Targeting membranous GRP78 through taxol-nanoparticles: Three in One against ovarian cancer

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Ovarian cancer is the first cause of death among gynecological cancers due to late diagnosis. In fact, this disease is asymptomatic at early stages implying the identification of the disease at late stages. Glucose regulated protein 78 (GRP78) has the specificity to be found at the cell surface in ovarian cancer cells and not in healthy ovarian cells. GRP78 is a chaperone protein found in the lumen of endoplasmic reticulum. In cancer cells, GRP78 is relocated at the cell surface by a mechanism which is not very well understood. Its specific cell surface location in cancer cells renders this protein very attracting for a specific targeting. In addition, in a previous work, we have shown that GRP78 antibodies purified from serum of ovarian cancer patients increase the taxol response of ovarian cancer cells, in contrast to GRP78 antibodies purified from malignant ascites. For this reason, we decided to assess an epitope mapping of GRP78 antibodies from serum and ascites of the same patient. Epitope mappings obtained with these two fluids are quite similar. However, some GRP78 antibodies were present in different quantities depending on their origin. Based on these differences, we selected 6 epitopes as potent epitopes involved in apoptosis. We synthetized peptides corresponding to these epitopes and added them in culture medium of ovarian cancer cells in presence or not of GRP78 antibodies purified from serum. In this way, we determined that one of these epitopes was able to modulate the effect of taxol. We thus decided to use a commercial antibody against this epitope (located in C-terminal domain of GRP78) to target membranous GRP78. This antibody was first tested, *in ovo* (CAM assay), on tumor development. When it was added in cell suspension before inoculation on CAM, it allows to decrease the tumoral development compared to IgG control. Nevertheless, and in contrast to in vitro results, this antibody does not induce synergic effect with taxol on tumor. We then used this antibody to coat taxol-loaded nanoparticles (NP-Tx-Ab). *In vitro*, no difference was observed on taxol response between antibody-coated and uncoated taxol-nanoparticles. However, *in ovo*, NP-Tx-Ab treatment significantly reduced the tumor size compared to uncoated-nanoparticles or free taxol. This suggests that the targeting of membranous GRP78, *in ovo*, allows to increase the response to taxol.

In conclusion, this study showed that it exists a multitude of GRP78 antibodies in ovarian cancer patient fluids. Depending on their specificity, some of them can increase cell apoptosis. Furthermore, the targeting of membranous GRP78 with these antibodies using taxol-loaded nanoparticles improves the response to taxol. This specific targeting of cancer cells through membranous GRP78 could be a very interesting way to treat patients in order to preserve healthy cells during chemotherapy.