Immunomodulatory Effects of Momordica charantia Extract in the Prevention of Oral Cancer

Chinthalapally V. Rao

Abstract

In recent times, bitter melon extract (BME) has gained significant attention for its anticancer efficacy against various malignancies. In this issue, Sur and colleagues show that BME prevents the development of 4-nitroheteroquino-line-1-oxide-induced oral dysplasia and squamous cell carcinoma (SCC) in an immunocompetent mouse model. Importantly, gene ontology and pathway analyses revealed an elevated expression of s100a9, IL23a, IL1β, and PDCD1/PD1 of immune system during oral cancer development, which was significantly suppressed by BME. Overall, this study demonstrates the potential clinical benefits of BME in preventing and delaying the progression of oral dysplasia to SCC. Cancer Prev Res; 11(4); 185–6. ©2018 AACR. See related article by Sur et al., p. 191

Worldwide, head and neck cancer, which includes all oral, laryngeal, and pharyngeal sites, is the sixth most common cancer, accounting for about 643,000 new cases annually (1). The 5-year survival rate in oral cancer patients varies from 81% for those with localized disease to 42% for those with regional disease and 17% if distant metastases are present (2). Oral squamous cell carcinoma (OSCC) is the most common histologic type, and it accounts for more than 90% of oral cancers (1, 2). Early diagnosis for oral cancer has not improved over time, and up to 77% of oral cancer cases are diagnosed at late stages. Approximately one third of treated patients (including surgery, radiotherapy, and chemotherapy) will experience local or regional recurrence and/or distant metastasis. The main risk factors for oral cancer are exposure to tobacco smoke, smokeless tobacco, alcohol excess, and human papilloma virus (1). Avoidance of risk factors has only been partially successful largely due to the addictive power of tobacco smoking and alcohol consumption (3).

A number of chemopreventive agents, both naturally occurring and synthetic, were studied using 4-nitroguino-line-1-oxide (4-NQO)–induced oral cancers in rodent models (2, 4). Multiple agents, including isotretinoin, celecoxib, and erlotinib, were used in randomized chemoprevention clinical trials; however, no effective and tolerable agent was identified for the prevention of OSCC (4). Bitter melon (Momordica charantia) extract (BME) has recently come into focus for its potential anticancer efficacy. It has been traditionally used as a folk medicine/ayurvedic medicine since ancient times for the treatment of type II diabetes and the associated metabolic aberrations. Ray and colleagues first demonstrated its antiproliferative effect on breast cancer cells (5). Subsequently, her group and other investigators showed that BME has chemopreventive effect in different preclinical cancer models like head and neck, breast, prostate, pancreas, skin, stomach, and colon without any side effects (5–7). In this issue of Cancer Prevention Research, Sur and colleagues of the same group discussed the novel immunomodulatory role of BME in the prevention of carcinogen-induced oral cancer (8).

In this study, the authors used 4-NQO to induce invasive OSCC, especially in the tongue, in immunocompetent mice. Carcinomas of the tongue are the most common OSCC (25%–80%; ref. 9). 4-NQO is a synthetic, water-soluble carcinogen, which exhibits a very strong mutational preference (A-G nucleotide substitution) for the oral cavity, and tumor progression at a particular site will depend on additional factors, such as inflammatory and immunologic responses, resulting in histologic and molecular alterations similar to human oral carcinogenesis (2, 9). The authors observed that administration of BME with the 4-NQO in drinking water prevented OSCC development with no remarkable pathologic and histologic sign in the mice.

Bhattacharya and colleagues recently showed the in vivo immunomodulatory role of BME in HNSCC in a syngeneic mouse model (10). From RNA-seq analysis,
the authors identified modulation in the immune system process in 4-NQO-induced OSCC and in the prevention of OSCC by BME. Immunosuppression and deregulation of inflammatory mediators, such as cytokine/chemokines, which are present in the tumor microenvironment, are one of the hallmarks of inflammation-mediated tumorigenesis. Preclinical and clinical evidence has revealed that early transformed cells express antigens that allow the immune system to recognize them and initiate an immune response. To overcome the antineoplastic effects of the immune system, tumor cells may transmit immunosuppressive signals mediated by inflammatory cytokines, immune checkpoint molecules to the tumor microenvironment, which enable cancer progression (11). Their study showed significant upregulation of proinflammatory genes s100a9, IL23a, IL1b as well as immune checkpoint gene PDCD1/PD1, during carcinogen-induced OSCC (Fig. 1). Upregulation of these immune system–associated markers was reported in human HNSCC (11). Pharmaceutical targeting of s100a9 and PD1 showed a promising effect in phase I–III clinical trials against different cancers (4). Their observations clearly demonstrated remarkable downregulation of these genes following BME treatment. Thus, these observations indicated the potential role of BME in the prevention of carcinogen-induced oral cancer. In addition, elevated expression of MMP9, one of the known OSCC oncogenes associated with ossification, invasion, and metastasis (2), showed significant reduction following the BME treatment. Their study also showed modulation in lipid metabolism pathways by BME treatment. Cancer cells frequently show alteration in cellular metabolism, and different in vitro and in vivo studies reported potential beneficial effects of bitter melon against lipid and glucose metabolic dysfunction (6). Thus, their observation indicates the modulation of multiple cellular events at a time during BME-mediated oral cancer prevention.

In conclusion, the authors proposed the potential anticancer efficacy of BME in prevention of oral cancer by modulating different biological processes, including those of the immune system. Thus, this study may have importance not only for the treatment of oral cancer but also for the treatment of other cancers.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Acknowledgments
We thank Agata Bien for editorial help.

Received November 21, 2017; revised December 14, 2017; accepted December 15, 2017; published OnlineFirst March 20, 2018.

References
1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
2. Tanaka T, Ishigamori R. Understanding carcinogenesis for fighting oral cancer. J Oncol 2011;2011:603740.
3. Saman DM. A review of the epidemiology of oral and pharyngeal carcinoma: update. Head Neck Oncol 2012;4:1.
4. Bhatia A, Burtness B. Novel molecular targets for chemoprevention in malignancies of the head and neck. Cancers 2017;9:pii: E113.
5. Ray RB, Raychoudhuri A, Steele R, Nerurkar P. Bitter melon (Momordica charantia) extract inhibits breast cancer cell proliferation by modulating cell cycle regulatory genes and promotes apoptosis. Cancer Res 2010;70:1925–31.
6. Raina K, Kumar D, Agarwal R. Promise of bitter melon (Momordica charantia) bioactives in cancer prevention and therapy. Semin Cancer Biol 2016;40:41:116–29.
7. Dandawate PR, Subramaniam D, Padhye SB, Anant S. Bitter melon: a panacea for inflammation and cancer. Chin J Nat Med 2016;14:81–100.
8. Sur S, Steele R, Aurora R, Vavares M, Schwetye KE, Ray RB. Bitter Melon prevents the development of 4-NQO-induced oral squamous cell carcinoma in an immunocompetent mouse model by modulating immune signaling. Cancer Prev Res 2018;11:191–201.
9. El-Bayoumy K, Chen KM, Zhang SM, SunYW, Amin S, Stoner G, et al. Carcinogenesis of the oral cavity: environmental causes and potential prevention by black raspberry. Chem Res Toxicol 2017;30:126–44.
10. Bhattacharya S, Muhammad N, Steele R, Peng G, Ray RB. Immunomodulatory role of bitter melon extract in inhibition of head and neck squamous cell carcinoma growth. Oncotarget 2016;7:33202–9.
11. Sandberg DP, Strome SE. The role of the PD-L1:PD-1 pathway in squamous cell carcinoma of the head and neck. Oral Oncol 2014;50:627–32.
Immunomodulatory Effects of *Momordica charantia* Extract in the Prevention of Oral Cancer

Chinthalapally V. Rao

*Cancer Prev Res* 2018;11:185-186. Published OnlineFirst March 20, 2018.

Updated version

Access the most recent version of this article at:
doi:10.1158/1940-6207.CAPR-17-0379

Cited articles

This article cites 10 articles, 2 of which you can access for free at:
http://cancerpreventionresearch.aacrjournals.org/content/11/4/185.full#ref-list-1

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, use this link
http://cancerpreventionresearch.aacrjournals.org/content/11/4/185.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.