BITS :: Call for Abstracts 2021 - Oral communication

Type	Oral communication
Session	Bioinformatics challenges in the SARS-Cov-2/COVID-19 pandemic
Title	A Resource for the Network Representation of Cell Perturbations Caused by SARS-CoV-2 Infection.
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Motivation

The coronavirus disease 2019 (COVID-19) pandemic has caused more than 3 million casualties worldwide and the lack of effective treatments is a major health concern. The development of targeted drugs is held back due to a limited understanding of the molecular mechanisms underlying the perturbation of cell physiology observed after viral infection. Recently, several approaches, aimed at identifying cellular proteins that may contribute to COVID-19 pathology, have been reported. Albeit valuable, this information offers limited mechanistic insight as these efforts have produced long lists of cellular proteins, the majority of which are not annotated to any cellular pathway. Our project aimed at bridging this mechanistic gap by developing a new bioinformatic approach to estimate the functional distance between a subset of proteins and a list of pathways.

Methods

The curation process consisted in the systematic search of articles containing signaling information on the molecular mechanisms triggered by SARS-CoV-2, SARS-CoV-1, and Middle East Respiratory Syndrome (MERS) viral infections, and on their impact on cellular phenotypes. The selected information was organized into nine cellular pathways that are the most relevant to describe cellular functions that are modulated by viral infection. The cellular pathways modulated in COVID-19 disease are available in a dedicated SIGNOR 2.0 webpage (https://signor.uniroma2.it/covid/).
To define the functional proximity of any protein in the proteome to a pathway, we make use of the graph representation of the causal network annotated in SIGNOR 2.0. We define the distance (d) between any two connected nodes as $d = 1 - s$ and the length (L) of a path including more than two nodes as the sum of the distance of the edges forming the path. Next, we define a global distance (GD), or proximity (P) between a query protein and a pathway, by considering the paths between the query protein and all the proteins in the pathway. In addition to distance, we associate to each protein pathway pair an empirical p-value estimated by calculating the distance of all the proteins in SIGNOR 2.0 from the considered pathway. Proteins that connect to the pathway with a p-value lower than a given threshold ($p\text{-value} \leq 0.01$) are associated with the pathway.

Results

A comprehensive literature search allowed us to annotate, in the SIGNOR 2.0 resource, causal information underlying the main molecular mechanisms through which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and related coronaviruses affect the host-cell physiology. Next, we developed a new strategy that enabled us to link SARS-CoV-2 interacting proteins to cellular phenotypes via paths of causal relationships.
Our strategy is general and can be applied to hit lists from any functional screening. Importantly, the proposed approach is independent from the expert decision of assigning a protein to a pathway or not. Once one chooses some key pathway-proteins, all the remaining proteins in the cell causal network can be assigned a score that estimates its functional proximity to the pathway. Thus, our strategy makes it possible to identify a larger number of proteins whose activity may modulate a pathway as compared with standard GSEA methods.

Remarkably, the extensive information about inhibitors of signaling proteins annotated in SIGNOR 2.0 makes it possible to formulate new potential therapeutic strategies. The proposed approach, which is generally applicable, generated a literature-based causal network that can be used as a framework to formulate informed mechanistic hypotheses on COVID-19 etiology and pathology.

Info	
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Figure	
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Availability	-

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