Editorial

The immune system, cancer, and pathogens: It takes three to tango!

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Evolutionary development of the immune system of a host is continuously shaped by environmental interactions between microbes and surrounding cells, including both healthy and cancerous cells. Such interaction requires cells to adapt to environmental pressures for survival, and the immune system's symbiotic processes adapt to allow for mutual benefits to microbes and hosts.[1]

The immune system's primary role is to protect the hosts from infections, but it has equally important functions to eliminate malignantly transformed cells while preventing autoimmunity. One of the oldest examples to demonstrate the role of microbes in inducing immune responses against cancer comes from Coley's toxin. Using a cocktail of heat-killed bacteria, Dr. William Coley induced tumor regression in cancer patients.[2] Several decades later, we understand that highly transformed malignant cells can escape immune responses by lacking danger signals "e.g., lack of HLA expression" and inducing immunosuppressive responses. Cancer immunotherapy aims to harness the immune system, overcome immune escape mechanisms, and reactivate antitumor responses.[3]

However, pathogens have not always been our friends when it comes to cancer. Chronic viral infections have a carcinogenic effect; examples are human immunodeficiency virus, hepatitis B and C virus, herpes viruses, and human papillomavirus. The general concept behind the carcinogenesis begins with the immune system's inability to eliminate the chronic virus. Subsequently, the virus integrates into the genome of the infected cells and transforms them into malignant cells. The chronically activated immune system eventually reaches a state of exhaustion and decreases antitumor activity against those malignantly transformed cells.[4,5] Although treating the underlying malignancy is the ultimate goal in patients with chronic viral infections, another significant concern is viral reactivation. For example, activation of chronic HBV could lead to fulminant hepatitis. In this special issue of the *Journal of Immunotherapy and Precision Oncology*, which is dedicated to microbes, cancer, and the immune system, Hwang and Yilmaz[6] provide a thorough review of published literature on HBV reactivation in the context of immune checkpoint inhibitor therapy and provide insight that such reactivation can be prevented and successfully managed using antiviral prophylaxis.

Beyond the local interactions between the immune system and infected organs, there are systemic alterations in immune responses against microbes seen in patients with cancer. These alterations are mostly evident by changes in the patient's intestinal microbiome composition, even if there is no direct gastrointestinal involvement. As an example, from this issue of *JIPO*, Sims et al.[7] reviewed the changes seen in the intestinal microbiome of women with HPV-related cervical cancer. Growing evidence suggests that microbiome alterations in patients with cancer might play a role in cancer progression, response to therapy, and even cancer-related symptoms.[8,9]

Finally, the COVID-19 pandemic has created an urgent need to understand the immune system responses to SARS-Cov-2 infection in general and particularly in the context of cancer. Delays in cancer treatment could be detrimental, while severe COVID-19 could be fatal. Several articles in this issue of *JIPO* discuss the impact of COVID-19 on cancer therapy.[10–12]

Our immune system will continue to evolve in the face of emerging infections and aberrant somatic cell trans-

formations. There is an urgent need to understand those interactions further to advance therapeutics that activate antitumor responses without risking organ- or life-threatening infections.

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