

Ultrastructural Mechanism of Mitochondrial Resistance to MKT-077 in Breast Carcinoma MCF-7Adr: A Model for Multidrug Resistance

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Multidrug resistance of cancerous cells is attributed to an efflux mechanism at the plasma membrane and cytoplasmic vesicles. In this study, we found that when a drug-resistant and P-gp overexpressing cell line was treated with MKT-077, a cationic drug that accumulated in the mitochondria, the mitochondria were capable of drug sequestration and vesicle production. This efflux mechanism in MCF-7Adr, a breast cancer cell line, involved a regional sequestration of the drug in the mitochondria, vesication, budding and separation of the storage vesicle from mitochondria, migration of vesicle to plasma membrane, and exocytotic secretion. This mechanism seems to be inefficient in the susceptible ancestral cell line MCF-7; it initially produced mitochondrial vesicles at a lesser rate, its mitochondria were later damaged, and the majority lost their integrity. After 7 hours of drug exposure, the resistant cells continued the efflux process and seemed to have a larger number of smaller size mitochondria in their cytoplasm, however, a small fraction of its mitochondria were totally damaged as well. Because mitochondrial population within a cell varies in their efficiency in response to drug toxicity, resistance to MKT-077 seems to be conferred by a selection process at the mitochondrial level. Additionally, since multidrug resistance of MCF-7Adr is attributed to its overexpression of P-gp, our described mechanism may be a P-gp efflux pump that is localized in the mitochondria, and suggests a model for multidrug resistance for mitochondria-accumulating drugs in cancerous cells.