Tracking Antiviral Responses Following Infection With Lassa Fever Virus

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Lassa Fever Virus

Lassa fever is severe hemorrhagic fever caused by the Lassa virus. It is estimated that Lassa virus infects more than 300,000 people per year in Western Africa and that it causes more than 3,000 deaths annually.

Its symptoms are often confused with those of other infections, such as Influenza which can delay proper care. The case fatality rate for hospital-admitted patients is approximately 15%, but in some cases has been reported to be greater than 50%. There are currently no effective therapies that can be offered to individuals infected with Lassa.

The confusing presentation of individuals infected with Lassa has driven considerable interest in developing better diagnostic tests. We were interested in determining whether analyzing the circulating immune system would allow us to identify "markers" of Lassa virus infection.

To test this hypothesis we investigated the gene expression patterns of cells that were extracted from Lassa infected animals over the course of infection.

Markers of Early Infection

The aim of the project is to identify a set of genes as possible biomarkers of early-stages of Lassa virus infection for subsequent experimental validation.

Acknowledgements

We thank Sara Garamszegi and Gary Benson for data analysis advice.

References

1. IPA, Ingenuity Systems, www.ingenuity.com

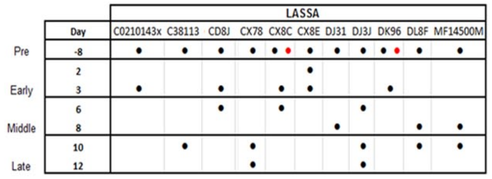
2. R Development Core Team (2010). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. http://www.Rproject.org/

3. Smyth, G. K. (2005). Limma: linear models for microarray data. Bioinformatics and Computational Biology Solutions using R and Bioconductor. R. Gentleman, V. Carey, S. Dudoit, R. Irizarry, W. Huber (eds), Springer, New York, pages 397--420

4. Zaas et al. (2009). Gene expression signatures diagnose influenza and other symptomatic respiratory viral infections in humans.

Experiment Design

We used Agilent microarrays to examine the gene expression levels in peripheral blood mononuclear cells (PBMCs) extracted from non-human primates at different stages of infection.



Samples taken at different stages of infection

PBMCs subtypes were als isolated and used for micrarray experiments.

PBMCs perform an important role in the immune response to infection and are easily extracted from human blood.

Analysis Pipeline

We used a linear regression model[2,3] to estimate the significance of the fold expression changes between the reference pre-infection samples and those obtained during early, middle and late stages of infection.

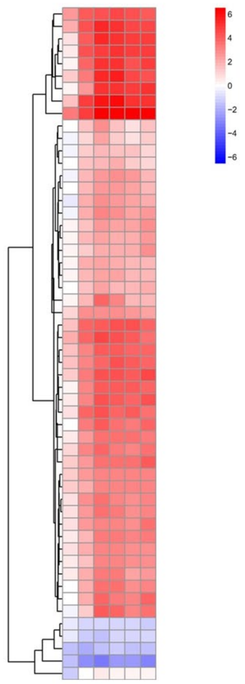
This gene set was further filtered to only include those genes whose expression appeared sustained during the intermediate stages of infection.

Top Differentially Expressed Genes

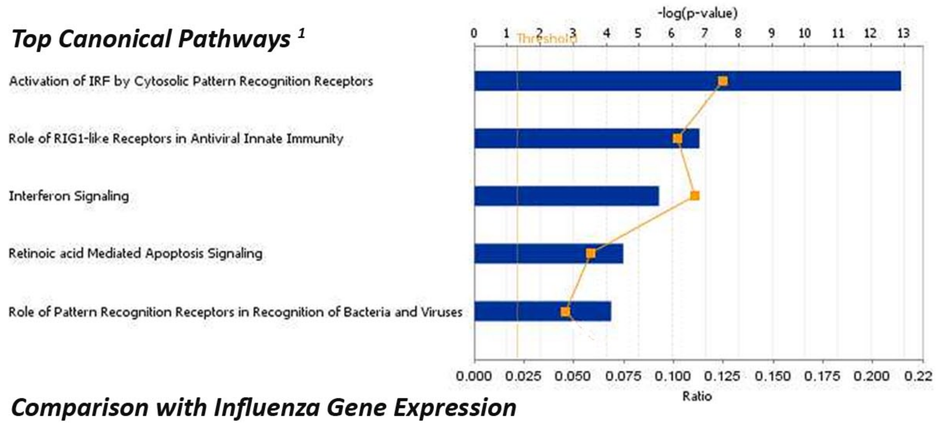
From this analysis we have identified a set of genes whose expression profiles in blood cells appear to be specific to Lassa infection.

Differentially expressed genes in PBMC may provide a reliable indicator of Lassa virus infection.

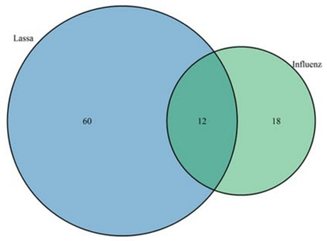
PBMC



Top Canonical Pathways [1]



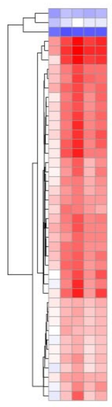
Comparison with Influenza Gene Expression



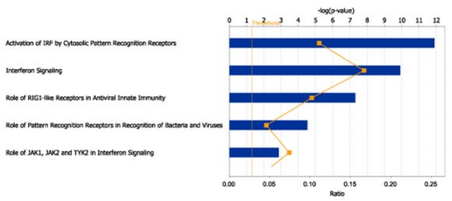
The top differentially expressed genes from our analysis were compared to a set of 30 genes reported to be characteristic of Influenza infection[4] There are several genes left that appear to be unique to Lassa, which makes them good candidates for markers

PBMC subtypes

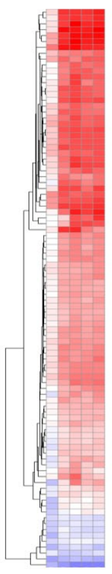
CD4



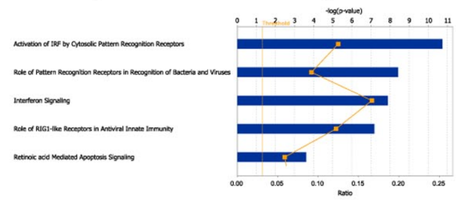
Top Canonical Pathways [1]



CD14



Top Canonical Pathways [1]



The analysis performed on the PBMC subtypes yields insight into the biological processes and supports the results obtained from the original dataset

We are currently carrying out experimental validation of their suitability as biomarkers of early-infection