

Influence of *Histoplasma capsulatum* Infection on Endothelin-1 mRNA Gene Expression in Bone Marrow Derived Macrophages.

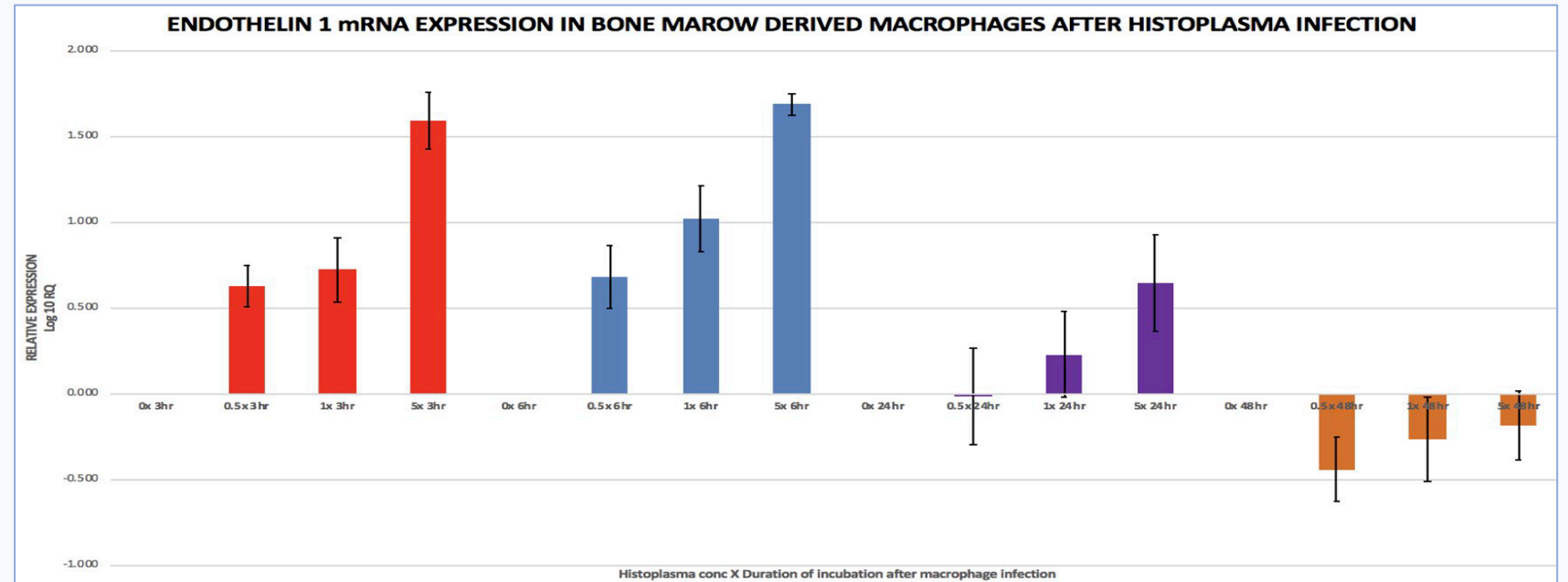
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BACKGROUND

- Endothelin-1 (ET-1) is increasingly recognized as an immune modulator; it exerts a pro-inflammatory effect by increasing the release of cytokines like interferon gamma. ET-1 is secreted by a variety of cells such as macrophages, neurons and endothelial cells.
- Activation of the endothelin system has been implicated in the pathogenesis of sepsis caused by bacteria, viruses and even parasites. However, there are no published studies that have explored the role of ET-1 in *Histoplasma capsulatum* infection.
- Studying the role of ET-1 in histoplasmosis is important because understanding its role in the host defense mechanism may serve as the foundation for future discovery of novel therapeutic options.

METHODS

- Bone marrow cells were isolated from mice and set up for tissue culture.
- Bone marrow derived macrophages (BMDM) were harvested after 5-7 days of incubation and infected with varying ratios (0.5,1 and 5) of yeasts to macrophages.
- RNA was extracted from the BMDM after 3, 6, 24 and 48 hours of infection. For comparison, RNA was also extracted from uninfected BMDM at the same time points.
- Real-time PCR (polymerase chain reaction) was performed on complementary DNA. ET-1 (*Edn1*) messenger RNA (mRNA) gene expression was quantified relative to the expression of the house keeping /endogenous control gene that encodes for beta-2 microglobulin (*B2m*).



RESULTS

- In BMDM infected with *H. capsulatum* there was upregulation of *Edn1* after 3, 6 and 24 hours of infection.
- During this same time points, the expression of ET-1 mRNA in the uninfected BMDM remained constant. Expression of *Edn1* was highest in the BMDM infected with 5x *H. capsulatum* after 3 and 6 hours of infection.
- After 24 hours, the expression of ET-1 mRNA decreased markedly in all concentrations of *H. capsulatum*.
- At 48 hours post-infection the *Edn1* was downregulated in the 0.5,1 and 5-fold quantities of *H. capsulatum* across all time the time intervals.

CONCLUSION

- Results from this study indicate that *H. capsulatum* infection induced an upregulation of the *Edn-1* in BMDM.
- This may correlate with an increase in levels of ET-1 production by the BMDM in the face of *H. capsulatum* infection.
- These results provide a platform in which to examine the influence of ET-1 on the host response to this fungus.