> *ERG* expression upregulated AR pathway genes and luminal lineage genes and downregulated cell cycle and mesenchymal and neuro-endocrine lineage genes

Cell line studies showed that ERG mediates cell cycle repression via the RB pathway by reducing expression of cell cycle genes. Treatment of ERG^{-}–AR^{low} cells in vitro and in vivo with enzalutamide alone had no effect, but combined treatment with enzalutamide and palboviclib, a CDK4 and CDK6 inhibitor, decreased expression of cell cycle genes and reduced cell and tumour growth.

Immunohistochemistry of human tissue microarray cores from patients with metastatic castration-resistant prostate cancer showed a strong association between AR and ERG.

This study reveals a new role for *ERG* in prostate cancer lineage plasticity. In *PTEN*–*TP53*-altered prostate cancer, *ERG* status could be used to guide treatment decisions.

Louise Stone

ORIGINAL ARTICLE Blee, A. M. et al. TMPRSS2-ERG controls luminal epithelial lineage and antiandrogen sensitivity in *PTEN* and *TP53*-mutated prostate cancer. *Clin. Cancer Res.* https://doi.org/10.1158/1078-0432.CCR-18-0653 (2018)

> CPAF absence enables clearance of the primary infection

active within the PMNs, and chlamydial infection prolonged PMN survival. By contrast, infection with the CPAF-mutant increased PMN death via NET-associated killing mechanisms, an effect prevented by addition of recombinant CPAF, indicating that CPAF has a direct effect on PMN survival. Infection with wild-type *Chlamydia*, but not the CPAF-mutant, blocked NET and ROS production after treatment with a PMN activator, further indicating a role for CPAF in PMN activation. This effect seems to occur via formyl peptide receptor 2 (FPR2), which provides a direct target of chlamydia on the cell surface, enabling hijack of neutrophils. *Chlamydia* infection interferes with FPR signalling, preventing neutrophil activation via the PKC and MAP kinase pathways.

These data identify CPAF as a mechanism by which *Chlamydia* can evade the immune system and could reveal potential therapeutic targets.

Annette Fenner

ORIGINAL ARTICLE Rajeeve, K. et al. *Chlamydia trachomatis* paralyses neutrophils to evade the host immune response. *Nat. Microbiol.* **3**, 824–835 (2018)

PROSTATE CANCER

DKK3 loss induces opposing effects

A new study shows that Dickkopf-3 (DKK3), which is downregulated in prostate cancer cells but has an unknown role in prostate stromal cells, has cell-specific effects on protein expression. DKK3 silencing in prostate stromal cells differentially affects levels of secreted transforming growth factor-β induced (TGFBI) and extracellular matrix protein 1 (ECM1), which seem to have opposing effects in prostate cancer. These observations have implications for developing therapies targeting DKK3 for this disease.

Immunohistochemistry of benign and malignant prostate tissue showed reduced DKK3 expression in the tumour epithelium and stroma. In vitro, DKK3 silencing in RWPE-1 prostate epithelial and WPMY-1 prostate stromal cells had cell type-specific effects. Silencing of DKK3 in WPMY-1 cells increased autocrine transforming growth factor-β (TGFβ)–mothers against decapentaplegic homolog 3 (SMAD3) signalling. Culture of DKK3-silenced RWPE-1 cells in conditioned media from control WPMY-1 cells increased the number of normal acini formed. Co-culture of DKK3-silenced WPMY-1 cells with RWPE-1 cells increased RWPE-1 proliferation.

Analysis of conditioned media from control and DKK3-silenced WPMY-1 and RWPE-1 cells revealed two proteins that were selected for further study: TGFBI and ECM1. Levels of TGFBI were elevated in media from DKK3-silenced WPMY-1 and RWPE-1 cells. Levels of ECM1 were decreased in conditioned media from DKK3-silenced WPMY-1 cells, but increased in conditioned media from DKK3-silenced RWPE-1 cells.

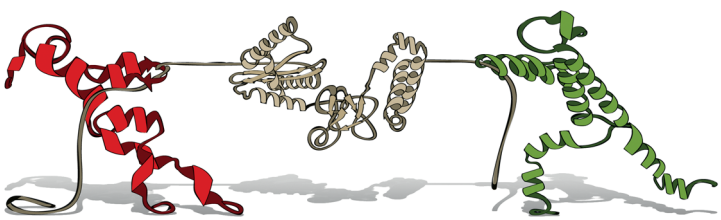
Acinar morphogenesis was improved in DKK3-silenced RWPE-1 cells on treatment with ECM1. In control RWPE-1 cells, ECM1 had no effect, but TGFBI reduced the numbers of normal acini formed.

PC3 cell invasion was increased when these cells were cultured in conditioned media from DKK3-silenced WPMY-1 cells, which was attenuated by treatment with a matrix metalloproteinase 2 (MMP2) inhibitor. Treatment with TGFBI increased cell invasion and ECM1 had no effect. However, ECM1 inhibited TGFBI-induced invasion.

In patient tumour samples, expression of DKK3 and TGFBI were inversely correlated. Relapse-free survival was positively correlated with DKK3 and ECM1 expression.

"We have found that DKK3 can inhibit TGFβ signalling in nonmalignant prostate cells and prostate cancer cells," explains Robert Kypta, corresponding author. "The loss of DKK3 can result in changes that can be bad news (TGFBI) or good news (ECM1) for the patient, at least early on in the disease," he continues. "We are currently using whole-genome approaches to compare the signals that DKK3 regulates in prostate epithelial, stromal, and cancer cells, so that we can identify common and cell type-specific effectors," he concludes. A DKK3 vaccine for prostate cancer is currently in clinical trials.

Louise Stone



Credit: P. Morgan/Macmillan Publishers Limited

ORIGINAL ARTICLE Al Shareef, Z. et al. Protective effect of stromal Dickkopf-3 in prostate cancer: opposing roles for TGFBI and ECM-1. *Oncogene* https://doi.org/10.1038/s41388-018-0294-0 (2018)