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INSTITUTO DE MEDICINA TROPICAL DE SÃO PAULO

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Tese apresentada ao Instituto de Medicina Tropical de São Paulo da Universidade de São Paulo para obtenção do título de Doutora em Ciências.

Área de Concentração: Doenças Tropicais e Saúde Internacional
Orientadora: Profa. Dra. Hiro Goto

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*Aprender é a única coisa de que a mente nunca se cansa, nunca tem medo e nunca se arrepende.*

***Leonardo da Vinci***

## RESUMO

Ozaki CY. Perfil de expressão gênica de célula monocítica humana infectada por *Leishmania (Leishmania) infantum* (Tese). São Paulo: Instituto de Medicina Tropical de São Paulo da Universidade de São Paulo; 2018.

As leishmanioses são um conjunto de doenças causadas por parasitos de diferentes espécies do gênero *Leishmania*, sendo a leishmaniose visceral a causa de grande morbidade e mortalidade, principalmente, em países em desenvolvimento como o Brasil. Apesar dos inúmeros estudos focados na participação dos sistemas imunes inato e adaptativo na proteção ou desenvolvimento da doença, pouco se conhece das alterações que ocorrem na célula hospedeira no início da infecção. Ao mesmo tempo em que as células suscitam respostas que levam à eliminação do parasito, esse pode induzir alterações nos processos celulares para sua evasão, sobrevivência e proliferação. Para o entendimento desses processos propomos identificar as vias biológicas moduladas na infecção de células THP-1 por *Leishmania infantum*. Para isso, células monocíticas humanas THP-1 foram infectadas ou não por *Leishmania infantum* por 6, 10, 24, 48 e 72 h. A partir do RNA total dessas células, bibliotecas de cDNA foram obtidas e submetidas ao sequenciamento pela técnica de *RNA-seq*. Posteriormente, o número total de sequências por gene foi obtido por meio do alinhamento das sequências de DNA ao genoma humano de referência GRCh37 (hg19) empregando o programa *CLC Genomics Workbench 7.1*. Esses dados foram então utilizados na composição da matriz de dados de expressão gênica global das amostras, que serviu como base para obtenção de duas redes de co-expressão gênica utilizando o programa *Weighted Gene Co-expression Network Analysis* (*WGCNA*). As redes foram compostas pelos dados de expressão gênica global das amostras controle e infectadas dos períodos 6 h e 10 h (Rede 1) e 24 h, 48 h e 72 h (Rede 2). A partir da análise dessas redes foi possível selecionar módulos altamente correlacionados às amostras controle e infectadas nos diferentes períodos, realizar o enriquecimento funcional dos genes contidos nos módulos, como também identificar genes *HGS-hub* (genes *hub* diferencialmente expressos). O enriquecimento funcional dos genes contidos nos módulos altamente correlacionados com as amostras mostrou que as maiores mudanças no perfil de expressão gênica das células infectadas, em relação às células não infectadas, ocorreram nas primeiras 10 h de infecção e que muitos dos genes relacionados com a resposta imune são expressos nas primeiras 6 h de infecção. Já a partir de 24 h de infecção, pequenas alterações no perfil de expressão entre as células não infectadas e infectadas foram observadas. A determinação dos genes *HGS-hub* mostrou que dentre os processos biológicos alterados por *Leishmania infantum* nas células THP-1, o metabolismo de lipídios foi o que mais apresentou genes diferencialmente expressos, além da resposta imune. Esses resultados sugerem que além do sistema imune, a *Leishmania infantum* também é capaz de modular o metabolismo de lipídios das células THP-1 infectadas.



Descritores: *Leishmania infantum*. Macrófagos. RNA. Sequenciamento genético. Expressão gênica. Lipídeos – metabolismo.

## ABSTRACT

Ozaki CY. Gene expression profile of human monocytic cell infected by *Leishmania (Leishmania) infantum* (Thesis). São Paulo: Instituto de Medicina Tropical de São Paulo da Universidade de São Paulo; 2018.

Leishmaniasis is a group of diseases caused by parasites of different species of the genus *Leishmania*, with visceral leishmaniasis being the cause of great morbidity and mortality, especially in developing countries such as Brazil. Despite the numerous studies focused on the participation of innate and adaptive immune systems in the protection or development of the disease, little is known about the changes that occur in the host cell at the beginning of the infection. At the same time as the cells elicit responses that lead to the elimination of the parasite, it can induce changes in the cellular processes for their evasion, survival and proliferation. To understanding these processes, we aim to identify the biological pathways modulated in THP-1 cell infected by *Leishmania infantum*. For this, THP-1 human monocytic cells were infected or not by *Leishmania infantum* for 6, 10, 24, 48 and 72 h. Using total RNA extracted from these cells, cDNA libraries were obtained and submitted to RNA sequencing. Subsequently, the total number of sequences per gene was obtained by aligning the DNA sequences to the reference human genome GRCh37 (hg19) using CLC Genomics Workbench 7.1 software. These data were then used to compose the samples' global gene expression data matrix, which was employed to obtain two gene co-expression networks using the Weighted Gene Co-expression Network Analysis (WGCNA) program. The networks were composed by the global gene expression data from the control and infected samples at 6 h and 10 h (Network 1) and at 24 h, 48 h and 72 h (Network 2). Analysis of these networks allowed the selection of modules highly correlated to the control and infected samples in different periods, as well as the identification of HGS-hub genes (differentially expressed hub genes). The functional enrichment of the genes showed that the major changes in the infected cells gene expression profile compared to uninfected cells occurred within 10 h of infection and the genes of the biological pathway related to the immune response are expressed in the first 6 h of infection. Starting at 24 h of infection, small changes in the gene expression profile between uninfected and infected cells were observed. The HGS-hub genes analysis showed that among the biological processes altered by *Leishmania infantum* in THP-1 cells, lipid metabolism was the one that presented a great number of differentially expressed genes, besides the immune response. These results suggest that in addition to the immune system, *Leishmania infantum* is also able to modulate THP-1 macrophages' lipid metabolism.



Descriptors: *Leishmania infantum*. Macrophages. RNA. Genetic sequencing. Gene expression. Lipid – metabolism.

## 7 CONCLUSÃO

Os resultados obtidos neste trabalho envolvendo a identificação de vias biológicas moduladas na infecção de células THP-1 por *Leishmania infantum*, nos permite concluir que:

a) No curso da infecção por *Leishmania infantum in vitro*, as maiores mudanças no perfil de expressão gênica das células infectadas, em relação às células não infectadas, ocorreram nas primeiras 10 h de infecção;
b) Nas primeiras 6 h de infecção, os genes modulados estão relacionados às vias biológicas pertencentes à resposta imune inata, como a do receptor *Toll-like*, a de sinalização das quimiocinas e de citocina-receptor de citocina, além das vias de sinalização mTOR e *HIF-1*, regulação do citoesqueleto, endocitose, como também ao metabolismo de lipídios, como metabolismo de ácidos graxos, de glicerofosfolipídio e de glicerolipídio e a via de sinalização de *PPAR*;
c) Após 10 h de infecção, somente a via de sinalização do fosfatidiinositol se destacou nas células infectadas, estando relacionada com o tráfego intracelular, proliferação e divisão celular e endocitose, podendo ser de grande importância na coordenação dos eventos da célula após a entrada do parasito;
d) A partir de 24 h de infecção, as células infectadas apresentaram pouca alteração no perfil de expressão gênica quando comparadas às células não infectadas e poucas vias biológicas relacionadas ao sistema imune estão presentes;
e) A modulação dos genes *IL18BP*, *ELMO1*, *SASH1*, *CD93* e *PIM1*, *MMP2* e *ALOX5* sugere um mecanismo de evasão do sistema imune pelo parasito;
f) A modulação dos genes *ITGB3*, *MGLL*, *NR1H3* e *DHCR7* sugere que a *Leishmania* estaria promovendo o acúmulo de colesterol e de

seus produtos nas células para a formação dos corpúsculos de lipídios e assim promover sua sobrevivência dentro das células;

g) Os dados apresentados neste trabalho abrem novas perspectivas para o estudo da interação macrófago-*Leishmania*, já que muitos dos genes apontados como diferencialmente expressos nas células infectadas ainda não foram investigados.

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