On the Mechanisms of Glycolytic Enzymes Negative Regulation by Clotrimazole in Human Breast Cancer Tissues

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Neoplastic cells show metabolic alterations including an increased glycolytic rate characterized by changes in intracellular distribution of glycolytic enzymes (GEs). It has been described that clotrimazole (CTZ), an imidazole derivative, reverses these changes in intracellular distribution of GEs and diminishes the viability of cancer cells. Our previous work show that CTZ inhibits phosphofructokinase (PFK) activity in both immortalized breast cancer cell line (MCF7) and in human breast cancer tissues obtained from patients subjected to mastectomy. The present study aims at investigating the mechanism by which CTZ modulates GEs. We show that despite decreasing the co-localization of PFK and f-actin in MCF-7 cells, CTZ does not alter the association of purified PFK and f-actin, suggesting that the previous described effect is not due to the direct effect of CTZ on these proteins. Moreover, CTZ inhibits hexokinase (HK) activity in tumor tissues decreasing the enzyme activity in a mitochondria enriched fraction (Mit). These effects were reproduced in a semi-purified assay using purified HK and Mit tumor tissue. The association of HK and Mit is an important anti-apoptotic mechanism and thus CTZ may increase pro-apoptotic signals as part of its antineoplastic mechanisms. However, despite the decreased HK activity observed in CTZ treated breast tumor tissues, no alterations in glucose consumption are observed upon CTZ treatment. Altogether, these results suggest that CTZ does not alter the ability of tumor cells to metabolize glucose, but probably the pathways involved in this metabolism.

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