**S5 Table:** Monotonically Enriched Pathways (MEPs) with the number of DEGs that were found to be involved in each stage with the corresponding gene symbols. Cluster and pathway category of each MEG are also presented.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Pathway Maps (2nd Level)** | **ALL KEGG Pathways** | **StageI** | **StageII** | **StageIII** | **StageIV** | **StageI - Genes** | **StageII- Genes** | **StageIII - Genes** | **StageIV - Genes** | **Cluster** | **Group** |
| Replication and repair | fanconi anemia pathway - homo sapiens | 0 | 3 | 4 | 6 |  | FANCI, BRCA1, BRCA2 | FANCI, BRCA2, BRCA1, ATR | UBE2T, FANCI, BRCA2, BRCA1, ATR, BLM | Cluster 3 | HPR |
| Signal transduction | mapk signaling pathway - homo sapiens | 2 | 5 | 6 | 7 | MYC, ANGPT2 | CDC25B, MET, MYC, ANGPT2, DUSP10 | MET,CDC25B, MYC, ANGPT2, IRAK1, DUSP1 | MET, CDC25B, MYC, ANGPT2, FGF18, STK3, IRAK1 | Cluster 2 | LPR |
| Signal transduction | camp signaling pathway - homo sapiens | 4 | 5 | 7 | 9 | SOX9, ATP2A3, SST, GCG | SOX9, ATP2A3, EDN3, SST, GCG | SOX9,HTR4,ATP2A3,EDN3,NPY1R,SST,GCG | SOX9, HTR4, PDE4D, PLD1, ATP2A3, NPY1R, PLCE1, SST, GCG | Cluster 1 | LPR |
| Signaling molecules and interaction | neuroactive ligand-receptor interaction - homo sapiens | 7 | 9 | 11 | 12 | AGT, F2RL2, PTGDR, INSL5, SST, GCG, PYY | F2RL2, NR3C1, P2RY1, EDN3, PTGDR, SST, INSL5, GCG, PYY | F2RL2,HTR4,NR3C1,P2RY1,EDN3,NPY1R,PTGDR,SST,INSL5,GCG,PYY | AGT, F2RL2, NMU, HTR4, NR3C1, P2RY1, NPY1R, PTGDR, SST, INSL5, GCG, PYY | Cluster 1 | LPR |
| Transport and catabolism | endocytosis - homo sapiens | 0 | 1 | 2 | 3 |  | ASAP3 | ASAP1,NEDD4L | ASAP1, ASAP3, PLD1 | Cluster 2 | LPR |
| Cell growth and death | cellular senescence - homo sapiens | 1 | 9 | 10 | 12 | MYC | MYC, FOXM1, CCNB1, CDK1, CDK4, CHEK1, CCNA2, E2F5, CDKN2B | CDK1,FOXM1,CCNB1,MYC,CHEK1,CCNA2,MYBL2,E2F5,ATR,ZFP36L1 | MYC, CDK6, CDK1, CDK4, CHEK1, E2F5, CCNB1, FOXM1, CCNA2, MYBL2, ATR, CDKN2B | Cluster 1 | LPR |
| Cellular community - eukaryotes | tight junction - homo sapiens | 3 | 4 | 5 | 7 | CLDN1, AMOTL2, CLDN8 | CLDN1, CDK4, CD1D, CLDN8 | CLDN1, AMOTL2, CD1D, NEDD4L, CLDN8 | CLDN1, CLDN2, CDK4, AMOTL2, ACTR3B, CD1D, CLDN8 | Cluster 1 | LPR |
| Infectious disease: viral | hepatitis b - homo sapiens | 1 | 3 | 4 | 5 | MYC | MYC, BIRC5, CCNA2 | MYC, BIRC5, CCNA2, IRAK1 | MYC, BIRC5, CCNA2, IRAK1, BID | Cluster 2 | LPR |
| Infectious disease: viral | human papillomavirus infection - homo sapiens | 4 | 10 | 11 | 14 | COL4A1, THBS2, COL9A3, WNT2 | THBS2, COL4A1, AXIN2, ITGA2, CDK4, WNT2, CCNA2, FZD3, COL6A3, LAMA1 | THBS2,COL4A1,WNT5A,ITGA2,AXIN2,COL6A3,WNT2,FZD3,CCNA2,PTGS2,ATR | SPP1, COL1A1, THBS2, COL4A1, COL9A3, AXIN2, ITGA2, WNT2, CDK6, COL6A3, CDK4, FZD3, CCNA2, ATR | Cluster 1 | LPR |
| Infectious disease: viral | human immunodeficiency virus 1 infection - homo sapiens | 1 | 4 | 6 | 7 | TRAF5 | CCNB1, CDK1, CHEK1, TRAF5 | CDK1,CCNB1,TRAF5,CHEK1,IRAK1,ATR | TRAF5, CDK1, CHEK1, CCNB1, IRAK1, ATR, BID | Cluster 2 | LPR |
| Cancer: overview | proteoglycans in cancer - homo sapiens | 3 | 7 | 8 | 10 | MYC, CD44, WNT2 | MET, MYC, ITGA2, CD44, WNT2, FZD3, ANK3 | MET,WNT5A,ITGA2,CD44,MYC,WNT2,FZD3,ANK3 | COL1A1, MET, MYC, ITGA2, WNT2, FZD3, CD44, ANK3, HPSE, PLCE1 | Cluster 1 | LPR |
| Lipid metabolism | steroid biosynthesis - homo sapiens | 0 | 1 | 2 | 2 |  | DHCR7 | CEL,DHCR7 | CEL, DHCR7 | Cluster 3 | HPR |
| Lipid metabolism | steroid hormone biosynthesis - homo sapiens | 0 | 2 | 3 | 3 |  | UGT2A3, HSD17B2 | HSD11B2,UGT2A3,HSD17B2 | HSD11B2, UGT2A3, HSD17B2 | Cluster 1 | LPR |
| Nucleotide metabolism | purine metabolism - homo sapiens | 0 | 5 | 5 | 7 |  | RRM2, PAICS, PPAT, GART, PDE9A | RRM2,PPAT,PAICS,GART,PDE9A | RRM2, PPAT, PAICS, GART, ATIC, PDE4D, PDE9A | Cluster 1 | LPR |
| Amino acid metabolism | glycine, serine and threonine metabolism - homo sapiens | 1 | 2 | 2 | 3 | PSAT1 | PSAT1, SHMT2 | PSAT1,SHMT2 | PSAT1, PSPH, SHMT2 | Cluster 1 | LPR |
| Carbohydrate metabolism | amino sugar and nucleotide sugar metabolism - homo sapiens | 0 | 1 | 1 | 2 |  | NANP | NANP | NANP, GNE | Cluster 2 | LPR |
| Lipid metabolism | glycerolipid metabolism - homo sapiens | 0 | 3 | 4 | 4 |  | DGAT2, MOGAT2, AKR1B10 | CEL,DGAT2,MOGAT2,AKR1B10 | CEL, DGAT2, DGKA, MOGAT2 | Cluster 1 | LPR |
| Metabolism of cofactors and vitamins | one carbon pool by folate - homo sapiens | 0 | 2 | 2 | 4 |  | SHMT2, GART | SHMT2,GART | GART, MTR, SHMT2, ATIC | Cluster 4 | HPR |
| Drug resistance: antineoplastic | antifolate resistance - homo sapiens | 0 | 3 | 3 | 4 |  | SHMT2, ABCC1, GART | ABCC1,SHMT2,GART | ABCC1, GART, SHMT2, ATIC | Cluster 3 | HPR |
| Drug resistance: antineoplastic | platinum drug resistance - homo sapiens | 0 | 3 | 3 | 5 |  | PMAIP1, BIRC5, BRCA1 | PMAIP1,BIRC5,BRCA1 | TOP2A, PMAIP1, BIRC5, BRCA1, BID | Cluster 1 | LPR |
| Replication and repair | nucleotide excision repair - homo sapiens | 0 | 1 | 1 | 2 |  | RFC3 | RFC3 | RFC3, RFC4 | Cluster 2 | LPR |
| Replication and repair | mismatch repair - homo sapiens | 0 | 2 | 2 | 3 |  | RFC3, EXO1 | RFC3,EXO1 | RFC3, RFC4, EXO1 | Cluster 3 | HPR |
| Replication and repair | homologous recombination - homo sapiens | 1 | 3 | 3 | 4 | RAD54B | RAD54B, BRCA1, BRCA2 | RAD54B,BRCA2,BRCA1 | RAD54B, BRCA2, BRCA1, BLM | Cluster 3 | HPR |
| Cell growth and death | oocyte meiosis - homo sapiens | 1 | 6 | 6 | 9 | ANAPC1 | BUB1, CCNB1, CDK1, MAD2L1, CDC20, MAD2L2 | BUB1,CDK1,CCNB1,CDC20,MAD2L2,ANAPC1 | BUB1, CDK1, MAD2L1, CCNB1, AURKA, PTTG1, FBXO5, ANAPC1, CDC20 | Cluster 1 | LPR |
| Cell growth and death | p53 signaling pathway - homo sapiens | 0 | 6 | 6 | 9 |  | RRM2, PMAIP1, CCNB1, CDK1, CDK4, CHEK1 | PMAIP1,CDK1,RRM2,CCNB1,CHEK1,ATR | PMAIP1, RRM2, CDK6, CDK1, CDK4, CHEK1, CCNB1, ATR, BID | Cluster 3 | HPR |
| Folding, sorting and degradation | protein processing in endoplasmic reticulum - homo sapiens | 0 | 3 | 3 | 4 |  | HSP90AB1, MBTPS2, UGGT2 | HSPH1,HSP90AB1,UGGT2 | HSPH1, UGGT2, HSP90AB1, MBTPS2 | Cluster 2 | LPR |
| Signal transduction | mtor signaling pathway - homo sapiens | 1 | 5 | 6 | 6 | WNT2 | SLC7A5, WNT2, FZD3, GRB10, SKP2 | SLC7A5,WNT5A,WNT2,FZD3,GRB10,SKP2 | SLC7A5, WNT2, GRB10, TTI1, FZD3, SKP2 | Cluster 1 | LPR |
| Signal transduction | ampk signaling pathway - homo sapiens | 1 | 4 | 4 | 5 | PCK1 | SCD, CCNA2, PPARGC1A, PCK1 | SCD,CCNA2,PPARGC1A,PCK1 | SCD, CCNA2, PFKFB3, PPARGC1A, PCK1 | Cluster 1 | LPR |
| Cell growth and death | apoptosis - homo sapiens | 1 | 2 | 2 | 4 | GZMB | PMAIP1, BIRC5 | PMAIP1, BIRC5 | PMAIP1, CTSH, BIRC5, BID | Cluster 2 | LPR |
| Cell growth and death | apoptosis - multiple species - homo sapiens | 0 | 2 | 2 | 3 |  | PMAIP1, BIRC5 | PMAIP1, BIRC5 | PMAIP1, BIRC5, BID | Cluster 3 | HPR |
| Cell growth and death | necroptosis - homo sapiens | 1 | 2 | 2 | 3 | TRAF5 | TRAF5, HSP90AB1 | TRAF5,HSP90AB1 | TRAF5, HSP90AB1, BID | Cluster 2 | LPR |
| Development and regeneration | axon guidance - homo sapiens | 3 | 8 | 8 | 9 | SEMA4D, SEMA6A, SEMA6D | MET, PLXNA1, FZD3, ROBO1, EPHB2, UNC5C, SEMA6D, SEMA6A | MET,WNT5A,PLXNA1,ROBO1,FZD3,SEMA6D,SEMA6A,CXCL12 | BMP7, MET, ROBO1, PLXNA1, FZD3, SEMA3A, UNC5C, SEMA6D, SEMA6A | Cluster 1 | LPR |
| Signal transduction | hippo signaling pathway - homo sapiens | 4 | 10 | 10 | 13 | AJUBA, MYC, WNT2, YAP1 | AJUBA, TEAD4, LEF1, MYC, AXIN2, BIRC5, WNT2, FZD3, BMP4, YAP1 | AJUBA,TEAD4,WNT5A,AXIN2,MYC,WNT2,BIRC5,FZD3,YAP1,BMP2 | AJUBA, TEAD4, LEF1, BMP7, AXIN2, MYC, WNT2, FZD3, BMP4, BIRC5, YAP1, STK3, NKD1 | Cluster 4 | HPR |
| Signal transduction | hippo signaling pathway - multiple species - homo sapiens | 2 | 3 | 3 | 4 | AJUBA, YAP1 | AJUBA, TEAD4, YAP1 | AJUBA,TEAD4,YAP1 | AJUBA, TEAD4, YAP1, STK3 | Cluster 3 | HPR |
| Immune system | hematopoietic cell lineage - homo sapiens | 3 | 4 | 4 | 5 | CD44, IL1R2, IL6R | ITGA2, CD44, CD1D, IL1R2 | ITGA2,CD44,CD1D,IL1R2 | ITGA2, CD44, CD1D, IL6R, IL1R2 | Cluster 1 | LPR |
| Immune system | fc gamma r-mediated phagocytosis - homo sapiens | 0 | 1 | 1 | 3 |  | ASAP3 | ASAP1 | ASAP1, ASAP3, PLD1 | Cluster 2 | LPR |
| thermogenesis | thermogenesis - homo sapiens | 2 | 4 | 4 | 5 | ACSL6, GCG | SMARCC1, DPF3, PPARGC1A, GCG | SMARCC1,DPF3,PPARGC1A,GCG | ACSL4, SMARCC1, DPF3, PPARGC1A, GCG | Cluster 2 | LPR |
| Cell motility | regulation of actin cytoskeleton - homo sapiens | 0 | 2 | 3 | 3 |  | ITGA2, DIAPH3 | ITGA2,DIAPH3,CXCL12 | ITGA2, DIAPH3, FGF18 | Cluster 2 | LPR |
| Endocrine system | progesterone-mediated oocyte maturation - homo sapiens | 1 | 8 | 8 | 9 | ANAPC1 | CDC25B, BUB1, CCNB1, CDK1, MAD2L1, CCNA2, MAD2L2, HSP90AB1 | CDC25B,BUB1,CDK1,CCNB1,CCNA2,MAD2L2,HSP90AB1,ANAPC1 | CDC25B, BUB1, CDK1, MAD2L1, CCNB1, AURKA, CCNA2, HSP90AB1, ANAPC1 | Cluster 3 | HPR |
| Digestive system | vitamin digestion and absorption - homo sapiens | 0 | 1 | 1 | 2 |  | ABCC1 | ABCC1 | SLC5A6, ABCC1 | Cluster 1 | LPR |
| Infectious disease: bacterial | pathogenic escherichia coli infection - homo sapiens | 2 | 3 | 3 | 4 | CLDN1, CLDN8 | CLDN1, MYO1A, CLDN8 | CLDN1,IRAK1,CLDN8 | CLDN1, CLDN2, IRAK1, CLDN8 | Cluster 2 | LPR |
| Infectious disease: bacterial | yersinia infection - homo sapiens | 0 | 0 | 1 | 2 |  |  | IRAK1 | IRAK1, ACTR3B | Cluster 2 | LPR |
| Infectious disease: bacterial | tuberculosis - homo sapiens | 2 | 2 | 3 | 6 | RIPK2, CEBPB | RIPK2,HSPD1 | RIPK2,CEBPB,IRAK1 | RIPK2, CEBPB, NOD2, IRAK1, HSPD1, BID | Cluster 2 | LPR |
| Infectious disease: viral | measles - homo sapiens | 0 | 1 | 1 | 4 |  | CDK4 | IRAK1 | CDK6, CDK4, IRAK1, BID | Cluster 2 | LPR |
| Infectious disease: viral | influenza a - homo sapiens | 0 | 1 | 1 | 4 |  | CDK4 | RAE1 | CDK6, CDK4, RAE1, BID | Cluster 2 | LPR |
| Infectious disease: viral | kaposi sarcoma-associated herpesvirus infection - homo sapiens | 2 | 3 | 3 | 5 | MYC, ANGPT2 | MYC, CDK4, ANGPT2 | MYC,PTGS2,ANGPT2 | MYC, CDK6, ANGPT2, CDK4, BID | Cluster 2 | LPR |
| Infectious disease: viral | herpes simplex virus 1 infection - homo sapiens | 2 | 2 | 3 | 4 | TRAF5, ZNF473 | TRAF5, ZNF275 | TRAF5,ZNF275,IRAK1 | TRAF5, IRAK1, ZNF473, BID | Cluster 2 | LPR |
| Infectious disease: viral | epstein-barr virus infection - homo sapiens | 3 | 6 | 6 | 9 | MYC, CD44, TRAF5 | MYC, CDK4, CD44, CCNA2, TRAF5, SKP2 | CD44,MYC,TRAF5,CCNA2,SKP2,IRAK1 | MYC, TRAF5, CDK6, CDK4, CD44, CCNA2, SKP2, IRAK1, BID | Cluster 1 | LPR |
| Cancer: overview | micrornas in cancer - homo sapiens | 3 | 11 | 11 | 12 | MYC, CD44, SOX4 | CDC25B, MET, MYC, CDCA5, KIF23, CD44, FZD3, SOX4, DNMT1, ABCC1, BRCA1 | MET,CDC25B,CD44,CDCA5,MYC,KIF23,SOX4,FZD3,ABCC1,PTGS2,BRCA1 | MET, CDC25B, MYC, SOX4, CDK6, CDCA5, FZD3, ABCC1, KIF23, CD44, GLS2, BRCA1 | Cluster 1 | LPR |
| Cancer: overview | central carbon metabolism in cancer - homo sapiens | 1 | 3 | 3 | 4 | MYC | SLC7A5, MET, MYC | SLC7A5,MET,MYC | SLC7A5, MET, MYC, GLS2 | Cluster 1 | LPR |
| Cancer: overview | choline metabolism in cancer - homo sapiens | 1 | 2 | 2 | 3 | GPCPD1 | SLC22A3, GPCPD1 | SLC22A3, GPCPD1 | SLC22A3, PLD1, DGKA | Cluster 2 | LPR |