EDITORIAL | bladder cancer

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COVID-19 Vaccine and Bladder Cancer: Friend or Foe?

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Abstract

This is a letter to the editor on the discussion on COVID-19 vaccine and bladder cancer.

Letter to the editor

Bladder cancer is the most common neoplasm in the urinary system. In the United States, it was responsible for an estimated 17,000 deaths and 80,000 new cases in 2022. Bladder cancer can be categorized as non-muscle invasive or muscle-invasive by the depth that the tumor has penetrated through the wall of the bladder. Non-muscle invasive bladder cancer (NMIBC) typically only invades the lamina propria whereas muscle-invasive bladder cancer has grown into the muscle and surrounding tissues of the bladder. Depending on tumor classification, bladder cancer is treated with a combination of surgery, platinum-based chemotherapy, or intravesical immunotherapy treatment known as Bacillus Calmette-Guérin (BCG). BCG is the most successful microbial immunotherapy for cancer, and it is recommended for most patients with NMIBC.

BCG was originally developed as a vaccine against tuberculosis. Over time, BCG has become utilized as a treatment against bladder cancer by training the innate immune system. Although the exact signaling pathway is still unknown, mechanistic studies have shown a role for T cells, mast cells, NK cells, and granulocytes in tumor growth inhibition and apoptosis [1]. Intravesical BCG is an effective approach to prevent recurrence of NMIBC, however, it has been shown to manifest side effects [2]. These side effects are rarely serious; however, there is the potential for serious infection. Moreover, there have been reports of adaptive immune resistance to intravesical BCG in NMIBC patients [3]. Recombinant strains of BCG are being studied to decrease side effects and increase efficacy, but other forms of immunotherapies may be required for more specific bladder cancer therapeutics.

It is well known that COVID-19 has been the most urgent public health concern worldwide for years, and many people have been vaccinated with the COVID-19 vaccine. There is significant literature on the safety and efficacy of the COVID-19 vaccines, but little is known about the effect of these vaccines, SARSCoV-2 or its spike protein on patients with cancers especially bladder cancer. In 2022, our research group evaluated the effects of isolated SARS-CoV-2 spike protein on survival of prostate cancer cells [4]. Our investigation revealed that the anti-proliferative effects of the SARS-CoV-2 spike protein on prostate cancer cells were associated with downregulation of the pro-proliferative molecule CDK4. The increased apoptosis on prostate cancer cells by SARS-CoV-2 spike protein was associated with the upregulation of pro-apoptotic molecule Fas ligand. Our study regarding the association of SARS-CoV-2 spike protein and growth of cancer may point to a possible effect of the COVID-19 vaccine in inhibition of certain cancers, possibly including bladder cancer.

Although there is a lack of data on the direct effects of COVID-19 infection/vaccination or SARS-CoV-2 spike protein on the development and progression of bladder cancer, some studies suggest COVID-19 may promote bladder cancer progression while other studies point to inhibition of cancer growth. Autophagy is induced by coronaviruses although the relationship between COVID-19 and autophagy is complicated and not fully understood. One study found that JAK-mediated autophagy is linked to chemotherapy resistance in bladder cancer cells [5]. Similarly,

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another study posits that COVID-19 induced autophagy may lead to cancer progression and tumor recurrence of other cancers [6]. As a result, the COVID-19 vaccines may lead to an increase tumor recurrence in bladder cancer patients. On the other hand, some patients with prostate cancer have shared anecdotally with our research group that their PSA, a marker for monitoring the progress of prostate cancer, has decreased significantly following COVID-19 vaccination. In addition, SARS-CoV-2 has been shown to activate necroptosis in human airway epithelial lung cancer cells [7]. At the molecular level, SARS-CoV-2 infection involves the spike protein which recognizes and binds to the cell-surface angiotensin-converting enzyme 2 (ACE2) receptor, allowing the virus to enter the host cell [8]. The ACE2 receptor plays a central role in severe SARS-CoV-2 infection and cancer. ACE2 is highly expressed in the genitourinary tract and therefore relevant to genitourinary cancers such as bladder cancer. After COVID-19 vaccination, the free-floating SARS-CoV-2 spike proteins interact with ACE2 receptors of nearby cells to modulate the ACE2/ACE ratio and downstream immune signaling that may disrupt cancer progression. More studies specific to bladder cancer are needed, but the COVID-19 vaccine may be the start of a novel treatment for NMIBC by carefully targeting ACE2 receptors and autophagy pathways.

In summary, COVID-19 infection and vaccination introduce new players that may improve susceptibility of NMIBC tumor cells to treatments. Controlling and attenuating the inflammatory response through targeted antigen presentation may be at the crossroads of bladder cancer therapeutics. Going forward, extensive large-scale animal and human research is required to reveal the efficacy of introducing spike proteins to beneficially stimulate the immune system in bladder cancer patients who already have a compromised immune system.

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None.

Ethical policy

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Approval from institutional ethical committee was taken.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

Yujiang Fang initiated the idea. Kevin Z. Qi, Miriam P. Palomino, Justin D. Murray and Madeline N. Agee wrote the draft. Yujiang Fang and Wakefield made critical revision to the draft.

Competing interests

The authors declare no conflict of interest.

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