Role of Herpesviruses dUTPases in the immune dysregulation associated with myalgic encephalomyelitis/chronic fatigue syndrome and Gulf war illness

Maria Eugenia Ariza[1,2], Marshall V Williams[1,2], Brandon Cox[2] and **Conner Nealer[2]**
[1]Wexner Medical Center - The Ohio State University, USA
[2]Institute for Behavioral Medicine Research, USA

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and Gulf war illness (GWI) are debilitating diseases presenting with complex immune, endocrine and neurological symptoms. Annual health care costs are estimated at $24 billion. Diagnosis is based on exclusion and there are currently no validated tests for definitive diagnosis of either syndrome. While there is accumulating evidence supporting the premise that some herpesviruses may act as possible triggers in ME/CFS, the mechanism by which they contribute to the pathogenesis of ME/CFS remains unclear. Our studies are the first to demonstrate that the deoxyuridine triphosphate nucleotidohydrolase (dUTPase) encoded by the human herpesviruses represents a new class of pathogen-associated molecular pattern (PAMP) proteins, which alter immune and neurocognitive functions. In this study, we demonstrate that ME/CFS and GWI patients' sera exhibit reactivation of multiple herpesviruses, differential antibody expression patterns to the herpesviruses-encoded dUTPase early protein as well as increased autoantibodies to the human nuclear dUTPase. A significant increase in IL-21 levels was also observed in a cohort of ME/CFS patients. Interestingly, IL-21 is produced at high levels by CD4+ follicular helper T cell (TFH) and regulates germinal center (GC) B cell survival and plasma-cell differentiation. Further *in vitro* studies in primary human cells demonstrated that the EBV-dUTPase induced activin A secretion by dendritic cells, which lead to the increased formation of CD4+ follicular helper T cells (TFH) and subsequent production of IL-21 and CXCL13 by TFH. Our data suggest a role for the herpesviruses dUTPase proteins in the immune dysregulation and pathophysiology observed in these patients possibly by altering the GC reaction and antibody responses as well as inducing the production of pleiotropic cytokines. Thus, screening for the presence of anti-herpesvirus dUTPase antibodies in these patients may serve as useful diagnostic biomarkers for the selection of appropriate treatments.

Recent Publications

1. Saito T, Miyagawa K, Chen S Y, Tamosiuniene R, Wang L, Sharpe O, Samayoa E, Harada D, Grow E, Moonen J R, Cao A, Chen P I, Hennigs J K, Gu M, Li C G, Leib R D, Li D, Adams C M, del Rosario, P A, Bill M, Haddad F, Montoya J G, Robinson W H, Fantl W J, Nolan G, Zamanian R T, Nicolls M R, Chiu C Y, Ariza M E and Rabinovitch M (2017) Upregulation of HERV-K is linked to immunity and inflammation in pulmonary arterial hypertension. Circulation 136(20):1920-1935.
2. Halpin P, Williams M, Klimas N G, Fletcher M A, Barnes Z and Ariza M E (2017) Differential antibody patterns to the herpesviruses-encoded dUTPases in myalgic encephalomyelitis/chronic fatigue syndrome and Gulf war illness. Journal of Medical Virology 89:1636–1645.
3. Williams M, Cox B and Ariza M E (2017) Herpesviruses dUTPases: A new family of pathogen-associated molecular pattern (PAMP) proteins with implications for human disease. Pathogens DOI: 10.3390/pathogens6010002.
4. Young N A, Williams M V, Jarjour W N, Bruss M S, Bolon B, Parikh S, Satoskar A and Ariza M E (2016) Epstein-Barr virus (EBV) encoded dUTPase exacerbates the immune pathology of lupus nephritis *in vivo*. International Journal of Immunology and Immunotherapy 3(2):023.
5. Aubrecht T G, Weil Z M, Salloum B A, Ariza M E, Williams M, Reader B, Glaser R, Sheridan J and Nelson R J (2015) Chronic physical stress does not interact with Epstein-Barr virus (EBV) encoded dUTPase to alter the sickness response. J Behavioral Brain Science 5:513-523.

Biography

Maria Eugenia Ariza received her PhD degree in Medical Microbiology and Immunology and is currently a Research Assistant Professor in the Department of Cancer Biology and Genetics, College of Medicine, at The Ohio State University. She has a long-standing passion for understanding how viruses contribute to the pathophysiology of human diseases, specifically the role that the human herpesviruses and human endogenous retroviruses (HERVs) have in the development of autoimmune diseases and cancer. Her studies were the first to demonstrate that the dUTPases from the human herpesviruses and HERV-K represent a new class of pathogen-associated molecular pattern (PAMP) proteins, which contribute to the immune pathology associated with several immune-mediated diseases, including chronic fatigue syndrome (CFS), SLE, psoriasis and pulmonary arterial hypertension. Her studies have identified this family of viral dUTPases as potential disease biomarkers and provide novel molecular targets for the development of alternative therapeutic agents/interventions for CFS, SLE and psoriasis.

maria.ariza@osumc.edu

Notes: