Programmed cell death in cancer cells: Overcoming resistance through paraptosis-inducing compounds

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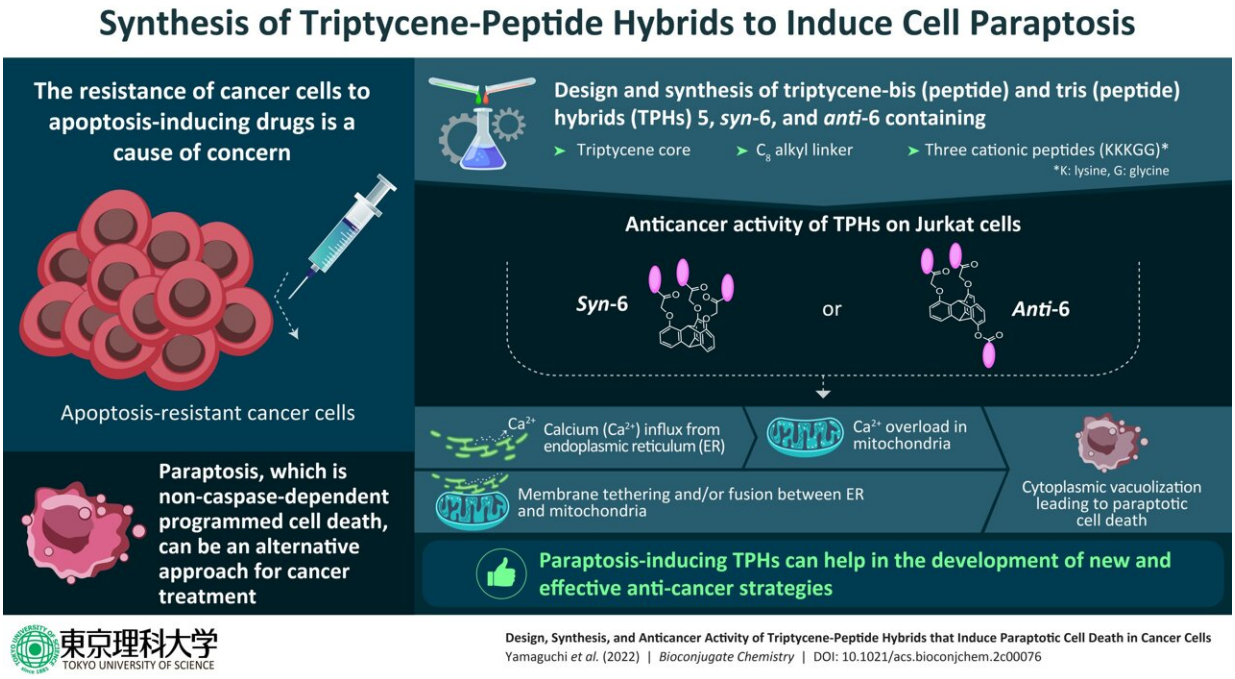

Researchers from Tokyo University of Science have developed novel complex-peptide hybrids, which can induce a type of programmed cell death called “paraptosis” in apoptosis-resistant cancer cells. Credit: Tokyo University of Science

Apoptosis, a type of programmed cell death (PCD), is a biological

process through which unwanted cells are eliminated in multicellular organisms. In most cells, certain proteins known as "caspases" trigger apoptosis. This process is especially important for the treatment of cancer, since inducing cell death in cancer cells can help in their elimination.

Other than apoptosis, several types of PCDs occur in cells, including paraptosis, necroptosis, and autophagy. Of these, paraptosis is the most recently identified type of PCD, which is caused by the influx of excess calcium in the cells, leading to cell death.

Cancer cells often become resistant to drugs that induce apoptosis and other types of PCDs. In such cases, inducing paraptosis, which is not dependent on caspases, could act as a promising anti-cancer treatment. Hence, the development of compounds that can induce paraptosis in cancer cells is crucial.

To this end, a team of researchers from the Tokyo University of Science, led by Prof. Shin Aoki in collaboration with Mr. Kohei Yamaguchi and Dr. Kenta Yokoi, conducted a study to develop novel complex-peptide hybrids with paraptosis-inducing potential. This study was published in *Bioconjugate Chemistry*.

"Previously, we synthesized an iridium complex-peptide hybrid compound and observed that it induced cell death in cancer cells, which was different from apoptosis. Since this compound was unlike other paraptosis-inducing compounds, we wanted to understand its mechanism of paraptosis induction. Our goal now is to synthesize new compounds and elucidate how they induce paraptosis in cells, before we share this crucial information with the public," explains Prof. Aoki while discussing the team's motivation behind this study.

The newly synthesized compounds were composed of a triptycene

core—an aromatic hydrocarbon—with two or three cationic peptides made of the amino acids lysine and glycine (represented as KKKGG) through a C_8 alkyl linker chain, at different positions of the triptycene units. As a result, three triptycene core hybrids (TPHs) were produced, namely, 5, syn-6, and anti-6.

The team subsequently performed experiments on Jurkat cells, a type of immortalized human lymphocytes used in research, to understand the type of PCD that occurred in these cells on treatment with syn-6 and anti-6. They found that death in these cells was inhibited by carbonyl cyanide m-chlorophenyl hydrazone (CCCP) which is an uncoupling reagent and an inhibitor of mitochondrial calcium uptake, RuRed, which is an inhibitor of the mitochondrial calcium channel), and 2-aminoethoxydiphenyl borate (2-APB), which is an inhibitor of D-inositol-1,4,5-trisphosphate receptor. However, cell death was not inhibited by inhibitors of the other types of PCDs.

Hence, they ruled out autophagy, necroptosis, and apoptosis, confirming that paraptosis is a major PCD pathway induced by syn-6 and anti-6 in Jurkat cells.

"Studies have indicated that the TPHs syn-6 and anti-6 induce the transfer of excess calcium from the endoplasmic reticulum (ER) to mitochondria, resulting in a loss of mitochondrial membrane potential. It is very likely that these phenomena are strongly related with the fusion of the ER with the mitochondria, followed by cytoplasmic vacuolization, resulting in cell death," said Prof. Aoki, when asked why these two TPHs were selected for the study. The TPHs syn-6, and anti-6 are more hydrophilic than other TPHs, which could also be a reason for their high paraptosis-inducing anti-cancer potential.

Through additional imaging experiments, the team detected the presence of cytoplasmic vacuolization, elevated mitochondrial calcium

concentrations, and the degradation of the ER in Jurkat cells treated with syn-6 and anti-6.

Based on previous findings, the team hypothesized that in Jurkat cells as well, the influx of calcium in the mitochondria might be facilitated by the close proximity of the ER and the mitochondria. As expected, they found that the ER and mitochondrial membranes were attached to one another, facilitating direct transfer of calcium.

These findings confirmed that Jurkat cells treated with syn-6 and anti-6 had undergone programmed cell death, owing to paraptosis. They also provide crucial information for the design of compounds that can be used as therapeutic agents against cancer and other diseases.

More information: Kohei Yamaguchi et al, Design, Synthesis, and Anticancer Activity of Triptycene–Peptide Hybrids that Induce Paraptotic Cell Death in Cancer Cells, *Bioconjugate Chemistry* (2022). DOI: 10.1021/acs.bioconjchem.2c00076

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