

Towards the Structure and Biological Activity of Genotoxic Compound, Colibactin

Morales-Lozada, Yermay¹, Báez-Bravo, Gabriela¹, Baerga-Ortiz, Abel². ¹University of Puerto Rico, Río Piedras; ²University of Puerto Rico, Medical Science Campus

Abstract:

Colibactin is the name given to the predicted product of a hybrid nonribosomal peptide-polyketide synthase complex (*pks island*) found in some strains of *Escherichia coli*. Bacterial strains harboring the *pks island* show a peculiar toxicity toward mammalian cells in culture with a distinctive phenotype that includes DNA damage, cell cycle arrest and megalocytosis of the infected cells. It has been shown by our group that the *pks island* can be found in the normal gut microflora and that its presence is positively correlated with colorectal cancer (CRC). Despite the obvious interest in elucidating the mode of action of the resulting colibactin compound, its structure remains unknown. The broad objective of this investigation is to develop molecular strategies towards the isolation of colibactin in pursuance of its structure and eventually, its mode of action. We hypothesized, that colibactin affects the integrity of the bacterial cell envelope, releasing components that are toxic to mammalian cells. With this possible mode of action in mind, we will test the effects of colibactin on the chemical composition and toxicity of one of the bacterial cell envelope components: the outer membrane vesicles (OMVs). We expect that the production of colibactin will affect the integrity of the bacterial cell wall, causing a fundamental difference in the OMVs. We will also measure the effect of colibactin-containing organic extracts on cultured mammalian cells. In all cases, we will compare a natural producer of colibactin, strain IHE3034 with a mutant lacking a key enzyme of the pathway, and thus cannot produce colibactin IHE3034 ($\Delta clbP$). We expect that the proposed work will advance the elucidation of the structure and mechanism of an enigmatic natural product.