BLADDER CANCER

Bovine milk protein complex has antitumour effect *in vivo*

The bovine equivalent of HAMLET (human α -lactalbumin made lethal to tumour cells) has been tested in an *in vivo* model of bladder cancer for the first time—with promising results—in a study by Zhengwen Xiao and colleagues published in the *British Journal of Urology International*.

HAMLET has been making waves in the oncology community for some time owing to its ability to selectively kill a wide range of cancer cells but not healthy tissue. In a small cohort of patients with bladder cancer treated with HAMLET, cell death was observed in tumours but not in surrounding healthy bladder tissue, implying a favourable toxicity profile. Given the known issues of toxicity associated with BCG treatment, HAMLET could be a welcome alternative.

Researchers keen to maximize the clinical potential of HAMLET have highlighted the limited availability of human milk and shifted their focus to its bovine counterpart. A therapeutic agent that can be derived from cow's milk could be produced on a large scale and, therefore, overcome this limitation.

HAMLET is a protein–lipid complex of human α -lactalbumin and oleic acid.

Bovine α -lactalbumin exhibits 71% amino acid homology to the human protein and can be complexed with oleic acid to form bLAC, which has demonstrated similar biological activity to HAMLET.

In this new study, Xiao and team first tested the cytotoxicity of bLAC in a panel of bladder cancer cell lines. bLAC induced apoptosis in a dose-dependent manner in all cell lines, including HT-1376 and UC14P1000, which are resistant to apoptosis induced by tumor-necrosis-factor-related apoptosis-inducing ligand—one of the downstream effects of BCG.

The investigators then tested the antitumour efficacy of bLAC in an orthotopic rat bladder cancer model. Animals treated with bLAC demonstrated a dose-dependent tumour response and significant survival benefits compared with rats that received intravesical saline. Survival was evaluated as the number of rats that survived for >90 days after tumour implantation. 10 of 12 rats treated with 10 mg/ml intravesical bLAC survived for >90 days, compared with only 2 of 11 rats that received saline instillations ($P = 0.004$). Moreover, bLAC demonstrated comparable efficacy to BCG (8 of 12 rats treated with BCG survived >90 days).

How HAMLET, and indeed bLAC, achieve their apoptotic specificity is not understood, but HAMLET seems to attack tumour cells from multiple angles, disrupting chromatin, triggering mitochondrial damage and causing macroautophagy.

These findings suggest that bLAC combines the antitumour activity of HAMLET with the ability for large-scale production. The next step will be to establish the clinical efficacy of bLAC for the treatment of non-muscle-invasive bladder cancer.

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Original article Xiao, Z., Mak, A., Koch, K. & Moore, R. B. A molecular complex of bovine milk protein and oleic acid selectively kills cancer cells *in vitro* and inhibits tumour growth in an orthotopic rat bladder tumour model. *BJU Int.* doi:10.1111/j.1464-410X.2012.11737.x.