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Letter to Editor

Transcriptome Analysis May Be Beneficial for Identification of Specific Pathways in Host Cell-Leishmania major Interactions

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Dear Editor

There are several reports about the modulatory effects of intracellular pathogens, such as *Leishmania* spp., to help survival and replication inside host cells. They alter host cells' defense and offence mechanisms, and in case of leishmaniasis, the pathogen creates a hostile environment inside macrophages. We performed an RNA sequencing analysis of transcriptome changes in *Leishmania major*-infected human macrophages at four hour post infection. In this study, we investigated gene expression pattern of the infected macrophages against microbead (4.16 µm) polystyrene particles phagocytized and non-polarized macrophages as controls. Monocytes with high purity were isolated from healthy donors by magnetic-activated cell sorting and then differentiated into macrophages after 6-9 days of incubation at 37 ˚C.

In this study, we focused on some key interaction events between host cell and the pathogen; so some feature steps resulting from dictation strategies of the pathogen are presented below.

Keywords: Leishmania major, Gene Expression, Sequence Analysis, RNA.

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1. Regarding entry events (this pathogen selects some receptors as shown in previous in vivo studies), we analyzed complement-based components and other elements critical in host cell-pathogen interactions. Complement receptors 1 (CR1) and CR3 that have already been reported to be upregulated in animal models (1), were insignificantly upregulated in our study. As we supplemented inactivated complement AB plasma, there possibly was no need for the pathogen to alter these receptors, as in vivo models. C1q, C1r, and C1s (basic initiative elements of the complement system) were non-significantly downregulated. We found a complement element with critical biological activity in host cell–pathogen interactions. This can be an important *Leishmania* spp. modulation capacity and a target for drug design. This element codes for a critical protein that inhibits apoptosis in host cells. The product of this gene degrades complement basic elements to prevent formation of membrane attack complex.
2. Through phagolysosome formation, we determined specific identified and unidentified genes, and found a critical novel gene involved in host cell-pathogen interactions. This gene codes for a protein involved in vesicular trafficking that might be also involved in host cell defense dysfunction. We postulated that altered expression of this gene may cause a defect in lysosome-dependent degradation of the pathogen.
3. Regarding metabolic changes, we found how the pathogen modulates the metabolic changes, especially shifting the oxidative pathway towards the glycolytic pathway. This have already been reported in cancer (2). Perhaps this is one reason for the host immune cells' inability to function well in chronic diseases. In this regard, we also found a gene, which triggers the glycolytic pathway. We also found other genes responsible for the metabolic changes associated with the pathogen.
4. Antigen presentation capacity changes in macrophages were normal at four hour post infection, but some critical receptors were upregulated in this study that contribute to T-cell receptor degradation (3). This might be responsible for non-responsiveness of T-helper-1 cells in leishmaniasis and some other chronic diseases. Accordingly, we performed successful clinical trials for treating cutaneous leishmaniasis and some other chronic diseases. We also found some alterations related to regulatory T-cells that suppress T-helper 1 responses in such diseases (4).
5. We found that *L. major* activates anti-apoptotic mechanisms in infected macrophages. We detected two important genes that had already been reported in cancer.
In summary, we believe that utilizing transcriptome analysis (RNA-sequencing) will help unveil critical points of cellular and molecular mechanisms involved in host cell–pathogen interactions.

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