ABSTRACT

.Sepsis is a process of severe immune dysregulation resulting from pathogenic disruption of immune homeostasis, leading to damage of multiple organ systems and high mortality. Case-fatality rates range from 10% to 60% or higher, with $24 billion spent yearly on sepsis in the United States alone. In addition, organ damage and continued immune insufficiency require hospital readmission in nearly 50% of severe sepsis survivors within 6 months. Current symptomatic treatments, while effective to a certain degree even in cases of severe sepsis, do not address the mechanisms of sepsis or prevent complications in survivors. Immunosuppressive treatments also fail to address the dysregulation that causes sepsis, and may increase the rate of metabolic and cardiovascular issues after treatment is completed. Utilizing a novel drug-screening method, we have found that retinoic acid (RA) significantly upregulates the anti-inflammatory protein MAP kinase phosphatase 1 (MKP-1). Our experiments show that RA has significant beneficial effects on both sepsis and endotoxemia. RA, which is used to treat diverse diseases due to its ability to re-regulate the immune system, significantly reduces morbidity and mortality of early sepsis in two mouse models. RA, when administered in a true bacterial sepsis model, significantly reduces mortality by 75% in mice, and significantly reduces both visible lung damage and neutrophil infiltration into the lungs. Levels of pro-inflammatory cytokines are reduced in mouse organs and serum, indicating systemic pro-regulatory effects. In addition, RA significantly reduces pro-inflammatory cell signaling, downregulating the transcription, translation, and/or translocation into the nucleus of pro-inflammatory proteins in human and mouse cells. While the mechanisms of these effects are as yet unknown, we hypothesize that RA functions through binding to MKP-1 and other regulatory proteins, and thus exerts anti-inflammatory and pro-differentiation effects on all stages of sepsis. Previous studies have indicated that RA induces a proliferation of adaptive immune cells that are protective during states of immunosuppression, which may allow a comprehensive protective effect in combination with its immunosuppressive effects in early sepsis. Further experiments are necessary to confirm if RA is a feasible treatment for sepsis caused by diverse pathogens in human patients, and to fully elucidate its mechanisms of action. However, should our results hold true upon clinical testing, RA may be a valuable addition to the current standards of sepsis treatment, and may both protect patient lives and free up manpower and financial resources for the healthcare system at large.

COLLEGE OF MEDICINE AND LIFE SCIENCES
THE UNIVERSITY OF TOLEDO

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1872

DISSERTATION PRESENTATION
by

Hallie Hanna Dolin

April 7th, 2020

Retinoic acid as a regulator of native inflammatory processes is a potential novel sepsis treatment

Ph.D. in Biomedical Sciences

AWARDS/ LEADERSHIP

2019—Awarded Travel Award by the International Shock Society to present at the 42nd International Conference on Shock, June 8-11.

2019—Awarded Best Poster Award by the Association for Women in Science—Northwest Ohio (AWIS-NWO), Midwest Graduate Research Symposium, April 6th, 2019.

2018-2019—College of Medicine and Life Sciences Representative, University of Toledo Graduate Student Association

PUBLICATIONS

Dolin HH, Papadimos TJ, Stepkowski S, Chen X, Pan ZK: A novel combination of biomarkers to herald the onset of sepsis prior to the manifestation of symptoms. *Shock* 49(4): 364-370, **2018**. *1 of 3 Editor's Choice articles from 14 total in the issue*.

Dolin HH, Papadimos TJ, Chen X, Pan ZK. Characterization of pathogenic sepsis etiologies and patient profiles: a novel approach to triage and treatment. Accepted by *Microbiology Insights* **17 Dec 2018**; published online **27 Jan 2019.** https://doi.org/10.1177/1178636118825081

Dolin HH, Dziuba M, Pappada SM, Papadimos TJ. Presumed antiphospholipid syndrome and thrombotic thrombocytopenic purpura: An infrequent association. *Clinical Case Reports* 9 September 2019. https://doi.org/10.1002/ccr3.2416

Dolin HH, Chen X, Pan ZK. Retinoic acid-induced regulation of native inflammatory pathways is a potential novel sepsis treatment. Manuscript in preparation; to be submitted to *Shock*.

FUTURE PLANS

Hallie plans to complete her MD and specialize in pathology, with an aim towards translational medicine.

PRESENTED ABSTRACTS

Dolin HH, Chen X, Pan ZK. Retinoic acid as inducer of MAP kinase phosphatase 1 (MKP-1) is a potential novel treatment for sepsis. Presented **7 April 2018**, Midwest Graduate Research Symposium, Toledo, OH.

Dolin HH, Dziuba M, Papadimos TJ. A Rare Case of SLE-Induced Antiphospholipid Syndrome Leading to TTP. Presented **28 July 2018**, Academic International Medicine Conference 2018.

Dolin HH, Chen X, Pan ZK. Retinoic acid-induced downregulation of native inflammatory pathways is a potential novel sepsis treatment. Presented 6 April 2019, Midwest Graduate Research Symposium, Toledo, OH.

Dolin HH, Chen X, Pan ZK. Retinoic acid-induced downregulation of native inflammatory pathways is a potential novel sepsis treatment. Presented 11 June 2019, 42nd International Conference on Shock, Coronado, CA.