Title: **HOST CYTOKINE PATTERNS DURING EXPERIMENTAL INFECTION WITH *Bacteroides fragilis* UNDER TREATMENT WITH SUBINHIBITORY CONCENTRATION OF METRONIDAZOLE**

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Abstract:

Bacteroides fragilis, common member of the gut microbiota, remains one of the most important pathogen associated to endogenous infections, and metronidazole is still the main drug used to treat *Bacteroides* infections. Considering that studies on drug-bacteria interactions usually are based on *in vitro* assays, issues about the actual implications of such interactions to the host's biology remain unclear. This study was focused on the evaluation of an *in vivo* murine model to investigate the drug-bacteria-host relationships. Wistar rats were subjected to laparotomy to insert a perforated table tennis ball into the peritoneal cavity, followed by challenge with *B. fragilis.* The animals were split into three groups: negative control; positive control infected with the bacterial strain; experimental group infected with the bacterial strain and treated with subinhibitory concentration of metronidazole for 8 days in 48 hour intervals. Bacteria-host relationship was evaluated 8 days after the treatment with metronidazole and 8 days post chemotherapy, at 16^{th} day post-infection. From the experimental tissue cage produced, total RNA was extracted from drawn exudates. The RNA quality was evaluated by on-chip microfluidic electrophoresis, and cDNA was synthesized by reverse transcription. The expression levels of cytokines IL-10, IL-6, IL-8, TNF-a, MCP-1 and IL-1b were measured by qPCR, using the $2^{-\Delta\Delta Ct}$ method. After 8 days, the expression of TNF-α was significantly increased 10-fold in the positive control group, while in the experimental group a 4-fold increase was observed. At the day 16 post-infection, IL-8 expression levels were increased in both positive control and experimental group (6.5-fold, and 14.7-fold). High expression of IL-6 and IL-1α were observed in the positive control group. The IL-10 relative expression was exacerbated in experimental group (30.0-fold) when compared to the positive control animals (3.0-fold). Increased expression of IL-10 cytokine may be beneficial for both host and to pathogen. The anti-inflammatory cytokine limits the damage to host tissue and may facilitate a persistent infection and proliferation of the bacterial population, as a persistency strategy. Our results suggest that low concentrations of metronidazole may influence bacteria-host relationships, with implications in the infection prognosis.

Keywords: *Bacteroides fragilis,* Metronidazole, Host response.

Financial support: CNPq, CAPES, FAPEMIG