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PROSTATE CANCER

Radiotherapy induces epigenetic changes

New data published in *Cancer Research* have shown that radiation can induce genetic and epigenetic changes in prostate cancer cells that confer stem-like properties and radioresistance in these cells.

Recurrence of prostate cancer after radiotherapy has been attributed to the presence of cancer stem cells and effective treatment might require total eradication of this cell population.

In vitro experiments using DU145 and LNCaP cells revealed that irradiation causes long-term and time-dependent changes in expression of stem-cell markers, enhanced ALDH activity, activation of the PI3K–AKT signalling pathway and gain of epithelial-to-mesenchymal transition signatures.

Analysis of DNA from both radioresistant and parental DU145 cells by comparative genome hybridization microarray showed that 53.5% of the genes analysed were differentially regulated, and gene expression profiling revealed that a number of these genes are involved in epigenetic regulation of protein expression via histone modification.

Irradiation induced changes in trimethylation of histone H3 at lysines 4, 27 and 36 (H3K4, H3K27 and H3K36, which are associated with transcriptional activation or gene silencing) that was observed for at least 6 weeks after therapy. Chromatin immunoprecipitation and luciferase reporter assays showed that the H3K36 methylation mark at the *ALDH1A1* promoter increased after radiation treatment, and ingenuity pathway analysis revealed that EZH2 expression (a histone methyltransferase) was significantly upregulated. Treatment with the methyltransferase inhibitor DZNep reduced the viability of radioresistant LNCaP and DU145 cells.

In primary cells from prostate cancer samples, treatment with DZNep prior to irradiation caused an increase in DNA double-strand breaks and apoptosis. DZNep was also observed to inhibit expression of EZH2 and ALDH1A1 and decrease H3K36 trimethylation.

In vivo, tumours originating from radioresistant DU145 cells pretreated with DZNep had significantly reduced growth rates and increased sensitivity to radiotherapy.

These data demonstrate that prostate cancer cells can undergo a phenotypic change when exposed to radiation and radiotherapy can induce histone modifications that can regulate tumorigenicity and radioresitance. Cotherapy with methyltransferase inhibitors could prevent these changes and hamper tumour cell reprogramming.

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ORIGINAL ARTICLE Peitzsch, C. *et al.* An epigenetic reprogramming strategy to re-sensitize radioresistant prostate cancer cells. *Cancer Res.* http://dx.doi.org/10.1158/0008-5472.CAN-15-2116 (2016)