中文題目: 同時針對 PI3K 及 mTOR 投予一專一性標靶抑制藥物的新策略可減緩頭頸癌的致瘤性

英文題目: Novel strategy of simultaneous blockage over PI3K and mTOR by a specific targeting inhibitor attenuates tumorigenesis of head and neck cancer

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Background: Aberrant expression of PI3K/AKT/mTOR signaling pathway is often observed, leading to the tumorigenesis in head and neck cancer. For the development of new targeting strategy, we investigated the impact of tumor cells after treatment with a dual PI3K/mTOR inhibitor.

Methods: A dual PI3K/mTOR inhibitor BGT226 was applied in this investigation. For determination of growth inhibition, various head and neck cancer cell lines with distinct characteristics were tested. The alteration of protein expression was assessed by Western blot. Cell cycle was determined by propidium iodide staining. For study of cell death, assays for cell apoptosis and autophagy were applied. A pharyngeal cancer cell line FaDu xenografted animal model was constructed to examine the *in vivo* drug potency.

Results: In all tested cell lines, BGT226 exhibited growth inhibitory effect with IC_{50} ranging from 7.4 – 30.1 nM. The drug effect in nasopharyngeal cancer cell line HONE-1 was similar in the parental and in the derived cisplatin resistant cells. In the study of AKT/mTOR signal alteration, the activation of AKT and mTOR was suppressed, and the associated cascade protein was down-regulated. The investigations of cell cycle revealed an accumulation of cells in the G0/G1 phase, and loss of those in the S phase concomitantly. Analysis of surrogate markers for apoptosis over fragmented DNA and caspase 3/7, PARP indicated lacking of the type I programmed cell death. On the contrary, the presence of type II programmed cell death, autophagy, was revealed by the aggregation and up-regulation of the microtubule-associated protein light chain 3B-II. In addition to the autophagosome formation, the process of autophagy flux was evidenced by p62 degradation, and with successful inhibition using chloroquine. Further determination of survival role using chlonogenic assay showed revival of cells from BGT226 effect when autophagy route was blocked by 3-methyladenine or siRNA targeting beclin-1. For *in vivo* studies, the tumor size in xenografted mouse was delayed in dose-dependent manner when the compound or empty vehicle was fed. Suppressed signal was shown by diminished immunohistochemical staining of p-p70 S6 kinase in the experimental group, along with the presence of autophagosome in electron microscopy. Finally, the tumor inhibitory effect of BGT226 in mouse model was comparable to rapamycin, a specific mTOR inhibitor. Both compounds were significantly effective comparing to LY294002, a pan-PI3K inhibitor.

Conclusions: Our study indicated the novel strategy for simultaneous blockage of PI3K and mTOR by BGT226 exhibited inhibitory effect in head and neck cancer, and are worthwhile for translation to clinical studies in the future. (Supported by DOH99-TD-C-111-004 and CA-099-PP-36 grant)