Editorial

Role of heat shock proteins in bladder cancer: potential biomarkers for treatment response and oncological prognosis

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Comment on: Mano R, Zilber S, Di Natale RG, *et al.* Heat shock proteins 60 and 70 are associated with long-term outcome of T1-stage high-grade urothelial tumors of the bladder treated with intravesical Bacillus Calmette-Guérin immunotherapy. Urol Oncol 2018;36:531.e9-531.e17.

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Transurethral resection of bladder tumor (TURBT) and BCG intravesical instillation have been the gold standard for non-muscle invasive bladder cancer (NMIBC) treatment in patients with intermediate and high-risk disease (1,2). However, patients with T1 high grade (T1HG) disease still have relatively poor outcomes with 11.4% and 19.8% of patients experiencing disease progression at 1 and 5 years, respectively and disease specific mortality rates of 4.8% and 11.2%, respectively (3). The identification of biomarkers that could appropriately select patients who will benefit from BCG therapy would be greatly beneficial for optimizing outcomes and minimizing overtreatment.

Heat shock proteins (HSPs) help to maintain protein structure and function and promote death of damaged cells. These molecules are overexpressed in bladder cancer (4) and have shown an immunomodulatory effect that may be involved in BCG response (5).

Mano *et al.* (6) evaluated the role of HSP60, 70 and 90 expression in predicting the long-term response to intravesical BCG in patients with stage T1HG bladder cancer. The authors used immunohistochemical (IHC) techniques from paraffin embedded formalin fixed (PEFF) TURBT sections. Although this study has several limitations such as a retrospective design, small sample size and the inherent limitations of IHC in the evaluation of the expression of biological markers in contrast to more advanced profiling techniques, the authors were able to show a positive correlation between HSP60 expression and risk of recurrence and progression when using a cutoff point of 65% expression Furthermore, the overexpression of HSP70 was associated with a significant decrease in risk of progression when using a cutoff point of 5%. Remarkably, all the patients who had HSP60+ staining over 65% and HSP70 of 5% or less recurred and progressed. However, this potentially high-risk group was only composed of 5 patients. On the other hand, no association was found between HSP90 expression and disease recurrence or progression after BCG intravesical treatment.

Prior studies have shown that HSP70, specifically HSP70-2, is associated with cellular motility and invasion; Inhibition of HSP70 can be hypothesized to lead to suppression of tumor growth (7). Surprisingly, this contradicts the findings of Mano *et al.* as they found that down-regulation of HSP70 was associated with worse long-term oncological outcomes. However, it has also been shown that besides its role in tumor progression, membrane-bound HSP70 from cancer cells promotes anti-tumor adaptive immune response. Patients with more extracellular membrane-bounded HSP70 may have a stronger immune response with BCG and therefore have better outcomes as found in this paper (8).

Combined HSP60 and HIF2a inhibition in gastric cancer cell lines has shown to induce apoptosis and inhibit cell mobility. Consistent with the findings from this manuscript, which found that overexpression of HSP60 was associated with worst oncological prognosis. *In vitro* studies on HSP bearing-exosomes, derived from anti-cancer drug resistant hepatocellular carcinoma cells, have shown to induce

specific natural killer cells (NK) response (9). Therefore, we could hypothesize that down-regulation of HSP60 would decrease the risk of disease progression and recurrence, but secretion of these molecules through exosomes could make the tumor more immunogenic and responsive to local immunotherapy such as BCG. Thus, cytosolic HSPs have shown to promote oncogenic activity by contributing to tumor cell propagation, metastasis and anti-apoptotic effects whereas, extracellular membrane-bound HSP have shown to promote anti-tumoral immune response, mediating the mobilization of immunogenic onco-peptides, antigen presentation, and becoming targets of the innate immune system (10).

The evidence is still controversial and although the relevance of HSPs in cancer biology is undeniable, the role of these molecules in bladder cancer has not been clearly elucidated. There is some evidence in other types of cancer that they are potential therapeutic targets. Moreover, in bladder cancer these molecules could be used as a potential biomarker to distinguish the best candidates for intravesical BCG therapy from those who would benefit from more aggressive treatment such as an early radical cystectomy. However, it seems that identifying the location of the HSPs is critical because when they are cytosolic they have shown more oncogenic characteristics whereas when they are extracellular membrane-bounded they promote anti-tumor immune response.

In summary, we consider that a better understanding of the biological role of these molecules, specifically in bladder cancer, is crucial to elucidate the potential benefits of identifying HSPs for therapeutic or prognostic implications.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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