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Abstracts

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10.017 Unveiling Seriniquinone Mechanisms: A Promising Strategy for Treatment of Chemoresistant Melanoma. Hirata AS¹, Carvalho LAC², Kinker GS³, Rezende-Teixeira P¹, Machado-Neto JA¹, Jimenez PC⁴, Santelli GMM¹, La Clair JJ⁵, Maria-Engler SS², Fenical W⁶, Costa-Lotufo LV¹ ¹ICB-USP; ²FCF-USP; ³A. C. Camargo Cancer Center; ⁴Unifesp, Institute of Marine Science; ⁵University of California, Dpt of Chemistry and Biochemistry; ⁶University of California, Scripps Institution of Oceanography

Introduction Melanoma is the most aggressive skin cancer due to its high risk of metastasis and resistance to conventional chemotherapy that still lacks effective treatments. Seriniquinone (SQ), a metabolite from the marine bacterium *Serinicoccus sp.*, attracted attention for its selectivity for melanoma cells and for dermcidin (DCD) as a novel molecular target inducing apoptosis via autophagy (Trzoss, LT. *Proc. Nat. Acad. Sci.* v. 111, p. 14687, 2014). Our previous results demonstrated that SQ was potent and selective, regardless of melanoma mutation, promoting cell death by different autophagic and apoptotic signaling (Hirata AS. *Mol.*, v. 26, p. 7362, 2021). Thus, the present study aims to unravel the mechanism of action of SQ in melanoma as a new therapy, and also using it as a new pharmacological tool to understand the contribution of DCD in survival, metastasis and resistance.

Methods Parental and vemurafenib-resistant melanoma cell lines (SK-MEL-28 and SK-MEL-28R, respectively) were used as models. Cytotoxicity of SQ was characterized by MTT and clonogenic assays with various therapeutic schemes, investigating synergism with vemurafenib as well. *In vitro* reconstructed human skin was explored to mimic *in vivo* model of cancer invasion. Public clinical database and RNAseq from SQ-treated cells were analyzed by bioinformatics and effects were validated by western blot, adhesion assay and immunofluorescence imaging. **Results** SQ exhibited an IC₅₀ of 0.8 µM for SK-MEL-28 and 2.3 µM for SK-MEL-28R, with a notable reduction in clonogenicity and synergistic effect in SK-MEL-28R. Tumors from both cell lines harbored in skins presented a slight reduction in size and dermis invasion; by contrast, we had no toxic signs in healthy tissues. Transcriptomics revealed strong activation of endoplasmic reticulum stress, subsequently validated in both lines by GRP78, p-eIF2α and XBP1s protein overexpression. Once DCD was already reported bound to GRP78 modulating migration by Wnt/β-catenin, this pathway and adhesion proteins were evaluated. Especially for SK-MEL-28R, only 6h-treatment was enough to decrease in 98% of adhesion capacity; N-cadherin and active β-catenin migration-related proteins were also reduced. **Conclusion** SQ demonstrated potent activity against melanoma, especially in the resistant scenario. Its importance as a new drug candidate also lies in its safety for healthy skin tissue, suggesting that its selectivity may mitigate possible side effects in patients. SQ is the only known compound to target DCD, being also considered a useful pharmacological tool to study this protein. Since our results have consistently pointed the DCD-GRP78 interaction as regulators of cell adhesion and consequent migration, our findings support that these proteins, which present overexpression in various cancers, contribute to melanoma metastasis and resistance. **Financial Support** FAPESP (2020/06613-8, 2015/17177-6); CNPq; CAPES.