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Interaction mechanisms between Cytochrome P450 3A4 and membrane models associated with drug resistance

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Cytochromes P450 (CYPs) are a family of hemoproteins responsible for the metabolism of several xenobiotics.(1) The catalytic activity and the amount of these enzymes can lead to the activation or deactivation of drugs (2), and therefore cytochromes P450 may be involved in cell resistance to chemotherapy. One strategy to investigate this problem is the use of membrane models such as Langmuir films that are formed at the air-water interface. Drugs and proteins can be included, and the interaction between these components evaluated by tensiometric, microscopic, and spectroscopic measurements. In this work, we developed a membrane model with the main lipids present in the endoplasmic reticulum where there is a large number of cytochromes P450 3A4 (CYP3A4). The lipids used were 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine (DPPE), L-α-phosphatidylinositol from bovine liver (PI) and Cholesterol (Chol). We studied the influence of cholesterol and phosphatidylinositol on the properties of the membrane as a potential alteration expressed in cancer cells. In addition, we investigated the incorporation of CYP3A4 and Doxorubicin (DOX) in these models. Preliminary results indicate that the increase in Chol causes condensation of the monolayer, while the increase in PI causes an expansion. The incorporation of CYP3A4 and DOX varied with monolayer composition. This property can impact CYP3A4 activity, modifying the effects caused by DOX. The next steps will be to investigate these systems through polarization-modulated infrared reflection absorption spectroscopy (PM-IRRAS) and Brewster angle microscopy (BAM). We hope to demonstrate the influence of membrane composition on CYP3A4 activity against DOX, seeking to understand the molecular mechanisms mediated by these enzymes. Such knowledge may be relevant to develop strategies for diminishing drug resistance.

Palavras-chave: Cytochrome P450 3A4. Doxorubicin. Langmuir films.

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