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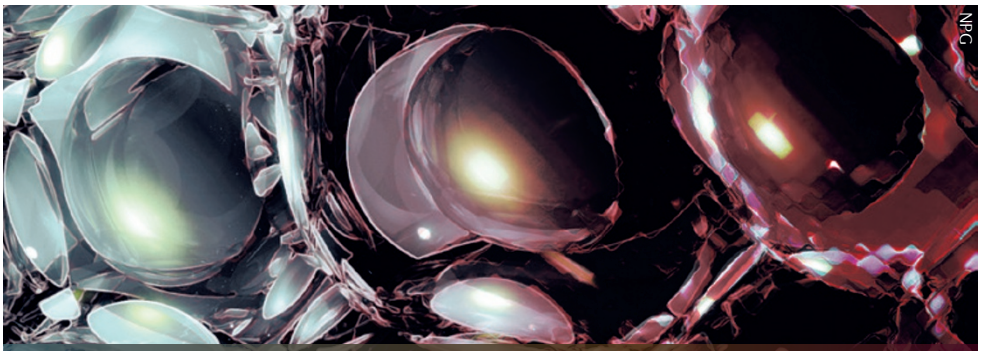

PROSTATE CANCER

Suppressing a wrong kind of transition

Epithelial–mesenchymal transition (EMT) of prostate tumour cells has a role in the development of metastatic castration-resistant prostate cancer (mCRPC). New research demonstrates that inhibition of the epigenetic regulator high mobility group protein HMGI-C (HMGA2) using a histone deacetylase inhibitor (HDACi) suppresses EMT and inhibits prostate tumour growth and metastasis *in vivo*. When combined with castration, HDACi treatment prolonged mouse survival and sensitized mesenchymal-like (MES) cells to castration.

The researchers had previously investigated pathways that promote EMT and mCRPC development and created a mouse model enabling isolation of tumour cell populations undergoing EMT or with MES characteristics. "Although EMT is thought to be involved in therapeutic resistance, the underlying molecular mechanisms are unclear," explains Marcus Ruscetti, first author of the new study. "We sought to uncover the processes regulating EMT and how they might contribute to mCRPC and therapeutic resistance."

The team first characterized their model system: using expression levels of an epithelial marker and a mesenchymal reporter they isolated epithelial, EMT and MES tumour cells from the mice and, subsequently, demonstrated that these cells could transition between each of the three states. Although the cell populations are genetically identical, the researchers found differing sensitivities to targeted inhibitors, suggesting epigenetic regulation. They then used RNA sequencing analysis to investigate differential transcriptional and epigenetic regulation. Epithelial and EMT cells differed in the expression of 591 genes, whereas EMT and MES cells differed in the expression of 4,234 genes, including some that might contribute to enhanced tumorigenic potential. Importantly, comparison of gene expression signatures revealed similarities between MES cells and cells from human mCRPC samples. When searching for epigenetic regulators that could explain differences in gene signatures, the team found that the chromatin remodelling protein HMGA2 was highly expressed in EMT and MES cells, as well as in human mCRPC cells, possibly pointing to a new marker for detection of patients likely to progress to mCRPC.

In vitro, stable knockdown of HMGA2 suppressed the MES state and treatment with a pan-HDACi reduced HMGA2 expression and induced p53-mediated apoptosis. Similar results were seen *in vivo* and, in addition, none of the mice treated with the pan-HDACi developed macrometastases.

Finally, the team explored the influence of castration resistance in this setting. They found that castration initially led to a decreased tumour burden; however, tumours soon grew back predominantly consisting of MES cells with a substantial downregulation of the androgen receptor signalling axis. Notably, when these castrated mice were treated with the pan-HDACi the number of MES cells was reduced and animal survival nearly doubled. Mechanistically, the researchers found that the HDACi reactivated the androgen receptor signalling axis, resensitizing MES cells to apoptosis caused by a lack of androgens.

"These findings provide some of the first *in vivo* evidence that direct targeting of EMT with epigenetic inhibitors can have therapeutic efficacy in blocking the onset of CRPC and preventing metastasis," summarizes senior author Hong Wu. "Clinically, they provide a rationale for the use of the pan-HDACi in combination with androgen deprivation in mCRPC; defining mCRPC-specific HDACis will be crucial to reduce off-target effects." The team will use their *in vivo* model to uncover other novel regulators of EMT that could be targeted therapeutically and also investigate their pan-HDACi in combination with current chemotherapy and radiotherapy strategies.

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