

**Table S1.** The 25 most relevant pathways from Reactome database sorted by p-value.

| Upregulated in 3D secretome |   |         | Downregulated in 3D secretome   |          |
|-----------------------------|---|---------|---|----------|
| No.                         | Pathway name  | p-value | Pathway name  | p-value  |
| 1                           | Retinoid metabolism and transport   | 2.73E-4 | Extracellular matrix organization   | 5.29e-13 |
| 2                           | Metabolism of fat-soluble vitamins  | 3.52E-4 | Degradation of the extracellular matrix   | 3.66e-09 |
| 3                           | Plasma lipoprotein assembly   | 1.37E-3 | Syndecan interactions   | 1.31e-08 |
| 4                           | Retinoid metabolism disease events  | 2.84E-3 | Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs) | 4.25e-08 |
| 5                           | Visual phototransduction  | 2.88E-3 | ECM proteoglycans   | 6.19e-08 |
| 6                           | Post-translational protein phosphorylation  | 3.48E-3 | Post-translational protein phosphorylation  | 4.54e-07 |
| 7                           | Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs) | 5.24E-3 | Non-integrin membrane-ECM interactions  | 6.11e-07 |
| 8                           | Formation of Fibrin Clot (Clotting Cascade)   | 5.57E-3 | Assembly of collagen fibrils and other multimeric structures  | 7.19e-07 |
| 9                           | Defective SLC40A1 causes hemochromatosis 4 (HFE4) (macrophages)   | 5.67E-3 | Collagen degradation  | 9.09e-07 |
| 10                          | Defective CP causes aceruloplasminemia (ACERULOP)   | 5.67E-3 | Platelet degranulation  | 1.28e-06 |
| 11                          | Regulation of Complement cascade  | 6.63E-3 | MET activates PTK2 signaling  | 1.52e-06 |
| 12                          | Complement cascade  | 8.21E-3 | Response to elevated platelet cytosolic Ca <sup>2+</sup>  | 1.59e-06 |
| 13                          | Alternative complement activation   | 1.41E-2 | Hemostasis  | 2.17e-06 |
| 14                          | Loss of proteins required for interphase microtubule organization from the centrosome                                       | 1.65E-2 | Activation of Matrix Metalloproteinases   | 2.21e-06 |
| 15                          | Loss of Nlp from mitotic centrosomes  | 1.65E-2 | Collagen formation  | 4.75e-06 |
| 16                          | PTK6 promotes HIF1A stabilization   | 1.69E-2 | MET promotes cell motility  | 5.18e-06 |
| 17                          | Metabolism of vitamins and cofactors  | 1.71E-2 | Platelet activation, signaling and aggregation  | 6.61e-06 |
| 18                          | AURKA Activation by TPX2  | 1.79E-2 | Signaling by MET  | 6.97e-05 |
| 19                          | Plasma lipoprotein assembly, remodeling, and clearance  | 1.79E-2 | Integrin cell surface interactions  | 8.80e-05 |
| 20                          | Cilium Assembly   | 1.95E-2 | Interleukin-4 and Interleukin-13 signaling  | 2.43e-04 |
| 21                          | Activation of C3 and C5   | 1.97E-2 | Collagen chain trimerization  | 2.49e-04 |
| 22                          | Centrosome maturation   | 2.23E-2 | Signaling by Receptor Tyrosine Kinases  | 5.57e-04 |
| 23                          | Recruitment of mitotic centrosome proteins and complexes  | 2.23E-2 | Collagen biosynthesis and modifying enzymes   | 8.43e-04 |
| 24                          | Transport of fatty acids  | 2.25E-2 | Crosslinking of collagen fibrils  | 0.001    |
| 25                          | HDL assembly  | 2.25E-2 | Cell-extracellular matrix interactions  | 0.001    |