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A Systems Biology Approach to Influenza Infection: Boolean Modeling of Cellular and Molecular Pathways

Christopher S*

Department of Microbiology and Immunology, University of Rochester Medical Center, Rochester, USA

Abstract

Systems virology integrates host-directed approaches with molecular profiling to understand viral pathogenesis. Self-contained statistical approaches that combine expression profiles of genes with the available databases defining the genes involved in the pathways have allowed characterization of predictive gene-signatures associated with outcome of the influenza virus infection. However, such enrichment techniques do not take into account interactions among pathways that are responsible for the IV infection pathogenesis. Thus, this paper integrates pathway analysis tools with the dynamic modeling approaches to reveal the regulation between signaling pathways and transcription factors using genome-wide transcriptional profiles measured upon influenza infection.

Keywords: Pro-apoptotic factors; Intracellular interactions; Immune cell activation; Particular influenza virus

Introduction

Genome-wide transcriptional profiling studies have been instrumental in measuring large-scale changes in the host upon viral infections. Pathogenic viruses, in particular influenza virus (IV), frequently cause mild respiratory disease. Influenza, commonly known as the flu, is a highly contagious respiratory illness caused by the influenza virus. The virus infects millions of people worldwide each year, resulting in significant morbidity and mortality [1]. Understanding the intricate cellular and molecular pathways involved in influenza infection is crucial for developing effective prevention and treatment strategies [2]. Combining these high-throughput data with the computational techniques, particularly the ones embedded in the theory of dynamical systems, improves our understanding about the emergent properties of the system that are clinically relevant. Dynamic models can bridge this gap by integrating the static network with a mathematical framework to describe the status of the system over time. Qualitative approaches such as discrete dynamic modeling can be developed for large systems even when knowledge of kinetic parameters is limited. Hence, they are ideal for understanding system-wide high-throughput assays. Particularly, Boolean networks have been used for modeling cellular and intracellular interactions relevant to immunology [3].

Methods

Boolean modeling and influenza infection

It represents biological entities, such as genes, proteins, and signaling molecules, as discrete variables that can exist in one of two states: active or inactive [4]. The interconnections between these variables are described using logical rules, which determine their activation or inhibition in response to various stimuli. By simulating the dynamic changes in the state of these variables over time, Boolean models can reveal the underlying mechanisms and dynamics of cellular and molecular pathways [5].

Cellular and molecular pathways in influenza infection

Influenza infection involves complex interactions between the virus and host cells. Understanding the key pathways involved in viral entry, replication, immune response, and host cell survival or death is critical for developing targeted therapeutic interventions. Boolean modeling offers a powerful approach to dissect these pathways and explore their dynamics in response to influenza infection [6].

Viral entry and replication

Boolean models can simulate the interactions between influenza virus and host cell receptors, which mediate viral entry. The activation or inhibition of specific receptors can be modeled, allowing for the exploration of factors that influence viral attachment, fusion, and endocytosis [7].

Immune response

Influenza infection triggers a complex immune response involving various cell types and signaling molecules. Boolean models can capture the interplay between pro-inflammatory and anti-viral pathways, such as the activation of pattern recognition receptors (PRRs), cytokine signaling, and immune cell activation. By integrating experimental data, these models can predict the activation or inhibition of specific immune response components, helping to identify key factors that determine the outcome of infection, such as viral clearance or immune dysregulation [8].

Host cell survival and death

Boolean modeling can shed light on the cellular pathways that determine the fate of infected host cells. It can simulate the activation or inhibition of pro-survival and pro-apoptotic factors [9]. By investigating the dynamics of these pathways, the models can provide insights into the mechanisms underlying cell survival, apoptosis, or necrosis in response to influenza infection. The construction of accurate models relies on high-quality experimental data and knowledge of pathway interactions. Obtaining such data can be time-consuming and

***Corresponding author:** Christopher S, Department of Microbiology and Immunology, University of Rochester Medical Center, Rochester, USA, E-mail: Christopher922@gmail.com

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technically demanding [10].

Conclusion

This was accomplished by integrating known information on the interactions between pathways to reduce the dimension of genome-wide transcriptional profiles. To our knowledge this is a first study integrating gene-set enrichment methods with dynamic modeling. Furthermore, the simplifications inherent in Boolean modeling may overlook the continuous nature of cellular processes and the fine-grained regulation of gene expression. Therefore, model refinement and validation with experimental data remain crucial for enhancing Development of a dynamic Boolean model reveals an operational network with underlying logic rules, and we experimentally validated the logic rule governing regulation. Despite the limitations of these experiments, the data can be utilized to elucidate the relationships among cell death, viral replication, and inflammatory responses. By contrast, one study showed that although the host protein CEACAM6 promotes cell survival, it also enhances viral replication. It is unclear why these in vitro cell assays have yielded paradoxical results; however, these contradictions may be related to the differences in the influenza viral strains used, infection times, and infection dosages in the testing regime. More scientifically rigorous methodologies must be developed to address this issue.

Moreover, analyses of clinical cases may provide some insights. A recent study of fatal cases of IAV infection revealed diffuse alveolar damage and cell death, providing insights into the relationships between cell death and disease prognosis. Importantly, cytokine storm has also been shown to be closely associated with cell death. In addition to cytokine storm in IAV infection, this phenomenon has also been observed in severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus, and SARS-CoV-2 infections and has been shown to be associated with disease severity and mortality. Accordingly, these findings suggest that excessive cell death may cause serious severe tissue damage and hypercytokinemia.

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