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PROSTATE CANCER

IGF2 imprinting loss promotes cancer

Although prostate cancer incidence increases with age, the mechanisms by which ageing leads to prostate cancer development and progression remain largely unknown. Now, new data suggest that loss of imprinting (LOI) of the insulin-like growth factor (IGF)-2 gene, *Igf2,* in the mouse prostate leads to neoplasia via upregulation of cancer-associated signalling.

Altered IGF2 regulation via LOI is known to arise in the ageing human prostate, so Damaschke and colleagues sought to determine whether *Igf2* LOI is involved in prostatic neoplastic changes with ageing. "We have found that the peripheral zone of the prostate from men with prostate cancer commonly contains biallelic expression of Igf2, a potent growth factor, in contrast to other organs where the gene is only expressed from one allele, and, therefore, demonstrates genomic imprinting," explains corresponding author David Jarrard.

Imprinted *Igf2* expression is achieved via allele-specific methylation at the differentially methylated region (DMR), affecting the insulator activity of transcriptional repressor CTCF. "Loss of CTCF-binding protein during ageing mechanistically underlies the relaxation in *Igf2* imprinting seen during ageing and, furthermore, is accelerated with oxidative stress, linking environment stress to epigenetic changes". The team used a mouse model with point mutations in the CTCF-binding sites at the H19 imprint control region, which results in biallelic *Igf2* expression that recapitulates the increased levels seen with ageing-induced LOI. By crossing this model with an *Nkx3.1*-mutant mouse model, they were then able to determine whether there was a synergistic effect with *Igf2* LOI on development of cancer or prostatic intraepithelial neoplasia (PIN). Biallelic expression occurred in all mice with *Igf2* LOI, with associated changes in *Igf2* mRNA, and these mice demonstrated increased levels of PIN. Crossing with *Nkx3.1*-mutant mice had an additive effect on PIN development.

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They then investigated the signalling pathways involved in the increased proliferation and PIN formation observed in *Igf2* LOI animals using immunohistochemistry of p-AKT and p-ERK. Levels of p-ERK were increased in LOI models, but not in the *LOI;Nkx3.1*$^{-/-}$ mice, in which p-AKT becomes more prominent, suggesting altered signalling when *Nkx3.1* is lost. Furthermore, they showed that downstream signalling pathways activated by *IGF2* LOI were activated in patients with prostate cancer.

"Our results establish that *Igf2* LOI is sufficient on its own to increase rates of neoplastic development in the prostate by upregulating critical cancer-associated signalling pathways," concludes Jarrard. "Thus, a degradation of the epigenome leads to a field of cancer susceptibility in the prostate, serving as a marker for the disease as well as a potential avenue for preventative therapy."

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ORIGINAL ARTICLE Damaschke, N. *et al.* Loss of IGF2 gene imprinting in murine prostate promotes widespread neoplastic growth. *Cancer Res.* http://dx.doi.org/10.1158/0008-5472.CAN-16-3089 (2017)