Additional file 3

**Additional file 3.** Original evidence for the depicted connections for “Blood and coagulation system”.

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| **Source** | **Relation** | **Target** | **Original Evidence** | **PMID** | **Resource** |
| COVID-19 | Decreases | Albumin | **Albumin** concentrations were significantly lower in deceased patients than in recovered patients. | 32217556 | COVID-19 KG |
| Albumin | Decreases | Heme | Serum **albumin** (SA) can act as the heme scavenger by  forming **heme**-SA complex [2, 4–8]. | 30324533 | Heme KG |
| COVID-19 | Increases | Ferritin | Levels of lactate dehydrogenase (LDH), concentrations of serum high-sensitivity C-reactive protein (hsCRP), **ferritin** and D-dimer levels were markedly higher in severe cases than moderate cases. | 32217835 | COVID-19 KG |
| Heme | Increases | Ferritin | In agreement with the electrical cell–substrate impedance sensing data described above, the proteome changes triggered by 10 μM **heme** were indicative of an adaptive response with prominent induction of HMOX1 and **ferritin** light (FTL) and heavy (FTH1) chains. | 26794659 | Heme KG |
| COVID-19 | Decreases | Plasminogen activation | Figure 2. GO-term and KEGG pathway enrichment of up-regulated expressed genes in BALF and PBMC of COVID-19 patients. [figure content] | 32228226 | COVID-19 KG |
| COVID-19 | Decreases | Platelet count | Remarkable abnormalities in the CBC were detected on January 29, including increased neutrophils (10.67×109/L), leukocytes (11.73×109/L), and decreased lymphocytes (0.51×109 /L), and on February 4 decreased erythrocytes (2.40×1012/L) and **platelets** (73×109 /L). | 32196678 | COVID-19 KG |
| Heme | Increases | Platelet aggregation | Heme induces platelet activation and aggregation through different pathways | 26875449 | Heme KG |
| Heme | Decreases | Fibrin | From another perspective, in vitro assays have demonstrated that **heme** can also bind to fibrinogen and decrease its thrombin-mediated cleavage, thus affecting the final common coagulation pathway and reducing **fibrin formation**, important in clotting (Figure 1). | 26875449 | Heme KG |
| Fibrin | Increases | Hemoglobin | During DIC, **fibrin** strands within the fibrin mesh formed could cut red blood cells, resulting in the formation of schistocytes (strongly deformed red blood cells or fragments of red blood cells) and the release of **hemoglobin**. | 29956069 | Heme KG |
| Hemoglobin | Increases | Heme | Toxicity of free **hemoglobin** is also caused by the release of cell-free **heme**, which produces lipid peroxidation and mitochondrial damage and increases the production of reactive oxygen species. | 27515135 | Heme KG |
| Hemoglobin | Increases | Platelet aggregation | When RBCs are damaged by high shear in continuous flow ventricular assist devices, free **hemoglobin** induces **platelet aggregation**, contributing to high risk of thrombotic complications. | 28458720 | Heme KG |