ABSTRACT

The innate immune system provides the first line of defense against virus infection. During virus infection, the transcription factor interferon (IFN) regulatory factor 3 (IRF3) gets activated to transcribe the antiviral genes, type I IFN (e.g. IFNβ) and the interferon stimulated genes (ISGs). The ISGs contribute to host defense by restricting virus replication at multiple stages of the virus life cycle. Additionally, we have uncovered another antiviral role for IRF3 as a mediator of a host apoptotic pathway, RIG-I-like receptor induced, IRF3-mediated pathway of apoptosis (RIPA), which protects the host from persistent infection. We hypothesize RIPA may provide an alternative cellular target in scenarios where the virus suppresses IFN production and signaling. In our study, our aim was to identify small molecule regulators of IRF3 that can be used to treat viral and non-viral diseases. We conducted a high-throughput screen of FDA-approved compounds to identify small molecule regulators of IRF3's apoptotic function. We isolated the drugs doxorubicin and pyrvinium pamoate from the primary screen and tested the hypothesis that RIPA-activators can function as antiviral agents. The screen was expanded to isolate inhibitors that could be therapeutic in diseases where IRF3 activity is detrimental to the host. We identified auranofin as a small molecule that negatively regulated both transcriptional and RIPA branches of IRF3 activity. In this study, we describe the translational potential of our RIPA-modulating drugs.

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Anna Glanz

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PRESENTATIONS

Glanz A., Chawla K., Fabry S., Gartland J., Jay B., Taylor T., and Chattopadhyay S. Midwest Virology Symposium, The Ohio State University, Columbus, OH, October 2019. (Flash Talk and Poster Presentation - Selected Abstract)

Chawla K., **Glanz A.**, Fabry S., Subramanian G., Altarshan D., Rahman T., Varghese M., Steimle G., Taylor T., and Chattopadhyay S. Midwest Microbial Pathogenesis Conference, Toledo, OH, September 2019. (Poster Presentation)

Subramanian G., **Glanz A**., Popli S., Chakravarty S., and Chattopadhyay S. Midwest Microbial Pathogenesis Conference, Toledo, OH, September 2019. (Poster Presentation)

PUBLICATIONS

Glanz A, Chawla K, Fabry S...Chattopadhyay S. High Throughput Screening of FDA-Approved Drug Library Reveals the Compounds that Promote IRF3-Mediated Pro-Apoptotic Pathway Inhibit Virus Replication. Viruses. 2020;12(4):442. Published 2020 Apr 14. doi:10.3390/v12040442

Glanz A, Chawla K, Subramanian G...Chattopadhyay S. Novel regulators of IRF3-mediated innate immune signaling pathways. Manuscript in preparation.

Glanz A, Chakravarty S... Chattopadhyay S. Interferon regulatory factor 3 (IRF3): activation and antiviral functions. Manuscript in preparation.

FUTURE PLANS

Anna is currently interviewing for positions in the medical research and biotechnology industries.

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