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Recombination in the substrate recognition domain of TcdB confers a variant glucosyltransferase activity and a distinctive cytopathic effect to a *Clostridium difficile* strain from the hypervirulent clade II

Quesada-Gomez C¹, Lopez-Urena D¹, Castro C², Kroh H², Chumbler N², Orozco-Aguilar J¹, Guzman-Verri C³, Moreno E³, Rodriguez C¹, Lawley T⁴, Lacy B² and Chaves-Olarte E¹

¹Universidad de Costa Rica, Costa Rica.

²Vanderbilt University School of Medicine, USA

³Universidad Nacional Heredia, Costa Rica

⁴Wellcome Trust Sanger Institute, UK

Clostridium difficile NAP1 strains are responsible for nosocomial outbreaks worldwide. The increased pathogenic potential of these strains has been attributed to overproduction of toxins and fluoroquinolone resistance. During a *C. difficile* nosocomial outbreak in Costa Rica, a strain was found to induce a distinct cytopathic effect (CPE) different from the canonical arborizing CPE. The strain was further identified as a NAP1 isolate (NAP1V) of the hypervirulent clade II that harbored a silent mutation in the *gyrA* gene. After toxin purification, cells treated with TcdB of the NAP1V strain (TcdBV), displayed a rounded and surface detached phenotype resembling that induced by *C. difficile* TcdB toxin A-negative strains. The effect mediated by the TcdBV was due to differences in substrate preferences that resulted in different glucosylation patterns of the various GTPases. Whereas TcdB from classical NAP1/027 strains glucosylated RhoA, Rac and Cdc42, TcdBV did not use RhoA as substrate and displayed less affinity for Cdc42. Sequence comparison of the functional domains of TcdBV with other *C. difficile* strains along with comparative genomic analysis revealed that TcdBV is a NAP1 toxin but with modifications within the enzymatic domain. The enzymatic domain is identical to that of a NAP9/017 strains (A-B+). We also provide evidence that the NAP1 strains glucosylate a broader spectrum of GTPases *in vitro* as both toxins glucosylated Rap and R-Ras. These findings provide insight into the role of the glucosyltransferase activity in the pathogenesis of *C. difficile* variant TcdB strains and the hypervirulent NAP1 strains.

Biography

Carlos Quesada-Gómez is a lecturer on Anaerobic Bacteriology, School of Microbiology, University of Costa Rica. He has a M.Sc. in Medical Bacteriology and is currently a PhD. Candidate working with *Clostridium difficile*. His research group is working on the molecular characterization of different isolates by PFGE, toxinotyping, MLST and whole genome sequence methods which have made possible the description of the hypervirulent NAP1/027 and other novel genotypes in Costa Rica and Latin America. *C. difficile* pathogenesis is another area of study in which the level of virulence is being associated with the genotypes and its toxins using cellular and animal models.

carlos.quesada@ucr.ac.cr

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