β-Apopicropodophyllin as novel radiosensitizer promotes ER stress signaling – ROS – cell death pathway.

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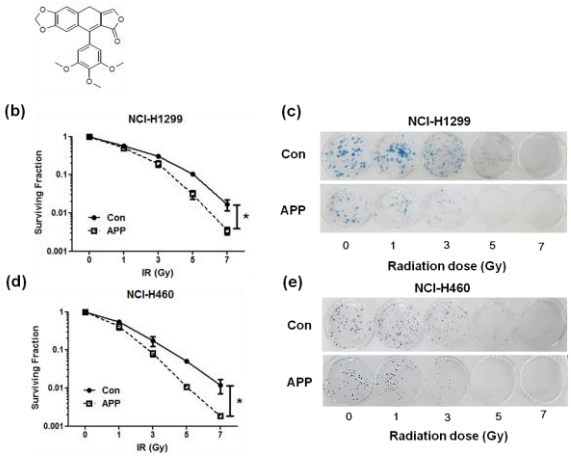
1. Introduction

β-Apopicropodophyllin (APP) is a synthesized derivative of podophyllotoxin (PPT), which is a natural product that has been used as a traditional drug to decrease immunosuppression, exert antiviral effects for the treatment of influenza, venereal warts, measles and herpes, and even to treat skin cancer [1]. Three representative semi-synthetic epipodophyllotoxin derivatives have been identified as anti-cancer drugs: the PPT-related chemicals, etoposide, teniposide, and etopophos [1]. All three were shown to reversibly bind tubulin and disrupt its polymerization to prevent mitotic spindle formation, induce cell cycle arrest, and inhibit cell proliferation [1]. Our group previously showed that treatment of lung cancer cells with APP altered microtubule polymerization and triggered DNA damage to induce cell cycle arrest, while also stimulating pro-apoptotic endoplasmic reticulum (ER) stress [2].

Here, we investigated whether APP could act as a novel radiosensitizer candidate to enhance the cancer treatment efficacy of ionizing radiation (IR) against NSCLC, both *in vitro* and *in vivo*. We found that the co-application of APP and IR synergistically triggered cancer cell death by disrupting the mitochondrial membrane potential and inducing apoptosis via the activation of ER stress signaling.

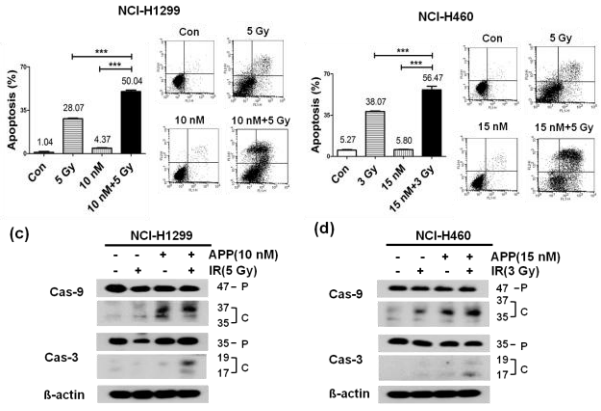
2. Methods and Results

2.1. APP acts as a radiosensitizer by retarding cell growth in vitro



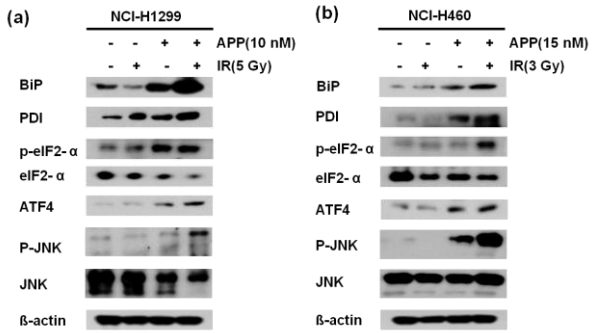
<Figure 1. APP enhances the ability of IR to decrease NSCLC cell growth>

2.2. Combination of APP and IR enhances apoptosis



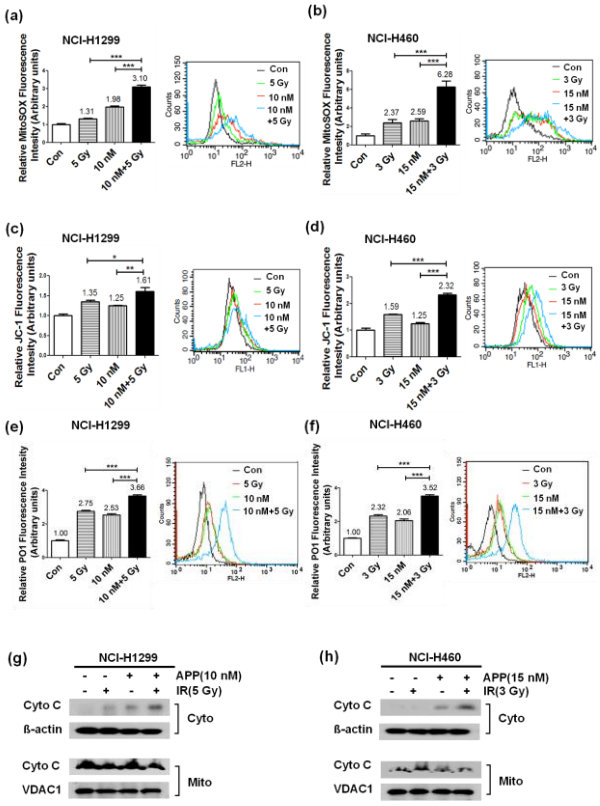
<Figure 2. Combination of APP and IR enhances apoptosis in NSCLC cells>

2.3. Combined treatment with APP and IR enhances ER stress



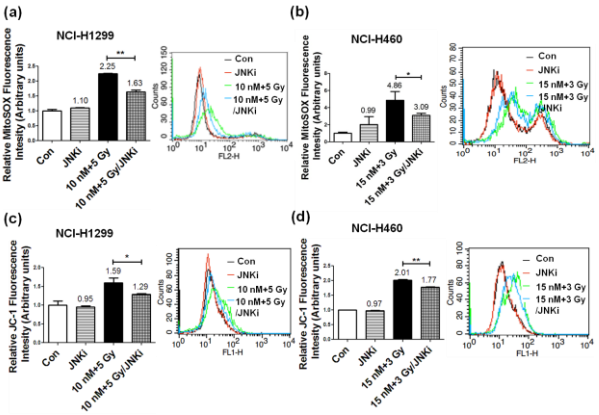
<Figure 3. Combination of APP and IR induces ER stress in NSCLC cells>

2.4. Mitochondrial ROS production is involved in the radiosensitizing effect of APP



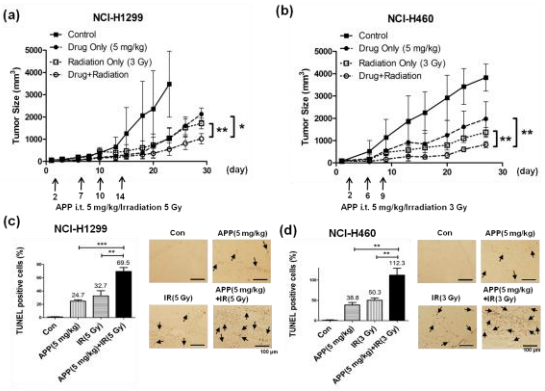
<Figure 4. Combination of APP and IR induces mitochondrial ROS accumulation in NSCLC cells>

2.5. JNK is a key molecule in the radiosensitizing effect of APP



<Figure 5. The radiosensitizing effect of APP is attributable to modulation of JNK activity>

2.6. In vivo radiosensitization effect of APP



<Figure 6. Combination of APP and IR enhances apoptosis *in vivo*>

3. Conclusions

APP is radiosensitizers candidate for NSCLC, and targeting ER-stress pathway followed by induction of ROS and apoptotic cell death *in vitro* and *in vivo*. Our results also showed that JNK might be a major target of radiosensitizing effect exerted by APP.

REFERENCES

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[2] J.Y. Kim, J.H. Cho, J.R. Choi, H.J. Shin, J.Y. Song, S.G. Hwang, H.D. Um, Y.D. Yoo, J. Kim, J.K. Park, A novel anti-cancer role of β-apopicropodophyllin against non-small cell lung cancer cells, Toxicol Appl Pharmacol 357 (2018) 39-49.