Systems Biology Research Symposium
Oral Presentation Session

Grand Ballroom
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Identification of Alternative Routes Circumventing HIV-1 Targeted Pathways in Human Signal Transduction Networks

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Human immunodeficiency virus-1 (HIV-1) is the causative agent for acquired immunodeficiency disease (AIDS), a world-wide epidemic that according to statistics from the world health organization has resulted in more than 2 million deaths; 33 million people are living with HIV, including 2 million at the age of 15 years and under. While current antiviral medication has dramatically improved the life expectancy of AIDS patients, the medicines are not available to everyone and drug resistance and side effects are increasingly recognized problems. Thus, novel avenues to anti-HIV-1 drug discovery are needed. One such avenue is systems biology. The virus has a minimal genome of only 9 genes, which encode for some 15 proteins, and thus depends on the human host for virtually every aspect of its life cycle. The universal language of communication in biological systems, including between pathogen and host, is via signal transduction pathways. The fundamental unit of these pathways is protein protein interaction, and more than 2500 interactions between human and HIV-1 proteins have been reported in the literature and a global human,HIV-1 interactome map has been created via information integration of numerous features such as gene expression, domain and motif identification, tissue distribution, functional annotation, subcellular localization and human network features and HIV-1's mimicry of human protein binding partners. This global view in light of known signal transduction pathway maps suggested that probably the majority of known human pathways are targeted through at least one HIV,human protein interaction. Some pathways are targeted by HIV-1 by interaction with disproportionately many proteins, intercepting a single pathway at multiple positions. Based on the known redundancy of human protein interactions and signal transduction pathways, we propose the hypothesis that it should be possible to identify alternative paths circumventing those disrupted by HIV-1. Here, we present an in-depth analysis of the pathways targeted by HIV-1 with the goal of testing this hypothesis. For each pathway, we define simple paths between start points (i.e. no edges going into a node) and end points (i.e. no edges leaving a node). We then identify which of these paths are targeted by HIV-1 proteins, and find alternate paths to the same end points. We supplement the combined map with functional information, namely which proteins are known drug targets and/or showed an effect on HIV function in recent siRNA screens. This approach yields experimentally testable hypotheses on how HIV-1 function may be compromised by pharmacological approaches.

Key words: protein-protein interaction prediction, signal transduction pathways, HIV-1, drug discovery, classification, human interactome, network features