

TABLE S5A Top enriched pathways of common genes after GRWD1, WDR5, or MLL2 knockdown in MM cells

| Inguenuity Canonical Pathways | -log(p-value) | Ratio | Molecules |
|--|----------------------|--------------|--|
| Kinetochore Metaphase Signaling Pathway | 39.9 | 0.324 | AURKB,BIRC5,BUB1,BUB1B,CCNB1,CDC20,CDCA8,CDK1,CENPA,CENPE,CENPH,CENPK,CENPO,CENPU,CENPW,DSN1,ESPL1,INCENP,KIF2C,KNTC1,MAD2L1,NDC80,NUF2,PLK1,PMF1/PMF1-BGLAP,PPP2R5D,PTTG1,RAD21,SKA1,SKA3,SPC25,TTK,ZW10,ZWILCH |
| Cell Cycle Control of Chromosomal Replication | 22.9 | 0.339 | CDC45,CDC6,CDC7,CDK1,CDK2,CDT1,MCM2,MCM3,MCM4,MCM5,MCM6,MCM7,ORC1,ORC6,PCNA,POLE,RPA2,RPA3,TOP2A |
| Mitotic Roles of Polo-Like Kinase | 18.2 | 0.258 | CCNB1,CDC20,CDC25B,CDC7,CDK1,ESPL1,FBXO5,KIF11,KIF23,PLK1,PLK2,PLK4,PPP2R5D,PRC1,PTPA,PTTG1,RAD21 |
| Role of CHK Proteins in Cell Cycle Checkpoint Control | 16.3 | 0.263 | BRCA1,CDK1,CDK2,CDKN1A,CLSPN,E2F2,E2F8,MDC1,PCNA,PLK1,PPP2R5D,PTPA,RFC2,RFC3,RFC5 |
| Cell Cycle: G2/M DNA Damage Checkpoint Regulation | 14.1 | 0.26 | AURKA,BORA,BRCA1,CCNB1,CDC25B,CDK1,CDKN1A,CKS1B,CKS2,GADD45A,MDM2,PLK1,TOP2A |
| Role of BRCA1 in DNA Damage Response | 13.9 | 0.188 | BARD1,BRCA1,CDKN1A,E2F2,E2F8,FANCB,FANCD2,GADD45A,MDC1,MSH6,PLK1,RFC2,RFC3,RFC5,TOPBP1 |
| ATM Signaling | 12.6 | 0.155 | BRCA1,CBX3,CCNB1,CDK1,CDK2,CDKN1A,FANCD2,GADD45A,MDC1,MDM2,PPP2R5D,PTPA,SMC2,SUV39H1,TOPBP1 |
| GADD45 Signaling | 12.4 | 0.45 | BRCA1,CCNB1,CCNE1,CCNE2,CDK1,CDK2,CDKN1A,GADD45A,PCNA |
| Cyclins and Cell Cycle Regulation | 12.3 | 0.167 | CCNA2,CCNB1,CCNE1,CCNE2,CDK1,CDK2,CDKN1A,CDKN2C,E2F2,E2F8,PA2G4,PPP2R5D,PTPA,SUV39H1 |
| NER (Nucleotide Excision Repair, Enhanced Pathway) | 9.64 | 0.121 | CHAF1A,CHAF1B,LIG4,PCNA,POLD2,POLE,POLE2,RFC2,RFC3,RFC5,RPA2,RPA3,TOP2A |
| Estrogen-mediated S-phase Entry | 9.54 | 0.308 | CCNA2,CCNE1,CCNE2,CDK1,CDK2,CDKN1A,E2F2,E2F8 |
| Mismatch Repair in Eukaryotes | 9.24 | 0.389 | EXO1,FEN1,MSH6,PCNA,RFC2,RFC3,RFC5 |
| Cell Cycle: G1/S Checkpoint Regulation | 8.37 | 0.147 | CCNE1,CCNE2,CDK2,CDKN1A,CDKN2C,E2F2,E2F8,MDM2,PA2G4,SUV39H1 |
| DNA damage-induced 14-3-3σ Signaling | 7.35 | 0.316 | BRCA1,CCNB1,CCNE1,CCNE2,CDK1,CDK2 |
| Hereditary Breast Cancer Signaling | 7.08 | 0.0833 | BARD1,BRCA1,CCNB1,CDK1,CDKN1A,FANCB,FANCD2,GADD45A,MSH6,RFC2,RFC3,RFC5 |
| Cell Cycle Regulation by BTG Family Proteins | 6.81 | 0.189 | CCNE1,CCNE2,CDK2,E2F2,E2F8,PPP2R5D,PTPA |
| p53 Signaling | 5.8 | 0.0918 | BIRC5,BRCA1,CDK2,CDKN1A,GADD45A,MDM2,PCNA,TOPBP1,TP53INP1 |
| Senescence Pathway | 5.75 | 0.0497 | CCNB1,CCNE1,CCNE2,CDC25B,CDK1,CDK2,CDKN1A,E2F2,E2F8,EZH2,GADD45A,ING1,MDM2,PPP2R5D,PTPA |
| Pancreatic Adenocarcinoma Signaling | 5.74 | 0.0781 | BIRC5,CCNE1,CCNE2,CDK2,CDKN1A,E2F2,E2F8,MDM2,PA2G4,SUV39H1 |
| Molecular Mechanisms of Cancer | 5.4 | 0.0397 | AURKA,BRCA1,CCNE1,CCNE2,CDC25B,CDK1,CDK2,CDKN1A,CDKN2C,CYCS,E2F2,E2F8,FADD,FANCD2,HAT1,MDM2,PA2G4,SUV39H1 |
| Small Cell Lung Cancer Signaling | 4.8 | 0.0808 | CCNE1,CCNE2,CDK2,CKS1B,CYCS,E2F2,PA2G4,SUV39H1 |
| Prostate Cancer Signaling | 4.31 | 0.069 | CCNE1,CCNE2,CDK2,CDKN1A,E2F2,MDM2,PA2G4,SUV39H1 |
| Glioma Signaling | 3.91 | 0.0606 | CDKN1A,CDKN2C,E2F2,E2F8,IDH2,MDM2,PA2G4,SUV39H1 |
| Protein Ubiquitination Pathway | 3.49 | 0.0394 | B2M,BRCA1,CDC20,DNAJC9,HLA-A,HSPA14,MDM2,UBE2C,UBE2S,UBE2T,USP1 |
| BER pathway | 3.44 | 0.231 | FEN1,PCNA,POLE |
| Granzyme B Signaling | 3.16 | 0.188 | CYCS,LMNB1,LMNB2 |
| Chronic Myeloid Leukemia Signaling | 2.89 | 0.0561 | CDKN1A,E2F2,E2F8,MDM2,PA2G4,SUV39H1 |
| Myc Mediated Apoptosis Signaling | 2.6 | 0.0784 | ADRB2,CYCS,FADD,MDM2 |
| Aryl Hydrocarbon Receptor Signaling | 2.58 | 0.0424 | CCNA2,CCNE1,CCNE2,CDK2,CDKN1A,MCM7,MDM2 |
| Regulation of Cellular Mechanics by Calpain Protease | 2.47 | 0.0556 | CCNA2,CCNE1,CCNE2,CDK1,CDK2 |
| Glioblastoma Multiforme Signaling | 2.43 | 0.0398 | CCNE1,CCNE2,CDK2,CDKN1A,E2F2,E2F8,MDM2 |
| Sumoylation Pathway | 2.12 | 0.0459 | MDM2,PCNA,RFC2,RFC3,RFC5 |
| Coronavirus Pathogenesis Pathway | 2.09 | 0.0345 | CCNE1,CCNE2,CDK2,E2F2,E2F8,PA2G4,SUV39H1 |
| Hypoxia Signaling in the Cardiovascular System | 2.02 | 0.0541 | MDM2,UBE2C,UBE2S,UBE2T |
| Bladder Cancer Signaling | 2.01 | 0.0431 | CDKN1A,E2F2,MDM2,PA2G4,SUV39H1 |
| Pyrimidine Deoxyribonucleotides De Novo Biosynthesis I | 2 | 0.075 | DUT,RRM1,RRM2 |
| DNA Double-Strand Break Repair by Homologous Recombination | 1.98 | 0.143 | BRCA1,GEN1 |
| Pyridoxal 5'-phosphate Salvage Pathway | 1.98 | 0.0526 | CDK1,CDK2,PLK1,TTK |
| Breast Cancer Regulation by Stathmin1 | 1.77 | 0.0218 | ADRB2,AURKA,AURKB,CDK1,CDK2,E2F2,E2F8,FOXM1,PPP2R5D,PTPA,SIVA1,STMN1,TUBB |
| Tumoricidal Function of Hepatic Natural Killer Cells | 1.53 | 0.0833 | CYCS,FADD |
| PD-1, PD-L1 cancer immunotherapy pathway | 1.49 | 0.0374 | B2M,CDK2,CIP2A,HLA-A |
| Ovarian Cancer Signaling | 1.47 | 0.0312 | BRCA1,E2F2,MSH6,PA2G4,SUV39H1 |
| Induction of Apoptosis by HIV1 | 1.44 | 0.0462 | CYCS,FADD,SLC25A10 |
| HOTAIR Regulatory Pathway | 1.42 | 0.0303 | CDKN1A,EZH2,FOXM1,MDM2,RBBP7 |
| Salvage Pathways of Pyrimidine Ribonucleotides | 1.39 | 0.0348 | CDK1,CDK2,PLK1,TTK |
| Sonic Hedgehog Signaling | 1.36 | 0.0667 | CCNB1,CDK1 |

TABLE S5B Top enriched pathways of common genes after GRWD1, WDR5, or MLL2 knockdown in KMM cells

| Ingenuity Canonical Pathways | -log(p-value) | Ratio | Molecules |
|--|----------------------|--------------|---|
| Kinetochore Metaphase Signaling Pathway | 32.6 | 0.229 | AURKB,BIRC5,BUB1,BUB1B,CCNB1,CDC20,CDCA8,CDK1,CENPE,CENPH,INCENP,KIF2C,KNTC1,MAD2L1,NDC80,NUF2,PLK1,PTTG1,RAD21,SKA1,SKA3,SPC25,TTK,ZWINT |
| Mitotic Roles of Polo-Like Kinase | 13.5 | 0.167 | CCNB1,CDC20,CDK1,FBXO5,KIF11,PLK1,PLK2,PLK4,PRC1,PTTG1,RAD21 |
| Cell Cycle Control of Chromosomal Replication | 12.6 | 0.179 | CDK1,MCM2,MCM3,MCM4,MCM6,ORC6,POLE,RPA2,RPA3,TOP2A |
| Cell Cycle: G2/M DNA Damage Checkpoint Regulation | 11.4 | 0.18 | AURKA,CCNB1,CDK1,CDKN1A,CKS1B,GADD45A,MDM2,PLK1,TOP2A |
| ATM Signaling | 6.16 | 0.0722 | CCNB1,CDK1,CDKN1A,FANCD2,GADD45A,MDM2,SMC2 |
| GADD45 Signaling | 5.52 | 0.2 | CCNB1,CDK1,CDKN1A,GADD45A |
| Role of BRCA1 in DNA Damage Response | 5.45 | 0.075 | CDKN1A,E2F8,FANCD2,GADD45A,PLK1,RFC5 |
| Estrogen-mediated S-phase Entry | 5.04 | 0.154 | CCNA2,CDK1,CDKN1A,E2F8 |
| Role of CHK Proteins in Cell Cycle Checkpoint Control | 4.95 | 0.0877 | CDK1,CDKN1A,E2F8,PLK1,RFC5 |
| Cyclins and Cell Cycle Regulation | 4.14 | 0.0595 | CCNA2,CCNB1,CDK1,CDKN1A,E2F8 |
| Hereditary Breast Cancer Signaling | 4 | 0.0417 | CCNB1,CDK1,CDKN1A,FANCD2,GADD45A,RFC5 |
| NER (Nucleotide Excision Repair, Enhanced Pathway) | 3.64 | 0.0467 | POLE,RFC5,RPA2,RPA3,TOP2A |
| Protein Ubiquitination Pathway | 3.22 | 0.0251 | B2M,CDC20,HSPB2,MDM2,UBE2C,UBE2S,USP1 |
| Pyrimidine Deoxyribonucleotides De Novo Biosynthesis I | 2.95 | 0.075 | DUT,RRM1,RRM2 |
| p53 Signaling | 2.79 | 0.0408 | BIRC5,CDKN1A,GADD45A,MDM2 |
| Granzyme B Signaling | 2.52 | 0.125 | LMNB1,LMNB2 |
| DNA damage-induced 14-3-3 σ Signaling | 2.38 | 0.105 | CCNB1,CDK1 |
| Pancreatic Adenocarcinoma Signaling | 2.37 | 0.0312 | BIRC5,CDKN1A,E2F8,MDM2 |
| Senescence Pathway | 2.33 | 0.0199 | CCNB1,CDK1,CDKN1A,E2F8,GADD45A,MDM2 |
| Glioma Signaling | 2.32 | 0.0303 | CDKN1A,E2F8,IDH2,MDM2 |
| Cell Cycle: G1/S Checkpoint Regulation | 2.29 | 0.0441 | CDKN1A,E2F8,MDM2 |
| Hypoxia Signaling in the Cardiovascular System | 2.18 | 0.0405 | MDM2,UBE2C,UBE2S |
| Pyridoxal 5'-phosphate Salvage Pathway | 2.15 | 0.0395 | CDK1,PLK1,TTK |
| Molecular Mechanisms of Cancer | 2.05 | 0.0155 | AURKA,CDK1,CDKN1A,E2F8,FANCD2,MDM2,RHOB |
| Sonic Hedgehog Signaling | 1.99 | 0.0667 | CCNB1,CDK1 |
| Aryl Hydrocarbon Receptor Signaling | 1.98 | 0.0242 | CCNA2,CDKN1A,HSPB2,MDM2 |
| Glioblastoma Multiforme Signaling | 1.89 | 0.0227 | CDKN1A,E2F8,MDM2,RHOB |
| Nucleotide Excision Repair Pathway | 1.86 | 0.0571 | RPA2,RPA3 |
| Chronic Myeloid Leukemia Signaling | 1.75 | 0.028 | CDKN1A,E2F8,MDM2 |
| Sumoylation Pathway | 1.73 | 0.0275 | MDM2,RFC5,RHOB |
| Mechanisms of Viral Exit from Host Cells | 1.73 | 0.0488 | LMNB1,LMNB2 |
| Salvage Pathways of Pyrimidine Ribonucleotides | 1.67 | 0.0261 | CDK1,PLK1,TTK |
| Melanoma Signaling | 1.53 | 0.0385 | CDKN1A,MDM2 |