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Exploring the potential of dichloroacetate in targeting oral cancer metabolism

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Abstract

Background: Oral cancer represents a significant global health burden, and its incidence is steadily rising [1]. A hallmark of cancer is metabolic reprogramming - most notably, a shift toward aerobic glycolysis, commonly known as the Warburg effect. This altered metabolic phenotype supports rapid proliferation, enhances survival under hypoxic conditions, and contributes to resistance to conventional therapies. As such, targeting dysregulated metabolic pathways has emerged as a promising therapeutic strategy [2]. Dichloroacetate (DCA), a small-molecule inhibitor of pyruvate dehydrogenase kinase (PDK), has attracted attention for its ability to reactivate mitochondrial oxidative phosphorylation [3]. **Objective:** This study aims to evaluate the therapeutic potential of DCA in oral cancer, focusing on its cytotoxicity and its ability to target key components of tumor cell metabolism. Specifically, we investigate DCA's interaction with monocarboxylate transporters (MCTs) and ATP-dependent efflux pumps involved in multidrug resistance. **Methods:** The cytotoxic activity of DCA was evaluated using the sulforhodamine B (SRB) assay to determine the GI_{50} in SCC09 and SCC25 human oral cancer cell lines. A non-tumor cell line (HOK, human oral keratinocytes) was also included. The expression of MCTs and ATP-dependent efflux pumps in oral cancer cells was evaluated, both in the presence and absence of DCA treatment, at the mRNA transcript and protein levels using qRT-PCR and Western blotting, respectively. The UALCAN and GEPIA databases were used to analyze the expression of the targets and correlate them with clinicopathologic indicators from head and neck squamous cell carcinoma tissue samples. **Results:** We found that DCA decreases oral cancer cell viability after 24 hours of treatment, and the cytotoxic effect on SCC09 and SCC25 cancer cells could modulate the protein expression of monocarboxylate transporters. From the UALCAN analysis, we observed an increase in the expression of MCT1 and MCT4 transporters in head and neck squamous cell carcinoma tissue samples compared to normal tissues. Moreover, we found a positive correlation between tumor stage and the overexpression of MCT1 and MCT4. Similar results were obtained for the P-gp efflux pump and CD147. Overall survival and disease-free survival were also analyzed with GEPIA. **Conclusions:** The results highlight the potential of DCA as a promising cytotoxic agent in oral cancer that deserves further investigation.

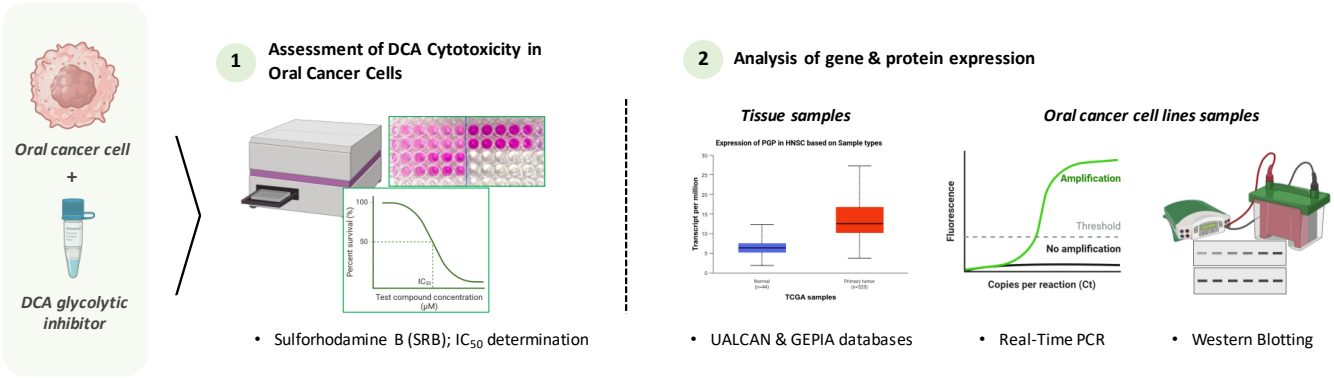

Figure 1. Schematic representation of the experimental approach to evaluate the effect of the glycolytic inhibitor dichloroacetate (DCA) on oral cancer cells.

Keywords: oral cancer; tumor metabolism; dichloroacetate

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References

1. Bray, F.et al. Global Cancer Statistics 2022: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2024**, *74*, 229–263, doi: 10.3322/caac.21834
2. Cunha, A. et al. Targeting Glucose Metabolism in Cancer Cells as an Approach to Overcoming Drug Resistance. *Pharmaceutics* **2023**, *15(11)*, 2610, doi: 10.3390/pharmaceutics15112610
3. Cunha, A. et al. Glycolytic Inhibitors Potentiated the Activity of Paclitaxel and Their Nanoencapsulation Increased Their Delivery in a Lung Cancer Model. *Pharmaceutics* **2022**, *14(10)*, 2021. doi: 10.3390/pharmaceutics14102021