Interaction of the antitumor alkylphospholipid perifosine with human erythrocytes and cell membrane models

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Abstract

Perifosine (octadecyl-(1,1-dimethylpiperidinio-4-y1)-phosphate) is a synthetic antitumor alkylphospholipid with promising results against a variety of cancers[1]. Alkylphospholipids (APL) do not target DNA, being the exact mechanism of APLs action on molecular level not yet known, but it is clear that they act at the level of cell membranes, where they interfere with apoptotic and mitogenic signal transduction pathways[2]. With the purpose to understand the molecular mechanisms of the interaction of perifosine with cell membranes, it was incubated with intact human erythrocytes, isolated unsealed human erythrocyte membranes (IUM) and molecular models of cell membranes. The latter consisted in bilayers built-up of dimyristoylphosphatidylcholine (DMPC) and dimyristoylphosphatidylethanolamine (DMPE), phospholipid classes present in the outer and inner monolayers of most cell membranes, respectively. The capacity of perifosine to perturb the bilayer structures of DMPC and DMPE was assessed by X-ray diffraction; DMPC large unilamellar vesicles (LUV) and IUM were studied by fluorescence spectroscopy, and intact human erythrocytes were observed by scanning electron microscopy (SEM). Experimental results obtained by X-ray diffraction and fluorescence spectroscopy showed that perifosine interacted with a class of lipids found in the outer moiety of the erythrocyte membrane. Fluorescence spectroscopy experiments in IUM showed a sharp decrease of laurdan generalized polarization, suggesting a perturbation on the water molecular dynamics in the polar headgroup region of phospholipids bilayer in a concentration range lower than 100 μM; SEM studies on human erythrocytes showed that 5 μM perifosine induced changes from the normal biconcave morphology of red blood cells into equinocytes. These results allowed us to conclude that perifosine interact with the outer monolayer of cell membranes.

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