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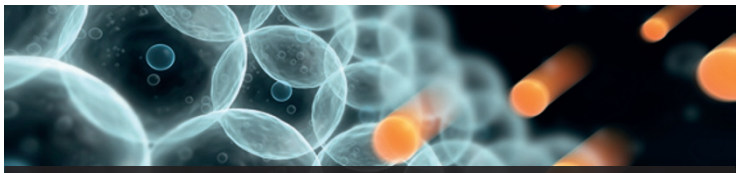

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BASIC RESEARCH

Therapeutic action of BCG mediated by H_2O_2?

The clinical effects of BCG on bladder cancer might be mediated by the production of hydrogen peroxide (H_2O_2), according to new research published online in *The Journal of Urology*.

Despite BCG being an established treatment option for non-muscle-invasive bladder cancer, its mechanism of action remains unclear. Existing data largely suggest that BCG triggers an immune response in the bladder, leading to tumour cytotoxicity. However, BCG has also been shown to generate oxidative stress in the bladder. To investigate this association further, Gopitkumar Shah and colleagues at the Medical College of Wisconsin in Milwaukee, USA, performed a series of experiments to assess the relationship between cellular redox status and the antitumour effects of BCG.

First, the investigators used fluorescent probes to profile the reactive oxygen and nitrogen species produced by BCG itself, and by urothelial cells that had been treated with BCG. They found that viable BCG generated H_2O_2 and superoxide (O_2^-), but not nitric oxide (NO), and that heat-killed BCG produced twofold less H_2O_2 than viable BCG, suggesting that H_2O_2 might be involved in clinical activity. The urothelial cell lines 253J and T24 showed early increases in H_2O_2 and NO production after BCG treatment, with H_2O_2 and NO levels peaking in the first 12–18 h and 6 h, respectively.

Using the spindle toxin cytochalasin b to prevent BCG uptake into urothelial cells, Shah and colleagues demonstrated that H_2O_2 production was dependent on BCG internalization; urothelial cells treated with both BCG and cytochalasin b generated significantly lower levels of H_2O_2, O_2^- and NO than cells treated with BCG alone.

Similarly, pretreating cells with the potent H_2O_2 scavenger ebselen significantly reduced the production of H_2O_2, O_2^- and NO compared with BCG alone, highlighting the importance of H_2O_2 generation in this system.

To clarify the role of H_2O_2, researchers studied the effects of ebselen on BCG-induced gene expression, intracellular signalling and cell proliferation. Scavenging H_2O_2 with ebselen treatment significantly reduced the expression of eight BCG-responsive genes, and inhibited the activation of a number of signalling molecules known to be downstream of BCG (NFκB, CEBP and NRF2) in urothelial cancer cells. In addition, ebselen blocked the cytotoxic effect of BCG on urothelial cells, measured using the MTT assay.

These findings suggest that H_2O_2 is a source of oxidative stress and cell damage downstream of BCG in the bladder. The authors postulate that pharmacological manipulation of oxidative stress might be used to optimize the clinical benefits of BCG.

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Original article Shah, G. *et al.* H_2O_2 generation by BCG induces the cellular oxidative stress response required for BCG's direct effects on urothelial carcinoma tumor biology. *J. Urol.* doi:10.1016/j.juro.2014.05.115

Further reading Redelman-Sidi, G. *et al.* The mechanism of action of BCG therapy for bladder cancer—a current perspective. *Nat. Rev. Urol.* **11**, 153–162 (2014)