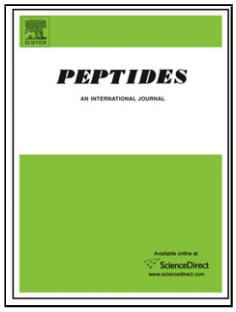

Title: Ultrashort cationic lipopeptides and lipopeptoids: Evaluation and mechanistic insights against epithelial cancer cells

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Title: Ultrashort cationic lipopeptides and lipopeptoids: evaluation and mechanistic insights against epithelial cancer cells

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Highlights

- The discovery of ultrashort cationic lipopeptides that possess promising anticancer activity is outlined
- The synthesized lipopeptides do not eradicate cancer cells via cell lysis or necrosis
- Ultrashort cationic lipopeptides may elicit different mechanism of cancer cell killing either by caspase-dependent apoptosis or caspase-independent cell death.

Abstract

Peptides present an attractive scaffold for the development of new anticancer lead agents due to their accessibility and ease of modification. Synthetic ultrashort cationic lipopeptides, with four amino acids or less conjugated to a fatty acid, were developed to retain the biological activity of longer peptides in a smaller molecular size. Herein, we report the activity of amphiphilic lipotripeptides, lipotripeptoids and lipotetrapeptides against breast (MDA-MB-231, JIMT-1), prostate (DU145) and pancreas (MiaPaCa2) epithelial cancer cell lines. The lipotripeptide C16-KKK-NH_2 and lipotetrapeptide C16-$P_{Cat}P_{Hex}P_{Hex}P_{Cat}$-$NH_2$ were identified to possess anticancer activity. The latter lipotetrapeptide possess a short polyproline scaffold consisting of only two L-4R-aminoproline (P_{Cat}) and two L-4R-hexyloxyproline (P_{Hex}). However, all the prepared lipotripeptoids lack anticancer activity. The amphiphilic C16-$P_{Cat}P_{Hex}P_{Hex}P_{Cat}$-$NH_2$ exhibited similar anticancer potency to the surfactant benzethonium chloride while superior activity was observed in comparison to myristylamine. Mechanistic studies revealed that the peptides do not lyse ovine erythrocytes nor epithelial cancer cells, thus ruling out necrosis as the mechanism of cell death. Surprisingly, the two lipopeptides exhibit different mechanisms of action that result in cancer cell death. The lipotripeptide C16-KKK-NH_2 was found to induce caspase-mediated apoptosis while C16-$P_{Cat}P_{Hex}P_{Hex}P_{Cat}$-$NH_2$ kills tumor cells independent of caspases.

Keywords:

Anticancer Peptides, Synthetic Peptides, Ultrashort Peptides, Lipopeptides, Lipopeptoids, Cationic Amphiphiles