD69	0,9117
GOTERM_CC_FAT	GO:0005887~integral to plasma membrane	6	0,1692	GPR183, TNFSF10, IL6, CD44, ENPP2, CD69	0,8158
UP_SEQ_FEATURE	glycosylation site:N-linked (GlcNAc...)	13	0,1880	NRG4, IL6, IL2RA, C15ORF27, ENPP2, IL9, LRIG1, GAS1, CD44, CD69, ADAM19, IL12B, IL1A	0,9994
GOTERM_MF_FAT	GO:0030246~carbohydrate binding	3	0,2031	CD44, ENPP2, CD69	0,9893
SP_PIR_KEYWORDS	glycoprotein	13	0,2327	NRG4, IL6, IL2RA, C15ORF27, ENPP2, IL9, LRIG1, GAS1, CD44, CD69, ADAM19, IL12B, IL1A	0,9469
UP_SEQ_FEATURE	topological domain:Extracellular	9	0,2429	GPR183, TNFSF10, NRG4, IL2RA, CD44, TNFRSF12A, CD69, LRIG1, ADAM19	0,9998
SP_PIR_KEYWORDS	receptor	6	0,2487	GPR183, RARRES3, IL2RA, CD44, TNFRSF12A, CD69	0,9464
GOTERM_CC_FAT	GO:0005886~plasma membrane	11	0,4431	GPR183, TNFSF10, IL6, NRG4, IL2RA, CD44, ENPP2, TNFRSF12A, CD69, LIG4, GAS1	0,9794
UP_SEQ_FEATURE	topological domain:Cytoplasmic	9	0,4767	GPR183, TNFSF10, NRG4, IL2RA, CD44, TNFRSF12A, CD69, LRIG1, ADAM19	0,9999
GOTERM_CC_FAT	GO:0031224~intrinsic to membrane	14	0,5957	GPR183, NRG4, IL6, IL2RA, ENPP2, TNFRSF12A, C15ORF27, LRIG1, GAS1, TNFSF10, CD44, TPTE2, CD69, ADAM19	0,9938
UP_SEQ_FEATURE	transmembrane region	11	0,6700	GPR183, TNFSF10, NRG4, IL2RA, TPTE2, CD44, C15ORF27, TNFRSF12A, CD69, LRIG1, ADAM19	1,0000
GOTERM_CC_FAT	GO:0016021~integral to membrane	13	0,6702	GPR183, NRG4, IL6, IL2RA, TNFRSF12A, C15ORF27, ENPP2, LRIG1, TNFSF10, CD44, TPTE2, CD69, ADAM19	0,9955
SP_PIR_KEYWORDS	transmembrane	11	0,6764	GPR183, TNFSF10, NRG4, IL2RA, TPTE2, CD44, C15ORF27, TNFRSF12A, CD69, LRIG1, ADAM19	0,9985
SP_PIR_KEYWORDS	membrane	12	0,8599	GPR183, TNFSF10, NRG4, IL2RA, TPTE2, CD44, C15ORF27, TNFRSF12A, CD69, LRIG1, ADAM19, GAS1	0,9999

Annotation Cluster 14 **Enrichment Score: 0.7494**

Category	Term	Count	P-value	Genes	Benjamini
GOTERM_CC_FAT	GO:0031226~intrinsic to plasma membrane	7	0,0762	GPR183, TNFSF10, IL6, CD44, ENPP2, CD69, GAS1	0,6187
GOTERM_BP_FAT	GO:0031175~neuron projection development	3	0,1409	IL6, CD44, GAS1	0,7594

GOTERM_BP_FAT	GO:0048666~neuron development	3	0,2170	IL6, CD44, GAS1	0,8745
GOTERM_BP_FAT	GO:0030030~cell projection organization	3	0,2458	IL6, CD44, GAS1	0,9025
GOTERM_BP_FAT	GO:0030182~neuron differentiation	3	0,3126	IL6, CD44, GAS1	0,9507

Annotation Cluster 15 Enrichment Score: 0.6658

Category	Term	Count	P-value	Genes	Benjamini
KEGG_PATHWAY	hsa05020:Prion diseases	3	0,0067	EGR1, IL6, IL1A	0,0669
GOTERM_BP_FAT	GO:0010604~positive regulation of macromolecule metabolic process	7	0,0210	EGR1, IL6, IL9, FOXC1, PRDM1, IL12B, IL1A	0,2588
GOTERM_BP_FAT	GO:0010557~positive regulation of macromolecule biosynthetic process	6	0,0251	EGR1, IL6, IL9, FOXC1, IL12B, IL1A	0,2871
GOTERM_BP_FAT	GO:0031328~positive regulation of cellular biosynthetic process	6	0,0301	EGR1, IL6, IL9, FOXC1, IL12B, IL1A	0,3224
GOTERM_BP_FAT	GO:0009891~positive regulation of biosynthetic process	6	0,0316	EGR1, IL6, IL9, FOXC1, IL12B, IL1A	0,3319

Supplementary Table 4

Gene	Forward primer (5'-3')	Reverse primer (5'-3')	Product size (bp)
IL-15	TCAATCTATGCATATTGATGCTACTTTA	TCAAGTGAAATAACTTGTAACTCCAAGA	110
IL-15Rα	ABI Taqman # Hs00542604_m1	ABI Taqman # Hs00542604_m1	82
IL-2Rβ/IL-15Rβ	CGGACAGACGGCGGTGGAAC	ACCCTCCATCGCACCCCCTC	159
IL-2Rγ	ACCCAATCCACTGGGGGAGCAA	CGGGGCATCGTCCGTTCCAG	141
GAPDH	CTCTGCTCCTCCTGTTCGAC	TTAAAAGCAGCCCTGGTGAC	143
ETV5	CCTCAGGAGGATCCCTTTTCCCCC	AGGCCGCCCTCTGCATTCCT	157
CCND2	AGCTCGCTCACTTGTGATGCCC	CGGCCCAACTGGCATCCTCAC	226
BCL6	CTGCCAGCCACCCATGGAGC	CGGGGAGAGCCCGTCATGGA	137
IL-1α	AGCTGCCAGCCAGAGAGGGAG	CAGCCTTCATGGAGTGGGCCATAG	197
IL-6	CGAGCCCACCGGGAACGAAAG	GCAACTGGACCGAAGGCGCT	90
IL-9	CTGCTCCTGTGCTCCGTGGC	GGTCTGGTGCAGTTGTCAGAGGG	169
IL-12β	GCCACGGTCATCTGCCGCAA	TGGATCAGAACCTAACTGCAGGGCA	112
IL-2Rα	GGCGCGATGCCAAAAAGAGGC	TGTGGGATCTCTGGCGGGTCA	190
CCL3	ACGGGCAGCAGACAGTGGTCA	AGCAGCAAGTGATGCAGAGAACTGG	157

List of primers used for quantitative PCR expression analysis of IL-15-regulated genes. For technical details of the real-time PCR procedure refer to Materials and Methods.

Supplementary Table 5

gene	HRS cells vs. naive/GC B cells (Brune et al., 2008; Tiacci et al., 2012)	HRS cells vs. FL/BL/DLBCL cells (Brune et al., 2008; Tiacci et al., 2012)	HRS cells vs. GC B cells (Steidl et al., 2012)
IL15	1.7	1.5	4.1
IL15Rα	6.4	2.5	2.5
IL15Rβ/IL2Rβ	7.3	3.3	1.6
common γ chain (IL2Rγ)	1.1	1	0.7

Expression of IL-15 and IL-15 receptor subunits in primary HRS cells compared to different non-malignant and malignant B cell populations. Listed is the fold change in gene expression in primary HRS cells compared to primary non-malignant or malignant B cell populations (GC, germinal center; FL, follicular lymphoma; BL, Burkitt lymphoma; DLBCL, diffuse large B cell lymphoma). Gene expression changes were calculated based on the original data files deposited in gene expression omnibus (GEO; accession no. GSE12453, Brune et al., J Exp Med, 2008 / Tiacci et al., Blood, 2012 and GSE39133, Steidl et al., Blood, 2012). Raw data were RMA background corrected and quantile normalized. To compute the gene-wise fold change between the specified groups, the moderated t-test implemented in the R package LIMMA was applied (Smyth, G. K., 2004. Linear models and empirical Bayes methods for assessing differential expression in microarray experiments. *Statistical Applications in Genetics and Molecular Biology* **3**, Issue 1, Article 3). All analyses were done in R v2.15.0.

Supplementary Materials and Methods

Cell lines and culture conditions. HRS (L428, L1236, KM-H2, L591, HDLM-2, L540, L540Cy) and B-ALL/B-NHL cell lines (Reh, Blin, Namalwa, Daudi, SU-DHL-4) were grown in RPMI 1640 medium (Life Technologies, Darmstadt, Germany) with 10 % fetal bovine serum (FBS; Biochrom, Berlin, Germany) supplemented with GlutaMAX (1:100), 100 U/ml penicillin, 100 μg/ml streptomycin and 1mM sodium pyruvate (all from Life Technologies). The IL-2 dependent cutaneous T cell lymphoma cell line Se-Ax was cultured under the same conditions as described above with 200 U/ml recombinant human IL-2 (Peprotech, Hamburg, Germany). All cell lines were grown at 37°C and 5% CO_2.

RNA preparation and quantitative PCR. Total RNA was isolated with the RNeasy kit according to the manufacturer's protocol (Qiagen, Hilden, Germany). For quantitative PCR, first strand hexamer-primed cDNA synthesis was carried out with SuperScript II reverse transcriptase (Life Technologies). Real-time PCR analysis was performed using the Power SYBR Green Mastermix and the ABI StepOnePlus real-time PCR system (Applied Biosystems, Darmstadt, Germany). Relative quantities were calculated using the $2^{-\Delta\Delta Ct}$ method. All PCR products were verified by sequencing. Primers used for quantitative PCR analyses are listed in Supplementary Table 4.

Flow cytometry. Surface protein expression of IL-15Rα, IL-2Rβ/IL-15Rβ and IL-2Rγ on HRS and B-ALL/B-NHL cell lines was determined by flow cytometry. Cells were stained with anti-IL-15Rα (AF247), anti-IL-2Rβ/IL-15Rβ (MAB224) and anti-IL-2Rγ (AF284, all R&D Systems, Wiesbaden, Germany), respectively. Primary antibodies were detected with PE-conjugated anti-goat (#705-116-147) or anti-mouse IgG antibodies (#115-116-071, both Dianova, Hamburg, Germany). Samples were acquired on a FACSCanto II and analyzed with the FACSDiva software (Becton Dickinson, Heidelberg, Germany).

Immunohistochemistry. For detection of IL-15 in fresh frozen samples of reactive tonsils and primary HL tissue**,** tissue slides were fixed in acetone for 5 minutes. All subsequent washing steps were done in Tris-buffer without Tween (pH 7.5). Antigen detection was carried out with an anti-IL-15 mouse monoclonal antibody (1:50; MAB2471, R&D Systems, Wiesbaden, Germany) or a corresponding isotype control (mouse IgG1, MAB002, R&D Systems). Bound antibody was detected with polyclonal rabbit anti-mouse immunoglobulin (Z0259, Dako, Glostrup, Denmark) and visualized using the alkaline phosphatase anti-alkaline phosphatase (APAAP) method (Dako).

Immunoblotting. Whole cell extracts were prepared by lysis in 20 mM HEPES pH 7.9, 350 mM NaCl, 1 mM $MgCl_2$, 0.5 mM EDTA pH 8.0, 0.1 mM EGTA pH 8.0, 1% NP-40, 1 mM NaF, 0.5 mM DTT, 1 mM Na_3VO_4 and complete mini protease inhibitor cocktail (Roche, Mannheim, Germany) for 10 min at 4°C followed by centrifugation for 10 min at 14 000 rpm, 4°C. Protein samples (30 μg per lane) were subjected to SDS polyacrylamide gel electrophoresis and transferred onto nitrocellulose filters (Schleicher and Schuell, Dassel, Germany). Filters were blocked with 1% nonfat dry milk, 0.1% Triton X-100, 150 mM NaCl, 50 mM Tris pH 7.5 and incubated with the following primary antibodies: pERK1/2 (#9101), pSTAT5 (#9359), ERK1/2 (#9102) and STAT5 (#9358, all Cell Signaling Technology, Frankfurt am Main, Germany). Detection was carried out by incubation with a horseradish peroxidase-conjugated secondary antibody (anti-rabbit; W4011, Promega, Mannheim, Germany) followed by visualization with the enhanced chemiluminescence system (Amersham/GE Healthcare Life Sciences, Freiburg, Germany).

Proliferation assays. DNA synthesis in IL-15-stimulated HRS cells (L591, KM-H2) was determined by [^{3}H]-thymidine incorporation. Cells were seeded in 96-well plates with $1.5x10^4$ cells per well, treated with rhIL-15 (50 ng/ml) or PBS control for 6 hours and pulsed with 0.037 Mbq [^{3}H]-thymidine for additional 18 hours before harvesting. The IL-2/IL-15

responsive cutaneous T cell lymphoma cell line Se-Ax was used as positive control following cytokine deprivation over night and re-stimulation with IL-15.

Analysis of cell viability and apoptosis. KM-H2 cells ($2x10^5$ cells per well in a 12-well plate) were pre-stimulated with rhIL-15 or PBS for 18 hours and subsequently treated with dimethyl sulfoxide (DMSO) or H_2O control, etoposide (#341205), doxorubicin (#324380; both Calbiochem, Darmstadt, Germany) or geldanamycin (ant-gI-5; Invivogen, Toulouse, France). After treatment for 72 hours, the percentage of viable and apoptotic cells was determined by flow cytometry following staining with annexin V-fluorescein isothiocyanate (FITC; Bender MedSystems, Vienna, Austria) and propidium iodide (PI; Roth, Karlsruhe, Germany). The fraction of viable cells, defined as double-negative for annexin V-FITC and PI, was expressed as percentage of total cell numbers. In parallel, KM-H2 cells were stained with a PE-conjugated anti-active caspase 3 antibody according to the manufacturer's protocol (PE Active Caspase-3 Apoptosis Kit, #550914, BD Pharmingen). The percentage of active caspase 3-positive cells was determined by flow cytometry.

Cytokine stimulation experiments, gene expression profiling and functional annotation of differentially expressed genes. For gene expression analysis of HRS cells following IL-15 stimulation, we used Illumina HumanHT-12 v4 Expression BeadChips (Illumina, San Diego, CA, USA). KM-H2 cells were stimulated with rhIL-15 or PBS control and harvested at 0, 4, 10 and 24 hours. Gene expression profiling was performed in triplicate from three independent stimulation experiments. Total RNA was isolated with the RNeasy kit (Qiagen, Hilden, Germany) and processed for gene expression analysis using the Illumina TotalPrep RNA Amplification Kit (Ambion/Life Technologies, Darmstadt, Germany). Biotin-labeled cRNA was hybridized to Illumina HumanHT-12 v4 BeadChips according to the manufacturer's protocol. Raw expression data were background corrected with Illumina's proprietary background correction routine and normalization was performed using quantile normalization; subsequently, data were $\log_2$ transformed. Expression profiles of PBS-treated

samples were subtracted from the expression profiles of the time-matching rhIL-15-treated samples to control for gene expression changes induced by growth in cell culture alone. Following correction for gene expression changes in PBS-treated cultures, statistically significant differential expression induced by rhIL-15 at different time points after stimulation (4, 10 and 24 hours) was assessed by linear models as implemented in Limma (Smyth, 2005). Adjusted p-values (p-value adj) were corrected for multiple testing by the FDR-based approach as suggested by Benjamini and Hochberg (1995). To extract enriched biological motives from our list of IL-15-regulated genes, we used the DAVID functional annotation tool which enables the identification of major biological functions associated with a given set of genes (Database for Annotation, Visualization and Integrated Discovery; http://david.abcc.ncifcrf.gov; Huang et al., 2009). Genes with a $\log_2$ fold change of at least 0.75 at 24 hours after rhIL-15 treatment in KM-H2 cells (see Supplementary Table 2) were subjected to DAVID functional annotation clustering using the following annotation categories: gene ontology (GO) terms, KEGG pathways, BIOCARTA-derived gene sets, COG ontology, Swiss-Prot (SP) and Protein Information Resource (PIR) keywords and Up Seq features.

Hierarchical clustering and heat map visualization of cytokine and cytokine receptor gene expression in Hodgkin and non-Hodgkin B cell lines. Gene expression profiles were determined for HRS (L428, L1236, KM-H2, HDLM-2, L540, L540Cy), B-NHL (Namalwa, SUDHL-4) and B acute lymphoblastic leukemia (Reh) cells using Affymetrix U133 Plus 2.0 oligonucleotide arrays (Köchert et al., 2011; GEO accession number GSE20011). Raw expression data were corrected for background with Bioconductor v2.4 RMA, and normalization was performed using quantile normalization; subsequently, data were $\log_2$ transformed. For construction of the heat map, probe sets mapping to the same gene were summarized to their median expression value. Gene-wise z-transformation was applied and the resulting matrix was used as input for the heat map. Cluster analysis was done using Pearson distance and complete linkage.

Statistical analyses. All statistical analyses were done in Graph Pad Prism v5.0. For analysis of proliferation assays as well as for real-time PCR experiments, *P*-values were determined by a Welch's unpaired *t*-test by using counts per minute (proliferation assay) or ΔCt values (real-time PCR experiments: ΔCt = Ct target gene minus Ct GAPDH). Relative quantification of mRNA of the various target genes relative to GAPDH was done using the Pfaffl method (Pfaffl, 2001) implemented in the ABI StepOnePlus software taking into account the efficiencies of each primer pair used. For analysis of apoptosis assays, *P*-values were determined by a Welch's unpaired *t*-test by using the percentage of viable cells of time-matched rhIL-15- vs. PBS-treated samples. *P*-values <0.05 were considered to be statistically significant (n.s. denotes not significant; * $P<0.05$; ** $P<0.01$; *** $P<0.001$).

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