

Evaluation of the toxicity of Versicolorin A, a dangerous emerging mycotoxin

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Mycotoxins such as aflatoxin B1 (AFB1) and Versicolorin A (VerA) are widespread toxic secondary fungal metabolites that contaminate food and feed. VerA is the biosynthetic precursor of AFB1, which is a known potent carcinogen. The toxicity of AFB1 has been widely documented but this is not the case for VerA. However, the similarity in the chemical structure of both molecules suggested a similar mechanism of action. Because the intestine is the first barrier in contact with mycotoxins after ingestion, the objective of my PhD is to obtain a global picture of the toxicity of VerA in intestinal cells in order to characterize for the first time the hazard associated with the presence of VerA in food.

I first combined multiple assays (RealTime-GloTMMT, CellTiter-GloTM, LDH-GloTM, CellToxTM Green, Promega) in order to assess the toxicity of VerA compared and combined to AFB1 in multiple exposure conditions. Results showed evidenced the toxicity of VerA and were employed to design a complete series of experiments that confirmed the high genotoxicity (induction of γ H2AX, phospho-P53 and comet assay) and mutagenicity of VerA (SOS/umu and Ames assays). Because the mutagenicity of AFB1 needs biotransformation by CYP enzymes and VerA can induce AhR signaling, we evaluated their interaction using P450-GloTM assays and genotoxicity assays to find out that VerA can enhance AFB1 toxicity.

Results were also useful to design studies using a combination of genome-wide transcriptomic and proteomic analyses. This study revealed that VerA altered several responses including Sirtuin and cGAS-STING-dependent γ IFN signaling, which may indicate a mitotoxic activity. Protein subfractionation of exposed cells combined with the use of SIRT-GloTM and Mitochondrial ToxGloTM confirmed that VerA affected mitochondrial activity and the role of Sirtuin signaling and warrants further research on the effect of VerA in cell mitochondrial respiration and glycolysis.

Indeed, our results show that VerA is a highly toxic emerging mycotoxin by itself, but that can also enhance the toxicity of other carcinogens. These data also highlight the need to expand toxicological knowledge on the precursors of mycotoxin biosynthesis in order to identify those that may constitute, directly or indirectly, a threat to human health.