Additional file 2

**Additional file 2.** Original evidence for the depicted connections for “Immune Response – Complement system”.

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| **Source** | **Relation** | **Target** | **Original Evidence** | **PMID/doi** | **Resource** |
| COVID-19 | Increases | C3 | **C3** activation products (C3 fragments C3a, C3b, iC3b, C3dg, and C3c) were detected by Western blotting in lung tissue of SARS-CoV MA15-infected mice, but not in control mice, as early as 1 day post infection (dpi) (Fig. 1B), confirming that SARS-CoV MA15 infection activates the complement pathway. | 30301856 | COVID-19 KG |
| Heme | Increases | C3 | Furthermore, the incubation of serum or whole blood with **heme** induces deposition of activation fragments (C3b, iC3b, C3dg) of **complement component 3** (C3) at the surface of erythrocytes | 26875449 | Heme KG |
| COVID-19 | Increases | Comple-ment activation | C3 activation products (C3 fragments C3a, C3b, iC3b, C3dg, and C3c) were detected by Western blotting in lung tissue of SARS-CoV MA15-infected mice, but not in control mice, as early as 1 day post infection (dpi) (Fig. 1B), confirming that SARS-CoV MA15 infection **activates the complement pathway**. | 30301856 | COVID-19 KG |
| Heme | Increases | Comple-ment activation | Hemolytic diseases are often accompanied by dysregulation and **overactivation of the complement system** [72–74], which may be induced by free extracellular **heme**. | 26875449 | Heme KG |
| COVID-19 | Increases | Neutrophil activation | The common clinical manifestations of fever and cough in conjunction with laboratory results of progressively increasing neutrophil counts and leukocytopenia in serum samples taken from **COVID-19** patients at various stages of the illness indicates uncontrolled **neutrophil** extravasation and **activation**. | 10.1101/2020.03.31.019216 | COVID-19 KG |
| Heme | Increase | Neutrophil activation | **Heme-induced neutrophils activation** leads to extracellular traps (NETs) release through a mechanism dependent on ROS generation. | 24904418 | Heme KG |
| Heme | Increases | C5a | C3a and **C5a** anaphylatoxins, as well as the soluble membrane attack complex (sC5b9), are generated by incubation of **heme** with human serum or blood in vitro, via the alternative complement pathway). | 26875449 | Heme KG |