ID de Contribution: **9** Type: **Non spécifié**

DNA topoisomerase I C-terminal domain is crucial for the pathogeny and stress response of adherent Invasive E. coli

Crohn's disease (CD) is a multifactorial disease characterized by chronic inflammation of the digestive tract. This inflammation leads to dysbiosis of the intestinal microbiota, resulting in abnormal colonization by proteobacteria such as invasive adherent E. coli (AIEC). These bacteria can adhere to epithelial cells, invade them, survive in macrophages and form an intracellular bacteria community (IBC), resulting in the secretion of pro-inflammatory cytokines, exacerbating existing inflammation. Antibiotics are one treatment. However, these bacteria often develop resistance to commonly used antimicrobials and are particularly resistant to stress, enabling them to survive in macrophages. In order to develop targeted approaches to counter them, the team is studying the modes of infection and survival that these bacteria can develop. To this end, I have studied the specific involvement of the C-terminal domain (CTD) of topoisomerase I in infection and stress response.

TopoI is an essential enzyme for E. coli. However, transposition insertion sequencing (TIS) screens revealed that transposon insertions were possible in the last part of the topA gene. This suggests that the TopoI CTD is not required in a rich medium and indeed the 14kDa CTD can be deleted and does not cause a growth defect. Nevertheless, its deletion causes a change in DNA topology which may be caused by an effect on the enzyme's function.

Following macrophage infection challenge, transposon insertions in the TopoI CTD region were counter selected. This finding strongly suggests the involvement of this domain in the pathogenicity of the infection. To confirm this hypothesis, a macrophage infection test was conducted, which demonstrated a significant reduction in intracellular bacteria and IBC formation when using the TopoI CTD mutant strain compared to the WT strain after 24 and 48 hours of infection. Additionally, an antimicrobial screening revealed that the absence of this domain was associated with increased susceptibility to antimicrobials.

These results emphasize the crucial role of DNA topology and its regulation of stress response during infection. In the face of emerging multidrug resistance, this study further supports the potential of bacterial topoisomerase I as a therapeutic target.

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