cancer. In vitro treatment of tumor cells with Irvalec® induces necrotic cell death, a process associated with rapid loss of membrane integrity and subsequent cell permeabilization. These results suggested an effect of the drug, either on an ion channel or in the plasma membrane. In order to explore this hypothesis patch-clamp experiments were performed in different tumor cell lines (HeLa, A549 and HCT116). Treated cells underwent rapid and dramatic morphological changes, including cell blebbing, severe swelling, plasma membrane permeabilization and cell lysis. Apart from the numerous small blebs, membranes from damaged cells also re-organized to form enormous bubbles surrounded by cell membrane. Using electrophysiological techniques, it was shown that Irvalec® induced an important increase in membrane conductance. The compound permeabilized the plasma membrane to ions, even when the cells were not pulsed, causing important changes in the holding current. It has been described that zinc attenuates the drastic effects of some membrane disrupting agents. Hence, to test if zinc exerted some protective effect against Irvalec® effects, cells were treated with this drug in the presence or absence of zinc salts and its membrane permeability was analyzed by using electrophysiology techniques, measuring the variations in the ion currents induced by the drug. Interestingly, in cells treated with zinc (10 mM), a decrease in the membrane permeability induced by Irvalec® was observed. Altogether, these results suggest that Irvalec® induces a rapid membrane permeabilization that lead to a necrotic cell death.

Supported by CICVT SAF2010-14916 and FIS (RD06/0014/0006) Grants.