Mechanism and Improvement of 5-Aminolevulinic Acid-Mediated Photodynamic Therapy of Prostate Cancer

Introduction and Objective: The aim of this study was to clarify the mechanism of the accumulation of 5-aminolevulinic acid (ALA)-dependent protoporphyrin IX (PpIX), ALA-photodynamic therapy (PDT)-induced cell death and enhancing efficiency by a ferrochelatase inhibitor in prostate cancer PC-3 cells. We aimed focal therapy for prostate cancer by ALA-PDT to develop a new therapeutic modality in clinical setting and investigated the potential of ALA-PDT.
Materials and Methods: The accumulation of ALA induced PpIX in PC-3 cells was observed by fluorescence microscopy and measured by flow cytometry analysis. The efficiency of ALA-PDT was analyzed by flow cytometry and assessed by cell death, caspase-3 activity and mitochondrial membrane potential. The ALA-PDT promoting effects of ferrochelatase inhibitors, such as deferoxamine and NOC-18, were also analyzed. We confirmed these results obtained *in vitro* with an animal model using nude mice.
Results: ALA-induced PpIX accumulation was increased in time and ALA concentration-dependent manners. ALA-PDT-induced cell death was both apoptosis and necrosis. Caspase-3 like activity was increased and the levels of mitochondrial membrane potential were decreased. Inhibition of ferrochelatase by deferoxamine and NOC-18 led to increase of PpIX accumulation and enhanced effect of ALA-PDT in PC-3 cells. *In vivo*, the degeneration of tumor tissue by ALA-PDT was observed within a broader range and led to apoptosis and necrosis. Apoptosis index of the degeneration tissue by single strand DNA stain was increased by ALA-PDT.
Conclusions: The results demonstrated that ALA-PDT induced cell death with accumulation of PpIX in PC-3 cells in both *vitro* and *vivo* systems. ALA-PDT induced PC-3 cell death by the mechanisms of both necrosis and apoptosis through a caspase-independent mitochondrial pathway. Inhibition of ferrochelatase enhanced these effects suggesting that ferrochelatase played a crucial role in ALA-PDT. ALA-PDT could be a new modality for focal therapy of prostate cancer as photodynamic therapy.