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PROSTATE CANCER

MCT4 is a novel target for prostate cancer

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Antisense oligonucleotides (ASOs) targeting *MCT4* represent a potential novel approach for the treatment of castration-resistant prostate cancer (CRPC), say researchers.

New strategies for the treatment of CRPC are urgently needed and studies have shown that altered energy metabolism in cancer cells offers a unique target. As a result of reprogrammed glucose metabolism (that is, a switch from oxidative phosphorylation to aerobic glycolysis), many cancer cells secrete large amounts of lactic acid, which facilitates tissue invasion, metastasis and neoangiogenesis. As secretion of lactic acid is largely mediated by MCT4 (a plasma membrane transporter protein), Choi and co-workers investigated targeting of the *MCT4* gene as a novel approach for the treatment of CRPC.

Firstly, the researchers stained a tissue microarray made up of tissues from human prostate cancers (Gleason grades 3, 4 and 5) for MCT4 protein. They found that MCT4 protein expression was significantly higher in grade 5 prostate cancer specimens than in grade 3 and 4 specimens. They also noted that increased MCT4 expression was associated with earlier time to relapse (defined by increases in serum PSA levels) and development of CRPC.

The researchers went on to show that treatment of PC3 CRPC cells with *MCT4*-targeting siRNAs resulted in inhibition of PC3 cell proliferation. Ten different *MCT4*-targeting ASOs inhibited PC3 cell proliferation and MCT4 expression to varying degrees. "A strong correlation was found between the reduced levels of MCT4 mRNA in PC3 cells treated with the various ASOs and the resulting cell numbers..." say the authors, "...indicating that the growth inhibition by the ASOs was directly related to MCT4 knockdown".

In vitro studies showed that treatment of PC3, DU145 and C4-2 CRPC cultures with the two most potent ASOs resulted in inhibition of MCT4 expression, reduced lactic acid secretion, increased intracellular lactic acid levels, decreased aerobic glycolysis and reduced cell proliferation.

Use of the candidate MC4 ASOs to treat male athymic nude mice with subcutaneous PC3 tumours resulted in inhibition of tumour growth without major toxic effects on the host.

"*MCT4*-targeting ASOs that inhibit lactic acid secretion may be useful for therapy of CRPC and other cancers characterized by excessive lactic acid secretion resulting from reprogrammed cellular energy (glucose) metabolism, an emerging hallmark of cancer," conclude the authors.

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ORIGINAL ARTICLE Choi, S. Y. The MCT4 gene: a novel, potential target for therapy of advanced prostate cancer. *Clin. Cancer Res.* http://dx.doi.org/10.1158/1078-0432.CCR-15-1624 (2016)

FURTHER READING Zhang, Y. & Yang, J. M. Altered energy metabolism in cancer: a unique opportunity for therapeutic intervention. *Cancer Biol Ther. Nature* **14**, 81–89 (2013)