Clostridium difficile associated disease: looking beyond the toxins.

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Clostridium difficile is the leading healthcare-associated infection in the United States. This gram-positive, spore-forming bacterium causes a toxin-dependent diarrheal disease. We have discovered strains of C. difficile from symptomatic patients that produce, at minimum, 10-fold less toxin compared to other strains of the same molecular type. The toxin produced by these low-toxin (LT) strains are equally potent compared to the high-toxin (HT) strains. Importantly, in the hamster model of acute disease, there was no difference in time-to-death, bacterial burden, or gross pathology between the LT and HT strains. However, we did find that in a mouse colonization model, the HT strain was eventually cleared with no recoverable bacteria or spores at the end of the study. In contrast, the LT strains actually persisted in the mouse model. Whole genome analysis indicated that LT strains have conserved genes that are not present in, or of low sequence similarity to, the high-toxin reference genome. Many of these genes are annotated as cell surface-associated or cell membrane-associated. Proteomic analysis also revealed several cell surface proteins that were more abundant among the low-toxin strains compared to the high-toxin reference. Preliminarily, we found that the LT strains induce a different immunological response, likely due to an altered cell surface display. These data underscore the importance of non-toxin virulence factors, and the need to understand their contribution to Clostridium difficile-associated disease.