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A structural basis for cholesterol inhibition of outer mitochondria membrane permeabilization

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The permeabilization of the mitochondrial outer membrane is an important and irreversible step in apoptosis. The point of no return occurs when Bcl-2 family proteins interact with the membrane to form pores and release toxic molecules into the cytosol of the cell. Addition of cholesterol to mitochondrial-like membranes has been shown to inhibit the pore formation process. The fact that the enantiomer of cholesterol also has this inhibitory effect provides support for an inhibition mechanism based on structural changes in the membrane as opposed to one based on direct interaction between the proteins and cholesterol. Structural investigations of phospholipid membranes consistently show that cholesterol increases both the thickness and rigidity of lipid bilayer. However, available studies were done for membranes containing, at most, three lipid components. We thus asked the question of whether cholesterol affects more complex membranes, such as the outer mitochondrial membrane, in the same way. We used both x-ray and neutron diffraction to probe the structure of a complex five component mitochondria-like membrane as a function of cholesterol content. X-ray diffraction was used to investigate the lamellar and in plane structure of the membrane, providing membrane thickness and average area per lipid as a function of cholesterol content. Neutron reflectivity was used to probe the position of cholesterol within the membrane. We find that, as for less complex membranes, cholesterol increases the head-to-head thickness of the membrane, the area per lipid, and the order parameter associated with lipid tail orientation.

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