

BLADDER CANCER

Pre-existing immunity to BCG can boost clinical response to intravesical therapy

Intravesical immunotherapy with BCG is standard of care for patients with non-muscle-invasive bladder cancer, although the clinical response rate is only 50–70%. New research published in *Science Translational Medicine* suggests that exposure to BCG prior to initiating intravesical treatment might improve clinical response.

Matthew Albert, an immunologist at the Institut Pasteur in Paris and corresponding author of the study, told *Nature Reviews Urology* about the motivation behind this research. “We had previously investigated the molecular and cellular signature of the immune response to BCG in the urine of patients undergoing BCG therapy. We observed that repeat instillations

were required for a robust inflammatory response. Understanding the basis for this boosted response was one of the main reasons we established a mouse model, which led to these latest findings.”

Researchers used female C57BL/6 mice for their initial experiments into the mechanisms of BCG-induced T-cell infiltration into the bladder. They found that while a single instillation was sufficient for BCG to disseminate to the periaortic lymph nodes and to prime interferon- γ -producing T cells, repeated instillations were necessary to achieve T-cell trafficking to the bladder. However, a single subcutaneous injection of BCG abolished the need for repeat instillations. Then, using an experimental model of bladder cancer (C57BL/6 mice implanted with MB49 tumour cells), the investigators made the striking observation that immunizing mice 3 weeks before starting intravesical BCG therapy resulted in 100% survival at day 70, compared with only 20% survival in mice treated with intravesical therapy alone.

Most notably, the immunologists evaluated the relevance of pre-existing BCG immunity in patients with bladder cancer in collaboration with a team of urologists at Basel and Bern Hospitals

in Switzerland. Clinical data were analysed from an observational study of 55 patients with high-risk non-muscle-invasive bladder cancer who received a purified protein derivative (PPD) skin test prior to BCG therapy. 23 patients had a positive PPD test, meaning they had been previously exposed to BCG, and these patients had a significantly better recurrence-free survival after standard BCG treatment than those who were PPD negative ($P < 0.02$).

Albert expressed his surprise that the effect of previous vaccination had not been explored previously. “In retrospect, our results seem quite obvious, and suggest that a delayed-type hypersensitivity response accounts for the boosted immune response observed after repeated BCG instillation. For patients with non-muscle-invasive bladder cancer who are PPD negative, the major implication of our findings is that their response to therapy might be improved by a parenteral vaccination with BCG prior to intravesical therapy.”

Sarah Payton

Original article Biot, C. *et al.* Preexisting BCG-specific T cells improve intravesical immunotherapy for bladder cancer. *Sci. Transl. Med.* 4, 137ra72 (2012)



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