TITLE: TRANSCRIPTIONAL REGULATION DURING *Bacteroides fragilis* OXIDATIVE STRESS RESPONSE

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ABSTRACT:

Bacteroides fragilis, an opportunistic pathogen from the gut, is one the most aerotolerant species among strict anaerobes. It is capable of surviving for up to 72 h when exposed to atmospheric oxygen. Under these circumstances, a strong oxidative stress response mechanism is activated, and the expression of 45% of *B. fragilis* genome is affected. OxyR is one of the most important regulators during this response, but additional regulatory systems are also present. In previous studies, it was described that the regulator BmoR also played a role in the oxidative stress response, but the mechanisms involved are yet to be determined. The aim of this study is to better characterize the regulation of gene expression during the oxidative stress response of *B. fragilis*. For this purpose, mutant strains for genes *bmoR* and *oxyR* were constructed and used in molecular and phenotypic experiments. Exposure to different oxidative stress sources revealed that BmoR is essential for growth in low oxygen tension, but not for peroxides or diamide resistance. When it comes to the species survival during extended atmospheric oxygen exposure, *bmoR* deletion did not affect the single mutation strain. However, when in double mutation with *oxyR*, *bmoR* reverted part of the sensibility phenotype caused by the absence of OxyR. Those regulators also favor peritoneal abscess formation on an *in vivo* model of infection. Transcriptomic analysis during oxygen exposure showed that the absence of BmoR leads to a significant increase in the expression of at least three genes related to the redox balance inside the cell. One of those genes, located directly upstream of *bmoR*, codes for a coenzyme A-disulfide reductase and is repressed by BmoR during both anaerobiosis and atmospheric oxygen exposure. Binding of purified Bmor to the promoter region of the two genes affected by BmoR deletion, located on the same operon and coding for a thiosulphate:quinone-oxidoreductase and a thioredoxin, could not be confirmed by EMSA. Their differentiated expression occurred only during oxygen exposure. Even though we could better describe the role of BmoR during *B. fragilis* oxidative stress response and correlate this regulator with OxyR, the regulation of this response is overly complex. Nevertheless, we hope our findings will contribute to a better understanding on the mechanisms involved in gene regulation and on the elements responsible for *B. fragilis* virulence and survival during the infectious process.

Keywords: *Bacteroides fragilis*; gene regulation; OxyR; BmoR; oxidative stress

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