Meta-analyses of Microarray Data Reveals Interferon Signaling is Top Canonical Pathway in HIV


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Abstract

Background:
Although many different studies have profiled gene expression for humans in response to HIV, most have been performed by only a single group or laboratory and suffer from a lack of generalizability of their results.

Methods:
In this work, we define robust gene signatures or specific patterns of gene expression for the human response to HIV phenotypes through two different meta-analyses. The first is a disease signature found in PBMCs for HIV versus control patients that consists of 24 series. The second is a signature in PBMCs for patients with an elite response to HIV versus patients with a standard response that consists of 5 series.

Results:
We have found interferon signaling to be the top canonical pathway with IFNA2 to be the top upstream regulator in HIV. We have also found that Myd88 is upregulated in HIV, but is not as upregulated in patients with an elite response. Related to this, we’ve found that TLRs 1, 2, 3, and 8 are all upregulated while TLRs 9 and 10 are downregulated in HIV and TLR5 and TLR7 are both expressed less in elite responders.

Conclusion:
Interferon has long been suspected as a potential treatment for HIV-infected patients, and our work support this hypothesis. The robust gene signatures we report here are a first step towards novel translational opportunities for better biomarkers and drugs for the disease.

Objectives

• To better characterize the pathways involved in the pathophysiology of AIDs in order to find better treatments and biomarkers.

• To better characterize the method of resistance in the patients that are elite responders

Background

While other studies have profiled the gene expression of the response to HIV in humans, they do not have the same sort of generalizability that meta-analyses allows. Much of this data is stored online in the Gene Expression Omnibus. This allowed us to generate a meta-analysis of the data in order to better characterize the expression of the response to HIV infection.

In addition, there is also a unique population of individuals who are known to respond to infection better than others. We also created a meta-analysis of these so called “elite-responders.”

Methods

Stargeo is a platform that was created to allow for easy searching and tagging of GEO. It allows non-computational researchers to find microarray data that fits the criteria and then perform meta-analyses of the data. Using this method, two sets of data were tagged. The first was HIV patients versus case-controlled healthy controls. The second set was patients that have an elite response to HIV versus patients that have a standard response to HIV.

Results

After the tagging process, the sets were analyzed against the controls to generate a signature.

The signature was then analyzed in IPA ingenuity to determine the pathway that is most heavily changed. In this case it was found to be Interferon. IFNA2 was found to be the top upstream regulator which was activated with a p value of 2.7 * 10^-12.

Conclusions

• Our data shows that Interferon is the top upstream regulator in HIV patients with IFNA2 being the top upstream activator

• TLR signaling is modified in elite responders of HIV as compared to standard responders