Glycan Alteration Imparts Cellular Resistance to a Membrane-Lytic Anticancer Peptide

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SUMMARY

Although resistance toward small-molecule chemotherapeutics has been well studied, the potential of tumor cells to avoid destruction by membrane-lytic compounds remains unexplored. Anticancer peptides (ACPs) are a class of such agents that disrupt tumor cell membranes through rapid and non-stereospecific mechanisms, encouraging the perception that cellular resistance toward ACPs is unlikely to occur. We demonstrate that eukaryotic cells can, indeed, develop resistance to the model oncolytic peptide SVS-1, which preferentially disrupts the membranes of cancer cells. Utilizing fission yeast as a model organism, we show that ACP resistance is largely controlled through the loss of cell-surface anionic saccharides. A similar mechanism was discovered in mammalian cancer cells where removal of negatively charged sialic acid residues directly transformed SVS-1-sensitive cell lines into resistant phenotypes. These results demonstrate that changes in cell-surface glycosylation play a major role in tumor cell resistance toward oncolytic peptides.

Cell Chemical Biology 24, 1–10, February 16, 2017

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Mercredi 15 février 2017, à 11 h 30
Auditorium du St-Patrick