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Mechanistic Study of Cell Death of Cancer Cells Induced by Cyclometalated Iridium(III)-Peptide Hybrids (IPHs)

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Cationic amphiphilic peptides (CAPs) have received considerable attention as reagents for nonviral gene delivery, the treatment of microbial infections and cancer therapy. It is generally thought that interactions of cationic amphiphilic molecules with cancer cell membranes explain their anticancer actions. However, the mechanisms responsible for the cationic amphiphile-induced cell death are complicated and not fully understood. Recently, we reported on the design and synthesis of Ir complex-peptide hybrids (IPHs) containing cationic peptides such as KKGG (K) sequence induce cell death in Jurkat cells.[1] Our mechanistic study suggests that IPHs bind to intracellular Ca^{2+}-calmodulin complex and release Ca^{2+}, resulting in the non-apoptotic programmed cell death via Ca^{2+}- dependent pathway.[2,3] In the present work, we examine the detail mechanism of cell death of IPHs by western blotting and so on. It was suggested that activation of endoplasmic reticulum (ER) stress and autophagy pathways are activated by IPHs, resulting in cell death via mTOR signaling pathway. These results will be presented in this paper.

(1) Hisamatsu, Y. *et al. Bioconjugate Chem.* **2015**, *26*, 857-879.
(2) Hisamatsu, Y. *et al. Bioconjugate Chem.* **2017**, *26*, 507–523.
(3) Yokoi, K. *et al. Eur. J. Inorg. Chem.* **2017**, 5295–5309.