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


Institution: Universidade Federal de Juiz de Fora (Rua José Lourenço Kelmer, s/n - Martelos, Juiz de Fora – MG, Brasil).

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 16th 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-α, MCP-1 and IL-1b were measured by qPCR, using the 2^ΔΔCT 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