

**Supplementary Table 4.** Biological functions of the genes with altered down-regulated expression by a factor of at least 1.5-fold in HeLa spheroid cells compared with HeLa monolayer cells, as determined by WebGestalt (Gene Set Analysis Toolkit).

| Category           | Function                             | Gene Symbol                                                                                                                                                                                                                      | No. of molecules |
|--------------------|--------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Biological process | Response to protein stimulus         | NR3C1, CYR61, ID2, DNAJB1, DDIT3, HSPB3, HERPUD1, HSPA6, HSPA1B                                                                                                                                                                  | 9                |
| Biological process | Response to unfolded protein         | DNAJB1, DDIT3, HERPUD1, HSPB3, HSPA1B, HSPA6                                                                                                                                                                                     | 6                |
| Biological process | Response to stress                   | C3, KCNIP3, OLR1, BTG2, KLRC3, EDN1, GRHL3, TP53, HIST2H2BE, C1R, DNAJB1, CXCL2, HERPUD1, HSPB3, HSPA1B, HSPA6, CTGF, TXNIP, GADD45B, ENO3, SREBF1, DDIT3, KLRK1, PPBP                                                           | 24               |
| Biological process | Response to chemical stimulus        | OLR1, NR3C1, BTG2, MGP, EDN1, TP53, ID2, CXCL2, DNAJB1, GH1, CCNE1, HERPUD1, HSPB3, HSPA1B, HSPA6, CYR61, TXNIP, ENO3, DDIT3, PPBP                                                                                               | 20               |
| Biological process | Response to external stimulus        | C3, OLR1, CTGF, CYR61, BTG2, MGP, ENO3, TXNIP, EDN1, SREBF1, GRHL3, TP53, C1R, CXCL2, CCNE1, DDIT3, PPBP                                                                                                                         | 17               |
| Biological process | Response to organic substance        | NR3C1, CYR61, BTG2, MGP, TXNIP, ID2, DNAJB1, GH1, CCNE1, DDIT3, HERPUD1, HSPB3, HSPA1B, HSPA6                                                                                                                                    | 14               |
| Biological process | Response to stimulus                 | OLR1, KLRC3, MGP, TP53, ID2, HIST2H2BE, DNAJB1, CXCL2, GH1, CCNE1, HSPB3, CTGF, CYR61, ENO3, TXNIP, SREBF1, KLRK1, PPBP, C3, CRB1, KCNIP3, NR3C1, BTG2, GRHL3, EDN1, TNFSF10, C1R, OR4X1, HERPUD1, HSPA6, HSPA1B, GADD45B, DDIT3 | 33               |
| Biological process | Response to biotic stimulus          | TP53, HIST2H2BE, DNAJB1, DDIT3, HSPB3, HERPUD1, HSPA6, PPBP, HSPA1B                                                                                                                                                              | 9                |
| Biological process | Cellular response to biotic stimulus | DDIT3, HERPUD1, TP53                                                                                                                                                                                                             | 3                |
| Biological process | ER-nuclear signaling pathway         | DDIT3, HERPUD1, TP53                                                                                                                                                                                                             | 3                |

|                    |                                    |                                                                                                                                             |    |
|--------------------|------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|----|
| Molecular function | Extracellular matrix binding       | OLFML2A, DCN, CYR61                                                                                                                         | 3  |
| Molecular function | Receptor binding                   | C3, SPRED2, TRIP12, CTGF, EDN1, TNFSF10, CXCL2, GH1, CCNE1, INSL4, KLRK1, PPBP                                                              | 12 |
| Molecular function | Carbohydrate binding               | DCN, OLR1, CTGF, PFKL, CYR61, KLRC3, KLRK1                                                                                                  | 7  |
| Molecular function | Cytokine receptor binding          | TNFSF10, SPRED2, CXCL2, GH1, PPBP                                                                                                           | 5  |
| Molecular function | Transcription repressor activity   | ID2, HES1, DMAP1, HESX1, KCNIP3, DDIT3                                                                                                      | 6  |
| Molecular function | Protein N-terminus binding         | DCN, HESX1, TP53                                                                                                                            | 3  |
| Molecular function | Insulin-like growth factor binding | CTGF, CYR61                                                                                                                                 | 2  |
| Molecular function | Hormone receptor binding           | TRIP12, GH1, CCNE1                                                                                                                          | 3  |
| Molecular function | Transcription factor binding       | DMAP1, KCNIP3, TRIP12, CCNE1, DDIT3, RFXANK, TP53                                                                                           | 7  |
| Molecular function | Calcium-dependent protein binding  | KCNIP3, MGP                                                                                                                                 | 2  |
| Cellular component | Extracellular region               | CRB1, C3, OLFML2A, DCN, COL9A3, OLR1, MGP, TMPRSS2, EDN1, TNFSF10, C1R, CXCL2, GH1, INSL4, CTRB1, CTGF, CYR61, SERPINI1, CFHR4, LUZP2, PPBP | 21 |
| Cellular component | Extracellular region part          | CTRB1, C3, OLFML2A, DCN, COL9A3, CTGF, MGP, EDN1, TNFSF10, CXCL2, GH1, INSL4, PPBP                                                          | 13 |
| Cellular component | Extracellular space                | CTRB1, C3, MGP, EDN1, TNFSF10, CXCL2, GH1, INSL4, PPBP                                                                                      | 9  |
| Cellular component | Replication fork                   | DMAP1, TP53                                                                                                                                 | 2  |
| Cellular component | Cytosol                            | ABL2, MCM3AP, IDI2, KCNIP3, RPL28, SLC12A3, PFKL, ENO3, TP53, ID2, CCNE1                                                                    | 11 |
| Cellular component | Extracellular                      | OLFML2A, DCN, COL9A3, CTGF, MGP                                                                                                             | 5  |

|                    |                            |                                                      |   |
|--------------------|----------------------------|------------------------------------------------------|---|
|                    | matrix                     |                                                      |   |
| Cellular component | Cytosolic part             | RPL28, PFKL, ENO3                                    | 3 |
| Cellular component | Vesicle                    | CAMKV, SPRED2, SLC12A3, SYNGR3, PPBP, SREBF1, GPR120 | 7 |
| Cellular component | Chromosomal<br>part        | ID2, HIST2H2BE, DMAP1, HIST1H2AD, TP53               | 5 |
| Cellular component | Large ribosomal<br>subunit | RPL28, MRPL13                                        | 2 |