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When cell death is better than cell survival: Monocyte response to lysates from different strains of Campylobacter jejuni

Campylobacter jejuni, a Gram-negative pathogen, is one of the leading bacterial causes of gastroenteritis world-wide. The invasion and multiplication of *C. jejuni* is a multistep process that includes interaction with the intestinal epithelial cells (IECs).

The only toxin of *C. jejuni*, called cytolethal distending toxin (CDT), appears to be important for cell cycle control and induction of host cell apoptosis. Furthermore, *C. jejuni* seems to survive intracellularly in human monocytes which, once in circulation, migrate to tissues where they can differentiate into macrophages or specific types of dendritic cells.

The aim of our work was to investigate the effects of *C. jejuni* virulence factors in human cells focusing the attention on cellular pathways activated or deactivated during host cell infection.

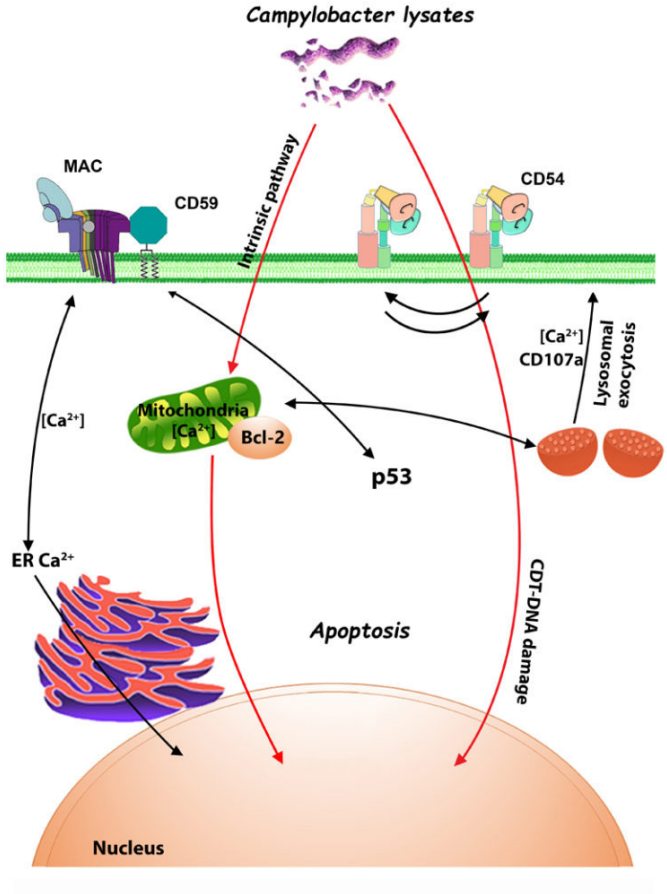

Fig. 1. Schematic representation of monocyte responses to Campylobacter jejuni lysates.

We described how human monocytes interact with cell lysates from two CDT producer strains, namely, *C. jejuni* ATCC 33291 and *C. jejuni* ISS 1, and the strain *C. jejuni* 11168H *cdt*A mutant.

Cytometric investigations revealed that the *C. jejuni* ATCC 33291 lysate was the best cell death-inducer, followed by the *C. jejuni* ISS 1 lysate, during the time course of our analysis.

Mitochondria and lysosomes was differently targeted by the different strains. Indeed, whereas *C. jejuni* ATCC 33291 wild-type strain showed to induce an intrinsic apoptotic pathway, characterized by the induction of mitochondria alterations, *C. jejuni* ISS 1 wild-type strain mostly induced lysosomal alterations. The lysates from all strains induced ER stress in monocytes compared to the untreated control cells; of note, an important stress was induced by the *C. jejuni* ATCC 33291. ER stress is consistent with the increase in cytosolic Ca^{2+} content. Lysates from the wild-type strains induced an important decrease in p53 intracellular content from T0 to 12 h; this effect was not shown in cells preincubated with the lysate from the mutant strain. Our findings also showed a strong decrease in Bcl-2 content, specifically after 12 h, in monocytes treated with the *C. jejuni* ATCC 33291 lysate: this pro-apoptotic response is coherent with the deep mitochondria alterations induced by this strain.

Adhesion molecules, such as ICAM-1, direct immune cells to the inflammation site by the process of rolling, activation, adhesion, and transmigration. An increase in ICAM-1 expression was detectable in monocytes, particularly at 3 h and 48 h. Furthermore, confocal pictures revealed a variation in surface ICAM-1 distribution: a ‘punctuate’ organization with a loss of ‘cap’ distribution occurred, confirming that a reshaping of the plasma membrane arose because of the infection.

CD59 is a cell surface protein that inhibits the formation of the Membrane Attack Complex (MAC), able to form the cytotoxic pores that cells activate in order to kill pathogens. The maximum increase of CD59 was registered at 48 h for *C. jejuni* ISS 1 and *C. jejuni* 11168H *cdt*A mutant lysates, CD59 was revealed to be a general infection marker in monocytes.
In conclusion, the lysates obtained from all *C. jejuni* strains induced endoplasmic reticulum (ER) stress in monocytes, suggesting that ER stress was not associated with CDT but to other *C. jejuni* virulence factors. On the contrary, the changes in lysosomal acidic compartments and p53 expression (occurring together from time 0, T0, to 24 h) were mainly due to the CDT. The loss of p53 may prevent or impede cell death and it was not observable with the mutant strain. CDT not only was responsible for specific death effects but also seemed to promote an apoptotic stimuli-resisting pathway.

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