ORAL COMMUNICATIONS

CELLULAR DYSHOMEOSTASIS AND REDOX IMBALANCE INDUCED BY CANTHARIDIN IN GLIOBLASTOMA MODELS

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Cantharidin (CTD), a toxic terpene derived from Meloidae beetles, has historically been shown to possess various therapeutic properties, including potential anti-tumor activity1. This study investigated the cellular uptake of CTD and its impact on the redox defense system in U373 glioblastoma cells.

Using the Parallel Artificial Membrane Permeability Assay, we first evaluated the entry mechanism of this molecule. The results showed that CTD can cross biological membranes via passive diffusion, independent of protein transporters.

Treatment with CTD induced a significant, time-dependent increase in reactive oxygen species (ROS) levels, peaking at 6 h. RT-qPCR and Western Blot analyses revealed that while the cystine transporter xCT and Heme Oxygenase-1 (HO-1) levels were strongly increased, the peroxide-scavenging enzymes catalase and GPX4 were not upregulated, showing a heterogeneous antioxidant response.

These findings are linked to the role of Nrf2, the main transcription factor orchestrating the antioxidant response2. Indeed, CTD treatment caused a 50-60% reduction in its nuclear levels. Notably, CTD prevented Nrf2 accumulation even in the presence of its activator, dimethyl fumarate. As Nrf2 mRNA levels remained unchanged, we hypothesized that the inhibitory effect occurs at the post-translational level, likely affecting nuclear trafficking dynamics.

Finally, we investigated the causal link between oxidative stress and cell death. Although the antioxidant N-acetylcysteine successfully neutralized ROS and restored the baseline levels of xCT and HO-1, it only partially restored cell viability. These findings suggest that while CTD disrupts redox balance and inhibits Nrf2-mediated defenses, oxidative stress is not the primary driver of its toxicity. Therefore, further studies are needed to improve our understanding of the pathways underlying the cytotoxic action of CTD.

Acknowledgments: This work was supported by the Rome Technopole PNRR grant (CUP F83B22000040006).

References

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