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LETTER TO THE EDITORS

Combining immunotherapy and natural immune stimulants: mechanisms and clinical implications

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Dear Editor,

The development of immunotherapy (IT) represents one of the most promising advances in oncology in the past several years. Indications for IT have expanded rapidly, and a growing number of patients with an increased variety of cancer diagnoses are being treated with these agents. At the same time, the use of complementary and integrative therapies among cancer patients is widespread (Tara et al. 2018), and many patients do not disclose or discuss these therapies with their physicians (Richardson et al. 2000). Patient use of nutritional supplements may include items that are considered natural immune stimulants (NIS). Our understanding of how NIS use may affect people who are being treated with IT is in its infancy. To the author's knowledge, there are no clinical trials, and extremely limited preclinical data, examining the effect of combining IT and NIS. It is critical to consider the shared mechanisms of IT and NIS and how this combination may affect patients. We offer the following examples of NIS and summarize their immunological mechanisms which may have important clinical implications for patients being treated with IT.

First, consider the example of medicinal mushroom extracts. Mushroom-derived compounds such as beta-glucan polysaccharide K (PSK) from Coriolus (*Trametes versicolor*) are well known for their immune-stimulating properties. Data supports a biological response modifier action of PSK. PSK may increase natural killer (NK) cell cytotoxic activity against tumors (Pedrinaci et al. 1999), and may also act directly on B cells to increase immunoglobulin production (Maruyama et al. 2009). Additionally, PSK may work via cytokine-modulated mechanisms. For example, PSK induces production of the pro-inflammatory cytokine interleukin 1-beta (IL-1β) via activation of inflammasomes (Yang et al. 2014). In a study of peripheral blood mononuclear cells from subjects with breast cancer, Coriolus was found to upregulate interleukin-12 (IL-12), interleukin-6 (IL-6), and TNF-alpha (Wang et al. 2013).

Second, consider use of high-dose melatonin supplementation, which may have benefits in subjects receiving chemotherapy (Wang et al. 2012). Melatonin's effects on the immune system are manifold. Melatonin may increase T helper 17 (Th17) cell differentiation (Kuklina 2014), antigen presentation to T cells, and production of cytokines interleukin-10, interleukin-1, and TNF-alpha (Pioli et al. 1993), resulting in downstream T cell proliferation. These effects may have important implications; preclinical models suggest that melatonin may influence or exacerbate autoimmunity (Hansson et al. 1990; Mattsson et al. 1994).

Lastly, Astragalus is another example of NIS, with a long history of use in Chinese medicine and western herbal medicine. Astragalus may stimulate phagocytosis and superoxide anion production in neutrophils and macrophages, activate B-cells and macrophages, and increase interleukin-2 (IL-2), interleukin-4 (IL-4), and interferon-gamma (IFN-γ) cytokines (Shao et al. 2004; Yang et al. 2008; Du et al. 2012; Vetvicka and Vetvickova 2014). In a mouse model of sepsis, Astragalus supplementation at higher doses led to increased Th17 (Hou et al. 2015). Astragalus has also been shown to increase NK cell activity (Zhao 1992). Human data indicate Astragalus can increase T-cell activity, increase dendritic cell numbers and activity, and increase IgA, IgG, and IgM antibodies (Dong et al. 2005; Cai et al. 2006; Yang et al. 2008).

There are many areas where IT and NIS may have overlapping mechanisms, raising the concern of an increase in

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adverse events. As described above, PSK may stimulate B cells and increase immunoglobulin production (Yang et al. 2008; Maruyama et al. 2009). In melanoma patients receiving either single agent or combined anti-CTLA4 and anti-PD1 therapy, increased circulating B cell levels were predictive of higher grade immune-related adverse effects (Das et al. 2018).

Also described above, NIS such as melatonin or Astragalus may increase Th17 differentiation or activity (Kuklina 2014; Hou et al. 2015), and PD-1 blockade may also augment Th17 activity (Dulos et al. 2012). This may be relevant for patients experiencing autoimmune effects while on these treatments. For example, one case report indicated an exacerbation of plaque psoriasis in a melanoma patient receiving nivolumab, possibly linked to upregulated Th1/Th17 activity (Matsumura et al. 2016). In addition, Th17 may be linked to a number of other autoimmune conditions. Patients with active multiple sclerosis (MS) have been found to have higher frequencies of Th17 cells in their cerebrospinal fluid compared to MS patients in remission (Brucklacher-Waldert et al. 2009), and patients with Hashimoto's thyroiditis have higher levels of Th17 cells infiltrating the thyroid (Li et al. 2013). Synovial fluid Th17 cell percentages correlate with symptomatology and inflammation in subjects with rheumatoid arthritis and spondyloarthritis (Zizzo et al. 2011). Levels of interleukin-17, a pro-inflammatory cytokine secreted by Th17 cells, are increased in patients with ulcerative colitis and Crohn's disease (Olsen et al. 2011), as well as in melanoma patients experiencing colitis on ipilimumab therapy (Callahan et al. 2011). Theoretically, co-administering NIS agents that increase Th17 activity or number may be reasonably expected to increase autoimmunity.

Additionally, PD-1 binding inhibits production of TNF-alpha (Keir et al. 2008); theoretically, PD-1 blockade could increase TNF-alpha production. Melatonin too may increase TNF-alpha (Pioli et al. 1993), as may Coriolus (Wang et al. 2013). Tumor necrosis factor plays a pivotal role in the pathogenesis of several autoimmune conditions (Blandizzi et al. 2014), and several TNF-alpha inhibitors are FDA-approved for the treatment of rheumatoid arthritis and Crohn's disease. Again, it seems possible that combining therapies that increase TNF-alpha may increase an adverse autoimmune profile.

One difficulty with IT lies in identifying patients who will respond to CTLA-4 or PD-1 targeting agents, and identifying those who will not respond. While this remains hypothetical, could non-responding subjects be converted to responders? Phase I and II clinical trials in metastatic melanoma patients have found that combination immunotherapy regimens lead to higher response rates, and also to higher rates of adverse effects (Wolchok et al. 2013; Postow et al. 2015). The question of whether or not natural agents with complementary immunostimulatory functions would have any impact on the efficacy of these drugs remains unanswered. Consider PSK, which may increase IL-1β (Yang et al. 2014). Boutsikou et al. found that increased levels of interleukins, including IL-1β, predicted response to pembrolizumab or nivolumab in patients with non-small cell lung cancer (Boutsikou et al. 2018). The concept of combining NIS and IT in this regard deserves careful consideration, and additional research in this area is much needed.

The potential effects of combining NIS and IT, whether beneficial or adverse, remain theoretical. There is a strong need for case studies and clinical trials on the use of NIS agents in conjunction with oncologic immunotherapy to help clarify potential risks and benefits. The examples we present here are limited, and a large number of supplements or therapies may be construed as NIS. Until data are available, the authors recommend an emphasis on Primum Non Nocere (First Do No Harm). Patients on IT should be screened for and educated on the use of NIS, and caution should be exercised in combining NIS and IT.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to disclose regarding this review.

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