Modulating the immune response to Bacillus Calmette–Guérin (BCG): A novel way to increase the immunotherapeutic effect of BCG for treatment of Bladder Cancer?

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The development and progression of cancer is critically dependent upon a relative immunodeficiency of the body in initiating an antitumour response. Bacillus Calmette–Guérin (BCG), a live attenuated form of Mycobacterium bovis, is commonly used for the treatment of high grade non-muscle invasive transitional cell carcinoma of the bladder and carcinoma in situ, to reduce the risk of recurrence and progression [1]. Without BCG, the body only activates the immune system non-specifically and weakly in an effort to clear bladder cancer cells. The precise mechanism of action of BCG is unknown however current research shows that it stimulates both an inflammatory tumour response as well as an adaptive (specific) immune response to clear residual bladder cancer cells [2]. A proposed model for the mechanism of action of BCG is shown in Figure 1.

The innate (non-specific) immune response acts against microbes to keep the urinary tract sterile [3]. One of the effectors of this innate response to microorganisms are antimicrobial peptides such as β Defensins [4]. Here Kim et al [5] show that bladder cancer cells produce Human β Defensin 2 (HBD2) when they are infected with BCG, to defend them against BCG and thus may play a role in the immunotherapeutic response of BCG.

The first step after intravesical administration of BCG in the bladder is to establish direct contact with the bladder urothelium using extracellular proteins such as fibronectin [6]. The second step is the uptake of BCG by bladder cancer cells (internalization), probably by endocytosis [7]. This sequence of events leads the body to mount an innate immune response to clear the foreign bacteria. Uptake of BCG by bladder cancer cells leads the body to mount an anti-tumour response consisting, initially of an inflammation mediated tumour response via cytokines. This primary response then activates the adaptive immune system to mount a BCG specific immune response via T lymphocytes and BCG activated killer cells (BAKs) via mycobacterial antigen presentation, leading to destruction of cells that have internalized BCG. This secondary immune response is dependent on the primary inflammatory response and requires live bacteria [2] hence the need for live attenuated *M. bovis* strain in BCG.

Since the specific downstream immune response resulting in clearing of BCG infected bladder cancer cells begins with attachment and internalization of BCG by bladder cancer cells, this represents a critical step in the effectiveness of BCG for treatment of bladder cancer. The authors have used bladder cancer cells in culture (whereby cells are grown in controlled conditions outside their natural environment) to investigate the effect of HBD2 on internalization of BCG into bladder cancer cells.

The authors report that the levels of HBD2 increase after exposure of BCG to bladder cancer cells in a dose and time dependent manner and that this reduces the effectiveness of BCG in reducing bladder cancer cell proliferation. They found that this increasing level of HBD2 prevents internalization of BCG into bladder cancer cells in a dose-dependent manner. They have achieved this using a stain to distinguish between internalized and extracellular BCG and examining these changes by confocal microscopy. They also show that increasing the levels of HBD2 using recombinant HBD2 protein further decreases internalization of BCG and blocking the action of HBD2 (by an anti HBD2 antibody) increases the internalization and effectiveness of BCG.

It is difficult to determine the exact relevance of these findings and this area merits further study through an animal model. The effect of HBD2 on the modulation of the immune response also remains to be elucidated. However, this study highlights the potential of blocking the body's innate response to BCG (which prevents its uptake by bladder cancer cells) to improve the effectiveness of BCG and potentially to reduce the dose related side effects of BCG.

Conflict of Interest

None declared

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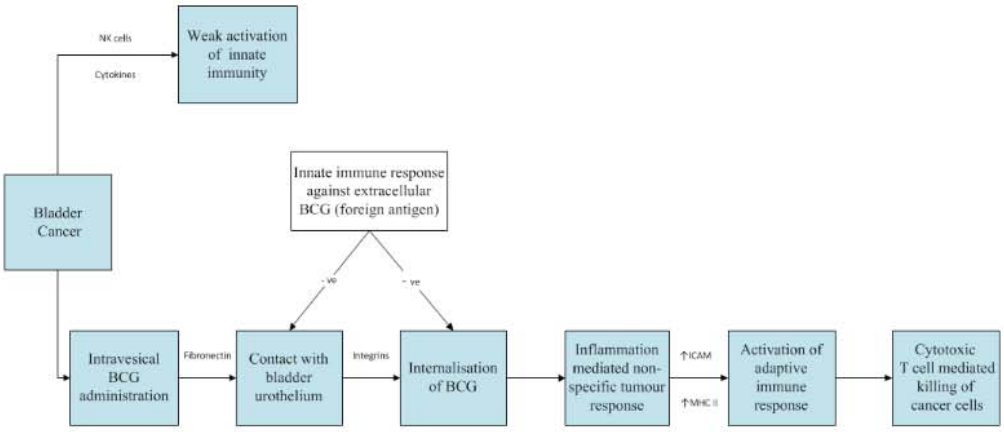

Figure 1: Mechanism of action of BCG: Internalization (uptake) of BCG by bladder cancer cells is a critical step in effectiveness of BCG and is affected by the body's innate immune response to BCG.