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O 22 - Ovarian cancer cells under ultrasound exposure of doxorubicin show an enhanced immunogenic cell death

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Abstract

Background. Ultrasound (US) is a mechanical wave that can be employed in many different fields. In recent years, the safety and very good tissue penetrating ability of US has prompted to the possibility of employing US-based strategies, not just as diagnostic tool, but also for therapeutic purposes. Therefore, US has been used for various therapeutic approaches such as promoting tissue healing, decreasing chronic pain, tumor ablation and drug release from drug delivery systems but, one of the most attractive approach, remains the sonodynamic therapy (SDT) [1]. SDT is an anticancer and antibacterial approach based on the use of US to activate a chemical compound, called sonosensitizer, through acoustic cavitation enhancing the sonosensitizer cytotoxicity. A chemical compound that can act as sonosensitizer, is doxorubicin, a potent anticancer agent used for the treatment of a huge variety of cancers. In particular it has a key role in the second line treatment of ovarian cancer. However, the overall survival rates of ovarian cancer remain considerably worse than those for other gynecological malignancies mainly because the cancer comes back, or recurs, after treatment in more than 70% of women with the disease. For this reason, many efforts in pharmacological research have been made in order to increase doxorubicin efficacy against ovarian cancer such as inducing immunogenic cell death (ICD) for a long lasting protective antitumor activity [2]. On this point, US-based strategies, as SDT, seems to be highly encouraging. **Methods.** In this work, we addressed the relapsing issue, proper of ovarian cancer, investigating the increase of doxorubicin-induced ICD through US. In this regard, experiments have been carried out on the human ovarian cancer cell line A2780 to test if the activation of low doxorubicin concentrations by US is effective in maximizing the doxorubicin-induced ICD. Moreover, hypericin, a natural well-known ICD inducer, has been used as yardstick, in comparison to doxorubicin. **Results.** The activity of doxorubicin and hypericin under US exposure was first investigated on A2780 cell proliferation, observing a statically significant decrease of cell proliferation over time. Along with this, specific biomarkers associated with ICD have been taken into consideration such as the expression of calreticulin (CRT) at the cell surface and the ATP production. US exposure of doxorubicin or hypericin was able to induce a statistically significant increase of ATP production and CRT expression. Finally, the expression of genes involved in the ICD pathway (such as CRT, LC3II and HMGB1) have been analyzed by real time RT-PCR after US exposure of doxorubicin or hypericin. **Conclusions.** The data obtained showed, for the first time, that the use of US is an efficient strategy to significantly boost doxorubicin-induced ICD, opening new encouraging developments in the treatment of ovarian cancer.

Keywords

Ultrasound (US), immunogenic cell death (ICD), Sonodynamic Therapy (SDT), Doxorubicin

References

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