POSTER - SYSTEMS BIOLOGY AND MODELING

INTEGRATIVE NETWORK MODELING REVEALS CROSSTALK BETWEEN RAAS, MHC, AND COAGULATION IN COVID-19-ASSOCIATED THROMBOSIS

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Since the onset of COVID-19 pandemic, several studies have reported a strong association between SARS-CoV-2 infection and coagulopathies, such as stroke, pulmonary embolism, and disseminated thrombosis. These complications have been linked to the interaction between viral Spike protein and ACE2, which disrupts vascular integrity and renin–angiotensin–aldosterone system (RAAS). Exploring these molecular effects—along with immune pathways like the major histocompatibility complex (MHC)—through protein interaction networks may uncover key regulatory hubs involved in COVID-19-induced coagulopathies. Thus, this study aims to evaluate the potential molecular pathways involved in coagulopathies development of patients infected with SARS-CoV-2. For this purpose a protein–protein interaction (PPI) analysis was performed using STRING v11.5, focusing on key proteins (AGT, HLA-A/B, F2, F3, F10, VWF) related to RAAS, MHC, and coagulation. Networks were built with high-confidence interactions (score ≥ 0.900), excluding text mining data. Modules were grouped by functional roles in inflammation, coagulation, and immunity.

Furthermore, a visual modeling was done using CellDesigner 4.4.2. Additionally, a literature review (2020–2024) was conducted to support proposed model validation and to functionally classify interactions identified through the PPI analysis. The expanded PPI analysis centered on key proteins from RAAS, MHC, and coagulation cascade revealed functional connections among these pathways, suggesting a possible molecular basis for coagulopathies observed in COVID-19. From the sixth interaction layer onward, integration between these systems became evident, highlighting shared nodes involved in immune regulation, vascular homeostasis, and thrombosis. Notably, proteins such as AT1R and ACE2 emerged as key molecular components integrating hemodynamic regulation, immune activation, and coagulation, reinforcing their potential role in thrombotic complications pathogenesis observed in COVID-19, while Protein C (PROC) emerged as a relevant mediator between RAAS and coagulation components. Moreover, the proposed model illustrates how SARS-CoV-2 binding to ACE2 reduces the formation of angiotensin 1-7, leading to the accumulation of angiotensin II, endothelial injury, and thrombin activation. Simultaneously, viral replication triggers antigen presentation via MHC, promoting T cell activation and cytokine storm (e.g., TNF-α, IL-2, IFN-γ). This exacerbates endothelial damage, reduces activation of Protein C through thrombomodulin and EPCR pathways, and enhances tissue factor exposure, collectively favoring coagulation. These interactions suggest that the convergence of hemodynamic imbalance, immune dysregulation, and impaired anticoagulant response may drive severe thrombotic outcomes during SARS-CoV-2 infection. In conclusion, this study's originality is highlighted by the graphical and interactive modeling of the proposed mechanisms, constructed using Systems Biology Graphical Notation (SBGN) in CellDesigner. The findings reveal connections between the RAAS, MHC, and the coagulation cascade, suggesting that these pathways, previously studied independently, may act in a coordinated manner in COVID-19 pathophysiology. Thus, our data reinforces the importance of integrative and multidisciplinary approaches to understanding COVID-19-associated coagulopathy, contributing to the advancement of therapeutic strategies aimed not only at containing the virus but also at mitigating its severe systemic consequences. Altogether, the proposed model offers a valuable framework for future experimental validation and may support the development of targeted interventions to reduce thrombotic risk in COVID-19 and related inflammatory conditions.

Palavras-chave: covid-19; ace2; coagulopathy; string.