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Urologic Oncology: Seminars and Original Investigations 37 (2019) 343–345

UROLOGIC ONCOLOGY

Letter to the Editor

Therapeutic rationale of targeting BCG and immune checkpoints in non–muscle-invasive bladder cancer: Is this the Future?

As Mukherjee et al. [1] have described in their review article, there is emerging evidence that supports the rationale of targeting bacillus Calmette-Guérin (BCG) and checkpoint inhibitors in BCG-resistant non–muscle-invasive bladder cancer (NMIBC). The Current results showed that BCG induces programmed death-ligand 1 $(PD\text{-}L1)^+$ regulatory T cells (Tregs) via interferon-β-mediated mechanisms in vitro. Moreover, the increased urinary levels of $PD\text{-}L1^+$ Tregs during BCG induction were associated with BCG failure [2]. These findings are of high translational importance and in line with results from previous studies in which PD-L1 expression was upregulated during BCG therapy, both in vitro and in vivo [3], especially in patients with BCG-resistant NMIBC. It is therefore thought that upregulation of PD-L1 is an immune escape mechanism exploited by BCG-treated NMIBC [4]. That is, further corroborated by the fact that high PD-L1 expression in BCG-refractory NMIBC was an independent predictor of tumor recurrence and progression, resulting in a decreased 5-year recurrence-free and progression-free survival (40.7% and 74.1%), compared to patients with low PD-L1 expression (72.9% and 94.1%) [5]. In addition, BCG granulomas in BCG-unresponsive patients exhibit high levels of PD-L1 expression [6]. Another study noticed greater expression of PD-1 in radical cystectomy (RC) tumor specimens from patients with a history of previous BCG instillations before undergoing RC [7]. This suggests that PD-L1 contributes to the failure of BCG treatment by suppressing an adequate T helper cell type 1 (Th1) cell immune response, with increased expression of $FOXP3^+$ and $CD25^+$ Tregs as well as tumor-associated macrophages within the tumor microenvironment [8]. Thus, combining immune checkpoint inhibitors that target regulatory pathways to restore and enhance T cell antitumor activity [2] with intravesical BCG may be a cornerstone to treat BCG-resistant NMIBC in the near future.

The positive effect of this novel combined therapeutic approach was demonstrated in orthotopic rat bladder cancer models, showing that BCG and anti-PD-L1 combination therapy resulted in an enhanced antitumor effect by reducing tumor burden and prolonging survival [3]. Clinical phase III studies combining checkpoint inhibitors such as Durvalumab (NCT03528694) or Pembrolizumab (NCT03711032) with intravesical BCG are currently recruiting patients with both BCG-naive and BCG-refractory high-risk NMIBC. In these trials, a particular consideration is given to patients with carcinoma in situ, due to high expression of PD-L1 within these lesions [6]. Early results from the single-arm phase II KEYNOTE-057 trial (NCT02625961) of Pembrolizumab in NMIBC patients with carcinoma in situ, who were unresponsive to BCG and refused or were ineligible for RC are encouraging. At 3 months, the complete response rate was 36.5%, and >85% of the responses lasted more than 6 months. No patient developed muscle-invasive bladder cancer or metastatic disease [9]. These findings indicate that a considerable proportion of patients failing BCG may not need RC and may indeed benefit from a "combined approach" with BCG reinduction and systemic checkpoint inhibition.

Previous studies showed that different immune parameters seem to influence the clinical response to BCG, including systemic and local release of Th1/Th2-related inflammatory metabolites and cytokines, dynamic changes of tumor-infiltrating immune cell subpopulations within the tumor microenvironment [3–4], and the intratumoral Th1/Th2 dysbalance [8,10]. However, the exact immune mechanism of BCG-induced antitumor activity appears to be complex and is not fully understood. Different cytokines such as, interleukin (IL)-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, tumor necrosis, factor-α, and interferon-γ can be released. Thus, BCG can induce production of both Th1-type and Th2-type cytokines [11]. Nevertheless, a predominant Th1 cell-mediated immunity with an enhanced recognition of cancer cells through infiltrating effector cells, activated macrophages, $CD8^+$ T cells, and natural killer cells into the bladder wall is required for subsequent BCG response [11], Fig. 1.

Taken together, in an era where immunotherapy has already reshaped the therapeutic landscape of advanced

https://doi.org/10.1016/j.urolonc.2019.02.001

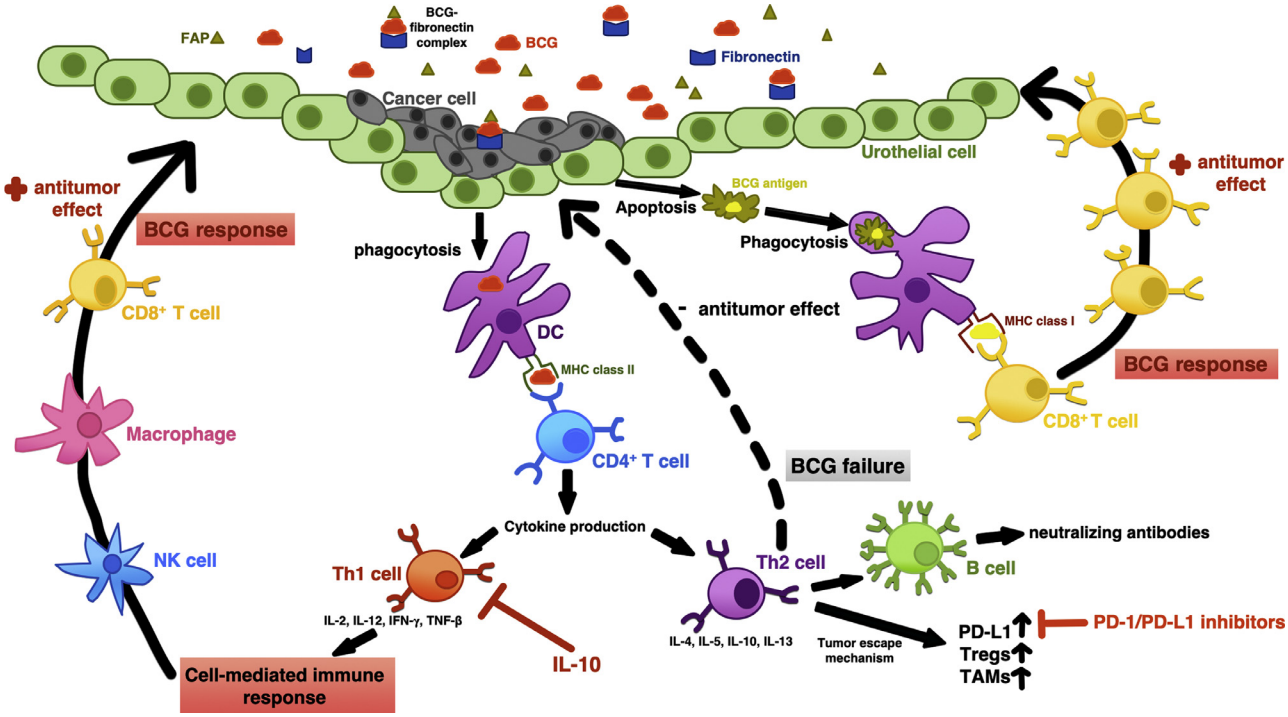

Fig. 1. Schematic overview of BCG-induced antitumor activity in NMIBC and different important cellular immune markers.
Abbreviations: FAP = fibronectin attachment protein; IL = interleukin; NK cell = natural killer cell; TAM = tumor-associated macrophage; Th = T helper cell type; Treg = regulatory T cell.

bladder cancer, there are now emerging preclinical and clinical data on a new strategy combining intravesical BCG and systemic checkpoint inhibitors in BCG nonresponders.

Andrea K. Lindner[a]
Tobias Klatte[b]
Eva Comperat[c]
Isabel Heidegger[a]
Renate Pichler[a,*]
[a] *Medical University Innsbruck, Department of Urology, Innsbruck, Austria*
[b] *Department of Urology, The Royal Bournemouth and Christchurch Hospitals, Bournemouth, UK*
[c] *Department of Pathology, Hospital Tenon, Sorbonne University, Paris, France*
E-mail address: Renate.Pichler@i-med.ac.at
(R. Pichler).
*Corresponding author. Tel.: +43-(0)-512-504-24811; fax: +43-(0)-512-504-28365.

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