THE USE OF AI AND ADVANCED COMPUTER SYSTEMS TO DEVELOP DRUGS AGAINST NEW EMERGING THREATS

In Silico Modeling to Repurpose FDA-approved Drugs For Treating Sepsis

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Exposure to mass casualty events often leads to the development of secondary sepsis from endogenous and exogenous organisms. During sepsis, systemic inflammation activates microvascular endothelial cells resulting in alterations in the barrier properties of endothelium leading to increased permeability and excessive recruitment of leukocytes, key elements in the development of acute vascular endothelial cell damage and dysfunction, often leading to multiple organ failure and death. All of the ~150 drugs recently developed in animal models to treat sepsis have failed in clinical trials and currently there are no therapeutics available for the treatment of sepsis. Therapeutic development is hindered because of the heterogeneous nature of the disease and the presence of multiple immune phenotypes that can impact function and response to therapeutics. To characterize immune phenotypes in sepsis patients, we used our novel micophysiological system (organ-on-chip). Based on ex vivo neutrophil adhesion and migration patterns across human lung microvascular endothelial cells, we identified three distinct neutrophil functional phenotypes in ICU sepsis patients (n=45 sepsis patient vs. n=7 healthy subjects): Hyperimmune patients had increased neutrophil adhesion and migration; Hypoimmune patients had deceased neutrophil adhesion and migration; Hybrid patients had increased neutrophil adhesion but decreased migration. These functional phenotypes were associated with distinct proteomic signatures and differentiated sepsis patients by important clinical parameters related to disease severity. Based on these results, we developed an in silico model integrating a synergistic combination of our novel organ-on-chip system incorporating patient cells, omic analysis and clinical data from sepsis patients to characterize relevant signaling pathways and identify immune phenotypes in patients. Employing our novel in silico model, we have leveraged these findings to identify FDA-approved drugs/small molecules that can therapeutically target the differential expressed proteins within and across three identified phenotypes. Additionally, network analysis was employed to prioritize these proteins, offering valuable insights into potential therapeutics warranting further investigation in sepsis research. Approximately 40 approved drugs/small molecules (or analogs of the small molecule or drug) targeting the druggable proteins were found to be associated with sepsis and/or neutrophil adhesion/migration. From these 40 drugs, three drugs were uniquely associated with the upregulated proteins in the Hypoimmune phenotype, two drugs were uniquely associated with the upregulated proteins in the Hybrid phenotype and one drug was uniquely associated with the upregulated proteins in the Hyperimmune phenotype. Druggable proteins that were a) unique to each phenotype, b) classified as hubs within each phenotype and c) targeted by approved antagonists included Isocitrate Dehydrogenase (NAD(+) 3 Catalytic Subunit Alpha (IDH3A - Hybrid), Cytochrome B5 Reductase 3 (CYB5R3 - Hypoimmune) and Palmitoyl-Protein Thioesterase (PPT1 - Hyperimmune). The novel methodology developed in this study not only outlines enriched pathways/processes within and across neutrophil functional phenotypes in sepsis but also identified those targets, and associated drugs, that should be prioritized for future validation. Furthermore, this in silico model will help repurpose current FDA-approved drugs for treatment of sepsis in a patient specific manner, thus enabling precision medicine.

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