GLOSSARY

WNT PATHWAY

A signaling pathway of highly conserved WNT proteins that regulate cell-to-cell interactions in embryogenesis and are implicated in cancer

METHYLATION-SPECIFIC POLYMERASE CHAIN REACTION

A technique used to detect CpG methylation in genomic DNA, using sodium-bisulphate-modified DNA as a template, and primers for specific methylated promoters

are at a substantially elevated risk for several cancers, and clinical suspicion for these tumors should be high in this population.

Carol Lovegrove

Original article Swerdlow AJ *et al.* (2005) Cancer incidence and mortality in men with Klinefelter syndrome: a cohort study. *J Natl Cancer Inst* 97: 1204–1210

Powerful new markers for invasive bladder cancer

Researchers in the US have demonstrated that bladder cancer patients with inactivated *SFRP* genes and altered TP53 tumor-suppressor proteins are over 30 times more likely to develop the deadly invasive form of the disease.

The *SFRP* genes encode antagonists of the WNT PATHWAY. Disruption of the WNT and TP53 pathways is thought to be important in the development of an invasive phenotype.

Marsit and colleagues used tumor samples from their population-based bladder cancer case series ($n = 355$) to investigate the usefulness of epigenetic silencing of *SFRP* genes as a diagnostic marker. Methylation-induced gene silencing was evaluated using METHYLATION-SPECIFIC POLYMERASE CHAIN REACTION.

The results showed that *SFRP* gene methylation was significantly associated with advanced bladder cancer, and that the risk of invasive disease increased with the number of *SFRP* genes methylated. This group has previously shown, using immunohistochemical staining, that alterations in TP53 protein are also significantly associated with an invasive phenotype. Here, using stratified multivariate logistic analysis, they showed that these effects occur independently of each other. They also found that *SFRP* gene methylation was significantly associated with reduced overall patient survival.

The authors conclude that *SFRP* gene methylation status and TP53 immunohistochemistry could be used together to identify tumors likely to progress to invasive disease.

With the growing interest in DNA-based diagnostic tools for bladder cancer, further investigation into this promising area is warranted.

Tamsin Osborne

Original article Marsit CJ *et al.* (2005) Epigenetic inactivation of *SFRP* genes and TP53 alteration act jointly as markers of invasive bladder cancer. *Cancer Res* 65: 7081–7085

A role for death receptors in BCG therapy for bladder cancer?

Intravesical instillation with bacillus Calmette-Guérin (BCG) is an established treatment for superficial bladder cancer and is the most effective prophylaxis for recurrent carcinoma following transurethral resection. Despite this clinical success, the mechanisms behind the antitumor effects of BCG remain unknown.

Death receptors belonging to the tumor necrosis factor superfamily, such as Fas ligand (FasL) and tumor-necrosis-factor-related apoptosis-inducing ligand (TRAIL) have recently been reported to be involved in tumor apoptosis. In addition, the Fas/FasL pathway has also been shown to be critical for the anti-tumor effects of interleukin 12. Using immunofluorescent staining, Mehmet and colleagues examined the expression of FasL and TRAIL in infiltrating leukocytes in bladder cancer, and Fas expression levels in bladder carcinoma cells, before and after BCG treatment.

The number of infiltrating leukocytes increased significantly after BCG instillation compared with pretreatment samples. Within this infiltrate there was a significant increase in CD4⁺ T cells and macrophages that express FasL and TRAIL, and in FasL-expressing CD8⁺ T and natural killer cells. In addition, Fas expression was upregulated, and the number of Fas-expressing tumor cells increased after BCG instillation.

These results imply that the enhanced infiltration of leukocytes that express FasL and/or TRAIL, and the induction of Fas on tumor cells, might play an important role in the therapeutic effect of BCG instillation in the treatment of bladder cancer.

Carol Lovegrove

Original article Mehmet M *et al.* (2005) Fas ligand and TNF-related apoptosis-inducing ligand induction on infiltrating lymphocytes in bladder carcinoma by bacillus Calmette-Guérin treatment. *Urol Int* 75: 80–87

Risk of contralateral testicular cancer: to biopsy or not to biopsy?

A large, population-based, cohort study of American testicular cancer patients has recently shown that the risk of developing cancer in the contralateral testis is low and long-term survival