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Lipid Membrane Composition Determines Binding, Disruption and Cytotoxicity of Gomesin Peptides

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1. Background.

Gomesin is a cationic peptide originally isolated from the haemocytes of the Brazilian tarantula *Acanthoscurria gomesiana* that shows in-vitro and in-vivo antitumoral activities against cancer. A number of mechanisms have been proposed to explain the antitumoral activity of Gomesin. These include binding and disruption of the plasma membrane, and modulation of signalling cascades that control cell death and proliferation. Gomesin shows affinity for membranes containing negatively-charged phospholipids with a weak affinity for membranes rich in neutral lipids. However, the influence of cholesterol content has not been fully explored. The present study aims to further investigate the importance of cholesterol in the ability of Gomesin to interact with artificial membranes and cellular models to exert its cytotoxicity.

2. Methods.

Electrochemical impedance spectroscopy and tethered bilayer lipid membranes assays were used to analyze protein binding to the membrane or membrane disruption induced by Gomesin, respectively. These assays were coupled to cellular models of BRAF-mutated melanoma and healthy fibroblast cells by studying changes in viability induced by Gomesin under the influence of modulators of the cholesterol content.

Results

Our investigations revealed that fibroblasts are less affected by Gomesin cytotoxicity and presented a higher content of cholesterol. Interestingly, we identified that two natural Gomesin variants, AgGom and HiGom, contain several consensus sequences for the binding of cholesterol. Studies in artificial membranes revealed that AgGom and HiGom bind preferentially to membranes containing phosphatidylserine and cholesterol in a manner that is dependent on both the cholesterol content and the peptide concentration. Additionally, cholesterol impaired membrane disruption induced by HiGom while differently regulating binding of AgGom and HiGom to artificial membranes. Moreover, the cytotoxicity of Gomesin was blunted by increasing concentrations of cholesterol in melanoma cells but potentiated by cholesterol depletion in healthy fibroblasts.

Conclusions

Our results support a specific role for cholesterol in the selective cytotoxicity of Gomesin peptides in a manner that can modulate membrane fluidity, peptide binding and membrane disruption.