

Transcriptomic Biomarkers of Fatal Immune Reconstitution Inflammatory Syndrome

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Abstract

Background: Cryptococcosis-associated IRIS (C-IRIS) affects 20% of HIV-infected patients with cryptococcal meningitis (CM) after they commence antiretroviral therapy (ART). It is often fatal. The goal this study is to identify transcriptomic biomarkers in peripheral blood that are associated with or predict the development of C-IRIS or death among patients with CM who were enrolled in the COAT Trial.

Results: We have identified twelve inflammatory immune pathways that were upregulated at baseline and predict fatal C-IRIS, including type 1 interferons, components of stress response kinases, and acute phase response signaling. The upregulation of biomarker transcripts involved in innate immunity (inflammasome and Toll-like receptor signaling), was observed at the time of the C-IRIS event in survivors' group, and many of these same transcripts were upregulated to even higher levels in fatal C-IRIS group. We have also found that patients who died from other causes, exhibited a trend to low expression of various HLA-, Th1- and Th2- pathway encoded genes, but upregulation of PD1/PDL1 and acute phase response molecules, which reflects severe immunosuppression, and poor antigen clearance. The effect of timing of ART initiation revealed that early ART initiation in C-IRIS survivors showed more dramatic proinflammatory gene expression shift than in C-IRIS survivors from deferred ART group, which may place patients at risk for the development of C-IRIS. At the time of fatal C-IRIS events, numerous transcripts within fMLP, Rho/GPCR, HMGB1 pathways were upregulated, as a result of severe systemic oxidative stress. These pathways are partially overlap between fatal C-IRIS and death no C-IRIS group.

Conclusions: Overactivated innate immune system via oxidative stress generated by activated neutrophils, in addition to TLR/inflammasome, lead to overexuberant inflammation and fatal outcome. This information may provide an insight into the molecular drivers of fatal C-IRIS and can inform future diagnostic tests developments or guide targeted treatments..

Keywords: Algae, Bacteria, Fungi, Microbes, Virus.

Biography:

Dr. St. Louis is appointed as an Assistant Professor at the Department of Medicine, University of Minnesota, USA. She

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disorders (IRD). Her primary research focuses on identification of biomarkers of immune reconstitution inflammatory syndrome (IRIS) in AIDS patients after initiation of antiretroviral therapy. Dr. St. Louis collaborates on several clinical trials, working on stratification of patients for optimal immunomodulatory treatment



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