

Supplementary File S1

Molecular Characterization of the Response to Conventional Chemotherapeutics in Pro-B-ALL Cell Lines in Terms of Tumor Relapse

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Supplementary Tables

Supplementary Table S1. Gene Ontology terms related to stress release and metabolism as reported in DAVID. This list was used to filter out the DEG sets.

Gene Ontology IDs and terms
GO:0000302~response to reactive oxygen species
GO:0001101~response to acid chemical
GO:0001501~skeletal system development
GO:0001816~cytokine production
GO:0001817~regulation of cytokine production
GO:0001819~positive regulation of cytokine production
GO:0005975~carbohydrate metabolic process
GO:0006000~fructose metabolic process
GO:0006022~aminoglycan metabolic process
GO:0006029~proteoglycan metabolic process
GO:0006082~organic acid metabolic process
GO:0006090~pyruvate metabolic process
GO:0006140~regulation of nucleotide metabolic process
GO:0006164~purine nucleotide biosynthetic process
GO:0006171~cAMP biosynthetic process
GO:0006259~DNA metabolic process
GO:0006575~cellular modified amino acid metabolic process
GO:0006730~one-carbon metabolic process
GO:0006733~oxidoreduction coenzyme metabolic process
GO:0006757~ATP generation from ADP
GO:0006760~folic acid-containing compound metabolic process
GO:0006793~phosphorus metabolic process
GO:0006796~phosphate-containing compound metabolic process

GO:0006809~nitric oxide biosynthetic process
GO:0006950~response to stress
GO:0006974~cellular response to DNA damage stimulus
GO:0006979~response to oxidative stress
GO:0008652~cellular amino acid biosynthetic process
GO:0009124~nucleoside monophosphate biosynthetic process
GO:0009127~purine nucleoside monophosphate biosynthetic process
GO:0009132~nucleoside diphosphate metabolic process
GO:0009135~purine nucleoside diphosphate metabolic process
GO:0009142~nucleoside triphosphate biosynthetic process
GO:0009145~purine nucleoside triphosphate biosynthetic process
GO:0009152~purine ribonucleotide biosynthetic process
GO:0009156~ribonucleoside monophosphate biosynthetic process
GO:0009163~nucleoside biosynthetic process
GO:0009165~nucleotide biosynthetic process
GO:0009168~purine ribonucleoside monophosphate biosynthetic process
GO:0009179~purine ribonucleoside diphosphate metabolic process
GO:0009185~ribonucleoside diphosphate metabolic process
GO:0009190~cyclic nucleotide biosynthetic process
GO:0009260~ribonucleotide biosynthetic process
GO:0009605~response to external stimulus
GO:0009607~response to biotic stimulus
GO:0009628~response to abiotic stimulus
GO:0009719~response to endogenous stimulus
GO:0009743~response to carbohydrate
GO:0009891~positive regulation of biosynthetic process
GO:0009892~negative regulation of metabolic process
GO:0009893~positive regulation of metabolic process
GO:0009991~response to extracellular stimulus
GO:0010033~response to organic substance
GO:0010035~response to inorganic substance
GO:0010243~response to organonitrogen compound
GO:0010562~positive regulation of phosphorus metabolic process
GO:0010563~negative regulation of phosphorus metabolic process
GO:0010604~positive regulation of macromolecule metabolic process
GO:0010605~negative regulation of macromolecule metabolic process
GO:0014070~response to organic cyclic compound
GO:0016052~carbohydrate catabolic process
GO:0016053~organic acid biosynthetic process
GO:0019220~regulation of phosphate metabolic process
GO:0019222~regulation of metabolic process
GO:0019362~pyridine nucleotide metabolic process
GO:0019751~polyol metabolic process

GO:0019752~carboxylic acid metabolic process
GO:0030203~glycosaminoglycan metabolic process
GO:0030799~regulation of cyclic nucleotide metabolic process
GO:0030801~positive regulation of cyclic nucleotide metabolic process
GO:0030802~regulation of cyclic nucleotide biosynthetic process
GO:0030804~positive regulation of cyclic nucleotide biosynthetic process
GO:0030808~regulation of nucleotide biosynthetic process
GO:0030810~positive regulation of nucleotide biosynthetic process
GO:0030814~regulation of cAMP metabolic process
GO:0030816~positive regulation of cAMP metabolic process
GO:0030817~regulation of cAMP biosynthetic process
GO:0030819~positive regulation of cAMP biosynthetic process
GO:0031098~stress-activated protein kinase signaling cascade
GO:0031323~regulation of cellular metabolic process
GO:0031324~negative regulation of cellular metabolic process
GO:0031325~positive regulation of cellular metabolic process
GO:0031328~positive regulation of cellular biosynthetic process
GO:0032101~regulation of response to external stimulus
GO:0032102~negative regulation of response to external stimulus
GO:0032268~regulation of cellular protein metabolic process
GO:0032269~negative regulation of cellular protein metabolic process
GO:0032270~positive regulation of cellular protein metabolic process
GO:0032787~monocarboxylic acid metabolic process
GO:0032872~regulation of stress-activated MAPK cascade
GO:0032874~positive regulation of stress-activated MAPK cascade
GO:0033554~cellular response to stress
GO:0034097~response to cytokine
GO:0034405~response to fluid shear stress
GO:0034599~cellular response to oxidative stress
GO:0034614~cellular response to reactive oxygen species
GO:0035690~cellular response to drug
GO:0036293~response to decreased oxygen levels
GO:0036294~cellular response to decreased oxygen levels
GO:0042221~response to chemical
GO:0042398~cellular modified amino acid biosynthetic process
GO:0042451~purine nucleoside biosynthetic process
GO:0042455~ribonucleoside biosynthetic process
GO:0042493~response to drug
GO:0042558~pteridine-containing compound metabolic process
GO:0043068~positive regulation of programmed cell death
GO:0043086~negative regulation of catalytic activity
GO:0043207~response to external biotic stimulus
GO:0043436~oxoacid metabolic process

GO:0044236~multicellular organism metabolic process
GO:0044262~cellular carbohydrate metabolic process
GO:0044281~small molecule metabolic process
GO:0044710~single-organism metabolic process
GO:0044711~single-organism biosynthetic process
GO:0044723~single-organism carbohydrate metabolic process
GO:0045935~positive regulation of nucleobase-containing compound metabolic process
GO:0045936~negative regulation of phosphate metabolic process
GO:0045937~positive regulation of phosphate metabolic process
GO:0045978~negative regulation of nucleoside metabolic process
GO:0045981~positive regulation of nucleotide metabolic process
GO:0046031~ADP metabolic process
GO:0046033~AMP metabolic process
GO:0046058~cAMP metabolic process
GO:0046129~purine ribonucleoside biosynthetic process
GO:0046209~nitric oxide metabolic process
GO:0046390~ribose phosphate biosynthetic process
GO:0046496~nicotinamide nucleotide metabolic process
GO:0046653~tetrahydrofolate metabolic process
GO:0046655~folic acid metabolic process
GO:0046939~nucleotide phosphorylation
GO:0048519~negative regulation of biological process
GO:0048583~regulation of response to stimulus
GO:0048584~positive regulation of response to stimulus
GO:0048585~negative regulation of response to stimulus
GO:0050790~regulation of catalytic activity
GO:0050896~response to stimulus
GO:0051052~regulation of DNA metabolic process
GO:0051053~negative regulation of DNA metabolic process
GO:0051054~positive regulation of DNA metabolic process
GO:0051094~positive regulation of developmental process
GO:0051129~negative regulation of cellular component organization
GO:0051173~positive regulation of nitrogen compound metabolic process
GO:0051174~regulation of phosphorus metabolic process
GO:0051246~regulation of protein metabolic process
GO:0051247~positive regulation of protein metabolic process
GO:0051248~negative regulation of protein metabolic process
GO:0051403~stress-activated MAPK cascade
GO:0051716~cellular response to stimulus
GO:0052652~cyclic purine nucleotide metabolic process
GO:0055114~oxidation-reduction process
GO:0060255~regulation of macromolecule metabolic process

GO:0070302~regulation of stress-activated protein kinase signaling cascade
GO:0070304~positive regulation of stress-activated protein kinase signaling cascade
GO:0070482~response to oxygen levels
GO:0070887~cellular response to chemical stimulus
GO:0071216~cellular response to biotic stimulus
GO:0071229~cellular response to acid chemical
GO:0071310~cellular response to organic substance
GO:0071345~cellular response to cytokine stimulus
GO:0071407~cellular response to organic cyclic compound
GO:0071417~cellular response to organonitrogen compound
GO:0071453~cellular response to oxygen levels
GO:0071495~cellular response to endogenous stimulus
GO:0071897~DNA biosynthetic process
GO:0072522~purine-containing compound biosynthetic process
GO:0072524~pyridine-containing compound metabolic process
GO:0072593~reactive oxygen species metabolic process
GO:0080090~regulation of primary metabolic process
GO:0080134~regulation of response to stress
GO:0080135~regulation of cellular response to stress
GO:0090407~organophosphate biosynthetic process
GO:1900371~regulation of purine nucleotide biosynthetic process
GO:1900373~positive regulation of purine nucleotide biosynthetic process
GO:1900542~regulation of purine nucleotide metabolic process
GO:1900544~positive regulation of purine nucleotide metabolic process
GO:1901031~regulation of response to reactive oxygen species
GO:1901135~carbohydrate derivative metabolic process
GO:1901136~carbohydrate derivative catabolic process
GO:1901137~carbohydrate derivative biosynthetic process
GO:1901293~nucleoside phosphate biosynthetic process
GO:1901564~organonitrogen compound metabolic process
GO:1901565~organonitrogen compound catabolic process
GO:1901566~organonitrogen compound biosynthetic process
GO:1901615~organic hydroxy compound metabolic process
GO:1901617~organic hydroxy compound biosynthetic process
GO:1901698~response to nitrogen compound
GO:1901700~response to oxygen-containing compound
GO:1901701~cellular response to oxygen-containing compound
GO:1902882~regulation of response to oxidative stress
GO:1903409~reactive oxygen species biosynthetic process
GO:1903510~mucopolysaccharide metabolic process
GO:1903579~negative regulation of ATP metabolic process
GO:2001057~reactive nitrogen species metabolic process

GO:2001169~regulation of ATP biosynthetic process

GO:2001171~positive regulation of ATP biosynthetic process

Supplementary Table S2. Number of DEGs before and after filtration for drug/stress release and metabolism. The DEGs are based on a p-value of $p < 0.05$, DEGs are calculated for the two pro-B-ALL cell lines after exposition to AraC and Dexa.

Agent	RS4;11	SEM
<u>before filtration</u>		
AraC	776	927
Dexa	3357	1025
<u>after filtration</u>		
AraC	353	366
Dexa	2183	379

Supplementary Table S3. miRNA enrichment for the AraC drug release in RS4;11. Based on a p-value of $p < 0.05$ the miRNA enrichment was used to identify disease and functional annotations.

Disease/ Ontology	adjusted p-value
Lymphoma, Primary Effusion	9.00E-13
Leukemia, Myeloid, Acute	0.0000133
Leukemia, Lymphoblastic, Acute, Childhood	0.000151
Leukemia, Myeloid, Chronic	0.000164
Leukemia, Myeloid	0.000839
Lymphoma, Hodgkin	0.00187
Acute Megakaryoblastic Leukemia	0.00187
Leukemia, Promyelocytic, Acute	0.00562
Leukemia, Biphenotypic, Acute	0.00893
Leukemia-Lymphoma, Precursor B-Cell Lymphoblastic	0.0204
Leukemia, B-Cell	0.0477
Tumor Suppressor miRNAs	5.21E-11
Cell Differentiation	1.16E-10
Cell Death	7.30E-10
Folliculogenesis	1.09E-09
Innate Immunity	2.16E-08
Glucose Metabolism	1.55E-07

Adipocyte Differentiation	2.76E-07
Anti-Cell Proliferation	4.19E-07
Hematopoiesis	4.95E-07
Cell Division	0.00000173
Cell Proliferation	0.0000129
T-Cell Differentiation	0.0000282
Epithelial-to-Mesenchymal Transition	0.000126
Hepatic Stellate Cell Differentiation	0.000147
Neural Stem Cell Differentiation	0.000289
Osteoblast Differentiation	0.000292
Aging	0.000721
Cell Cycle	0.000749
Mesenchymal Stem Cell Proliferation	0.000781
Inflammation	0.00127
Cardiac Regeneration	0.00187
Hormone-mediated Signaling Pathway	0.00269
Megakaryocyte Differentiation	0.00605
Immune Response	0.00675
Apoptosis	0.0145
Plasma Cell Differentiation	0.0161
Wound Healing	0.019
Lipid Metabolism	0.0251
Bone Regeneration	0.0386
Carbohydrate Metabolism	0.2088

Supplementary Table S4. miRNA enrichment for the Dexa drug release in RS4;11.
Based on a p-value of $p < 0.05$ the miRNA enrichment was used to identify disease and functional annotation for the Dexamethasone drug release in RS4;11.

Disease/ Ontology	adjusted p-value
Lymphoma, Primary Effusion	1.26E-13
Leukemia, Myeloid, Acute	3.81E-09
Leukemia, Myeloid, Chronic	5.26E-08
Lymphoma, Hodgkin	1.57E-07
Leukemia, Lymphocytic, Chronic	3.00E-06
Leukemia, Lymphoblastic, Acute	5.73E-06
Leukemia	3.09E-05
Leukemia, Lymphoblastic, Acute, T-Cell	4.18E-04

Leukemia, Lymphocytic, Chronic, B-Cell	6.00E-04
Lymphoma, Mantle-Cell	6.24E-04
Lymphoma, Large B-Cell	1.07E-03
Lymphoma, B-Cell	6.73E-03
Leukemia, Lymphoblastic	0.0294
Cell Differentiation	2.97E-21
Tumor Suppressor miRNAs	1.16E-16
Cell Division	1.58E-15
Cell Death	6.50E-15
Cell Cycle	2.47E-14
Aging	3.04E-14
Epithelial-to-Mesenchymal Transition	6.07E-12
Cell Proliferation	4.24E-11
T-Cell Differentiation	1.77E-10
Anti-Cell Proliferation	1.95E-10
Apoptosis	5.10E-10
Hormone-mediated Signaling Pathway	6.08E-10
Neuron Differentiation	1.78E-09
Glucose Metabolism	4.08E-09
Adipocyte Differentiation	1.89E-08
Innate Immunity	3.30E-07
Folliculogenesis	3.63E-07
Hematopoiesis	7.63E-07
Immune Response	2.66E-06
Inflammation	4.50E-06
Osteogenesis	9.45E-06
Regulation of NF-κB Pathway	3.34E-05
Bile Duct Proliferation	3.35E-05
Neutrophil Differentiation	3.35E-05
Cardiac Regeneration	4.47E-05
Regulation of Stem Cell	1.35E-04
Hepatic Stellate Cell Differentiation	3.19E-04
Muscle Development	4.20E-04
Circadian Rhythm	5.31E-04
Neural Stem Cell Differentiation	6.24E-04
Regulation of WNT Signaling Pathway	6.24E-04
Osteoclastogenesis	6.24E-04
Peritoneal Cavity Homeostasis	6.62E-04
Brain Development	8.27E-04
Angiogenesis	8.71E-04
Osteoblast Differentiation	9.96E-04
Neuron Apoptosis	1.07E-03

DNA Damage Response	1.40E-03
Transdifferentiation	1.67E-03
Embryonic Development	1.78E-03
Smooth Muscle Cell Proliferation	2.24E-03
Cardiomyocyte Differentiation	3.13E-03
Granulopoiesis	3.41E-03
Cell Motility	4.07E-03
Skeletal Muscle Cell Differentiation	4.86E-03
Cardiomyocyte Proliferation	6.12E-03
Osteoclast Differentiation	9.44E-03
Natural Killer Cell Activation	9.99E-03
Chondrogenic Differentiation	0.0147
Cardiotoxicity	0.0165
Nephrotoxicity	0.0165
Embryonic Stem Cell Differentiation	0.0169
Adipogenesis	0.0258
Chemosensitivity of Tumor Cells	0.0263
Autophagy	0.0263
Toxicity	0.028
Cholesterol Homeostasis	0.0331

Supplementary Table S5. miRNA enrichment for the AraC drug release in SEM. Based on a p-value of $p < 0.05$ the miRNA enrichment was used to identify disease and functional annotation for the AraC drug release in SEM.

Disease/ Ontology	adjusted p-value
Lymphoma, Large B-Cell, Diffuse	1.00E-02
Leukemia, Myeloid, Acute	0.0113
Leukemia	0.0457
Skeletal Muscle Cell Differentiation	9.81E-05
Apoptosis	1.02E-03
Autophagy	3.84E-03
Tumor Suppressor miRNAs	6.60E-03
Response to Hypoxia	8.80E-03
Epithelial-to-Mesenchymal Transition	0.0157
Nephrotoxicity	0.0175
Smooth Muscle Cell Proliferation	0.0195
Multiciliated Cell Differentiation	0.0246
Muscle Development	0.0263
Peritoneal Cavity Homeostasis	0.0312
Osteogenesis	0.0329
Actin Filament Network Formation	0.0367

Aging	0.039
Inflammation	0.0425

Supplementary Table S6. miRNA enrichment for the Dexa drug release in SEM. Based on a p-value of $p < 0.05$ the miRNA enrichment was used to identify disease and functional annotation for the Dexa drug release in SEM.

Disease/ Ontology	adjusted p-value
Lymphoma, Primary Effusion	1.39E-09
Thyroid Lymphoma	8.56E-05
Leukemia, Myeloid, Chronic	3.29E-04
Lymphoma	1.22E-03
Lymphoma, Extranodal NK-T-Cell	1.31E-03
Leukemia, Myeloid, Acute	2.36E-03
Lymphoma, Mantle-Cell	6.31E-03
Lymphoma, Hodgkin	0.0103
Lymphoma, Large-Cell, Anaplastic	0.0256
Leukemia, Lymphoblastic, Acute, B-Cell	0.0299
Lymphoma, Large B-Cell, Diffuse	0.045
Innate Immunity	2.93E-09
Tumor Suppressor miRNAs	1.87E-08
Folliculogenesis	1.29E-06
Aging	2.44E-06
Cell Differentiation	1.03E-05
Adipocyte Differentiation	1.23E-05
Cell Division	1.59E-05
Ovarian Follicle Development	3.47E-05
Hepatic Stellate Cell Differentiation	8.56E-05
Neural Stem Cell Differentiation	1.69E-04
T-Cell Differentiation	2.56E-04
Chromatin Remodeling	2.91E-04
Adipogenesis	6.42E-04
Cell Death	8.54E-04
Cardiac Regeneration	9.41E-04
Epithelial-to-Mesenchymal Transition	1.25E-03
Glucose Metabolism	2.41E-03
Cell Proliferation	5.45E-03
Hematopoiesis	5.95E-03
Cell Cycle	6.55E-03
Skeletal Muscle Cell Differentiation	0.0103
Immune Response	0.0108
Anti-Cell Proliferation	0.0115

Peritoneal Cavity Homeostasis	0.0117
Inflammation	0.027
Retinal Pigment Epithelium Development	0.0425
Angiogenesis	0.0463
Latent Virus Replication	0.0495