Spotlight

By M.O.

Making "Antisense" for Prostate Cancer Therapy

Hensley *et al.*
http://doi.wiley.com/10.1002/ijc.25634

In recent years, antisense oligonucleotides have emerged as promising therapeutic agents for the treatment of cancer. Antisense oligonucleotides hybridize with target mRNAs and can thereby suppress expression of tumor-promoting or therapy-impeding genes. The oligonucleotides must be properly modified to prevent enzymatic digestion. Gem231 is a prototypic mixed-backbone oligonucleotide targeting the regulatory subunit α of type I protein kinase A (PKARIα). PKA is a central cyclic AMP-dependent protein kinase involved in a wide variety of cell functions. PKARIα is overexpressed in many cancer cell types, and overexpression correlates with poor prognosis in patients with breast, lung, colon and prostate cancers.

Hensley and colleagues show that application of Gem231 sensitizes prostate cancer cells to the combination of androgen deprivation and radiotherapy, a common but suboptimal clinical treatment of localized intermediate-to high-risk prostate cancer. Smaller tumors and lower levels of circulating prostate-specific antigen were observed in nude mice with orthotopically implanted prostate tumors (LNCaP) when Gem213 was added to the common treatment. This effect was linked to enhanced apoptosis in tumor cells, increased levels of p53 and p21 as well as reduced levels of phosphorylated mitogen-activated protein kinases in Gem213-cotreated cells. The authors conclude that addition of Gem231 to the common regimen of radiotherapy and androgen deprivation may clinically benefit men carrying prostate tumors overexpressing PKARIα. This may be particularly valuable in patients with apparently localized disease but at high risk of distant microscopic metastasis.