> HFD-induced local inflammation accelerates prostate cancer growth via IL-6 signalling

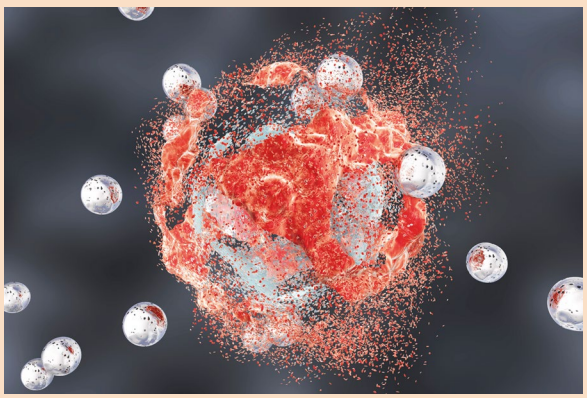
suppressed tumour growth and the MDSC and pSTAT3$^+$ tumour cell fractions in HFD-fed, but not CD-fed, mice, suggesting that macrophage-derived IL-6 controls STAT3 activation in tumour cells and local MSDC expansion.

Radical prostatectomy specimens from overweight or obese men also had higher tumour-infiltrating CD11b$^+$ MDSC counts than those from lean men, suggesting that HFD-induced MDSC infiltration exists in the clinical setting.

The findings suggest that HFD-induced local inflammation accelerates prostate cancer growth via IL-6 signalling. "Other inflammatory mechanisms could stimulate tumour growth in this model, which we are now investigating," says author Kazutoshi Fujita.

*Conor A. Bradley*

**ORIGINAL ARTICLE** Hayashi, T. et al. High-fat diet-induced inflammation accelerates prostate cancer growth via IL6 signaling. *Clin. Cancer Res.* https://doi.org/10.1158/1078-0432.CCR-18-0106 (2018)



Credit: Kateryna Kon/Science Photo Library/Getty

Regarding safety, treatment-related adverse events were acceptable; the most common were grade 1 or 2 fatigue (69%), nausea (55%), diarrhoea (45%), and neuropathy (33%).

Overall, BIND-014 was well tolerated and exhibited efficacy in patients with mCRPC, highlighting the promise of PSMA-directed therapy.

*Conor A. Bradley*

> BIND-014 was well tolerated and exhibited efficacy

**ORIGINAL ARTICLE** Autio, K. A. et al. Safety and efficacy of BIND-014, a docetaxel nanoparticle targeting prostate-specific membrane antigen for patients with metastatic castration-resistant prostate cancer. *JAMA Oncol.* https://doi.org/10.1001/jamaoncol.2018.2168 (2018)

BLADDER CANCER

# BCG enriches $T_{reg}$ cells

A study suggesting that BCG therapy affects levels of regulatory T ($T_{reg}$) cells has shed light on immune regulatory responses to BCG.

BCG therapy represents one of the earliest immunotherapies and it is an effective treatment in a majority of patients. However, 20–30% of patients will develop recurrent disease that requires surgery. Thus, identifying targets to optimize BCG therapy could improve outcomes.

Studies have shown that patients with higher numbers of T cells than myeloid-derived suppressor cells respond better to BCG therapy. However, as T cells include various subpopulations, Derré and colleagues investigated levels of conventional regulatory T ($cT_{reg}$) cells and PD-L1$^+$ $T_{reg}$ cells in peripheral blood mononuclear cells (PBMCs) of healthy donors and patients with urothelial cancer, as well as in the urine of patients during BCG therapy. PD-L1$^+$ $T_{reg}$ cells are a novel subset that are different from $cT_{reg}$ cells as they do not express FOXP3.

A small, but significant, increase in $cT_{reg}$ cell frequency was noted in PBMCs of patients with urothelial cancer compared with healthy donors, and $cT_{reg}$ cells were also enriched in the urine of patients undergoing BCG therapy. However, no differences were noted between preinstillation and postinstillation samples, suggesting a BCG-independent mechanism. Further investigation into the presence of the regulatory PD-L1$^+$ CD4 T cell subset found that PD-L1$^+$ $T_{reg}$ cells were not clearly detectable in the blood of healthy donors or patients with urothelial cancer, but were found at high (variable) levels in the urine of patients during BCG treatment. In contrast to the effect of BCG on $cT_{reg}$ cells, a higher frequency of PD-L1$^+$ $T_{reg}$ cells was detected in post-BCG-instillation urine than in pretreatment samples.

In vitro co-culture was performed to investigate PD-L1$^+$ $T_{reg}$ induction. Culture of T24 bladder tumour cells alone induced only low levels of PD-L1$^+$ $T_{reg}$ cells and BCG alone also had limited ability. However, combined T24 and BCG had a strong synergistic effect, inducing high levels of PD-L1$^+$ $T_{reg}$ cells. The team then tested the effect of PD-1–PD-L1 blockade in an autologous T cell proliferation assay in the presence of PD-L1$^+$ CD4 T cells. In this study, CD4 T cells containing, or not containing, PD-L1-expressing cells (BCG and T24-stimulated or not stimulated, respectively) were sorted and co-cultured with autologous labelled total T cells with or without antibodies blocking PD-1–PD-L1 interaction. Antagonism of PD-1–PD-L1 had no effect on T cell proliferation when co-cultured with untreated CD4 T cells, but significantly increased CD4 and CD8 T cell proliferation when co-cultured in the presence of stimulated CD4 T cells. These data suggest that blocking PD-1–PD-L1 interaction might increase immune-related BCG activity.

The use of PD-L1–PD-1 axis blockade has revolutionized the treatment of bladder cancer. These data suggest that, in addition to PD-L1 expression on tumour cells or antigen-presenting cells, T cells themselves might be an important source of PD-L1 during BCG therapy. "A 2014 study showed that the level of PD-L1 expression on immune cells, but surprisingly not on tumour cells, was associated with clinical response to PD-L1 blockade in muscle-invasive bladder cancer patients," commented Derré. "Thus, it could be interesting to study which immune cells express (or overexpress) PD-L1 upon BCG treatment in vivo." Trials investigating the combination of BCG and checkpoint blockade are already underway, and this study provides further rationale for such trials to improve bladder cancer outcomes.

*Annette Fenner*

**ORIGINAL ARTICLE** Derré, L. et al. Conventional and PD-L1-expressing regulatory T cells are enriched during BCG therapy and may limit its efficacy. *Eur. Urol.* https://doi.org/10.1016/j.eururo.2018.06.045 (2018)
**FURTHER READING** Pettenati, C. & Ingersoll, M. A. Mechanisms of BCG immunotherapy and its outlook for bladder cancer. *Nat. Rev. Urol.* https://doi.org/10.1038/s41585-018-0055-4 (2018)