

The marine toxin palytoxin induces necrotic death in HaCaT cells through mitochondrial permeability transition pore (MPTP) opening

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Palytoxin (PLTX) is the reference compound of a family of marine biotoxins named PLTX-like compounds, detected in zoanthid corals of the genus *Palythoa*, dinoflagellates of the genus *Ostreopsis* and cyanobacteria of the genus *Trichodesmium*. PLTX is one of the largest non-proteinaceous natural molecules, known for its high toxicity and potential lethality after oral exposure after contaminated seafood consumption. Adverse effects in humans ascribed to PLTXs are also associated to inhalational and cutaneous exposure, the latter characterized by irritation and inflammation of the skin. At the molecular level, PLTX binds to the Na⁺/K⁺ ATPase, transforming it into a cationic channel that in turn induces a massive intracellular Na⁺ influx, the crucial step in mediating rapid cell death. However, from a mechanistic point of view, the features and the intracellular pathways leading to PLTX-induced cell death are still not completely characterized. Hence, considering the increasing human cases of dermatotoxicity ascribed to palytoxins, this study was carried out on skin HaCaT keratinocytes, a predictive model for evaluating irritative properties of xenobiotics at the skin level. This study demonstrates that: i) PLTX induces necrotic cell death: propidium iodide uptake was observed already after 1 h exposure and necrotic-like morphological features were evidenced by confocal microscopy. Apoptosis occurrence was excluded since no caspasis 3/7, 8 and 9 activation as well as no apoptotic bodies formation were recorded; ii) Necrosis seems to be related to a very early opening of mitochondrial permeability transition pores (MPTPs), induced by the toxin in a concentration-dependent manner already after 5 minutes exposure; iii) MPTPs opening is not regulated by the classic intracellular pathway (cyclosporine A is unable to counteract their formation), but is strictly controlled by the ionic imbalance (mainly by Na⁺) induced by the toxin. The rapidity of MPTPs opening and necrosis induction rises a serious concern about the very fast onset of PLTX toxic effects.