Journal of Functional Foods 40 (2018) 625–633

Contents lists available at ScienceDirect

Journal of Functional Foods

journal homepage: www.elsevier.com/locate/jff

Role of probiotics in the management of lung cancer and related diseases: An update

Anshul Sharma[a,c], Buddolla Viswanath[b], Young-Seo Park[a,*]

[a] Department of Food Science and Biotechnology, Gachon University, Seongnam 13120, Republic of Korea
[b] Department of Bionanotechnology, Gachon University, Seongnam 13120, Republic of Korea
[c] Department of Biotechnology, Shoolini University of Biotechnology and Management Sciences, Bajhol, Solan, Himachal Pradesh, India

ARTICLE INFO

Keywords:
Probiotics
Cancer
Lungs
Diseases
NK cell activation

ABSTRACT

Worldwide, lung cancer remains to be the most common cause of cancer-related deaths. A wealth of data has shown that probiotics play essential roles in different types of tumor prevention and treatment. However, data specifically linking probiotics with lung cancer is very limited. This review summarizes the utilization of probiotics directly for the treatment by mentioning *in vivo* and *in vitro* case studies, and also indirectly by discussing their impact on various causes responsible for lung cancer growth and thus playing important role in the prevention of cancer. The main findings of the review include that with probiotics treatment better survival rates with an augmented expression of tumor suppression genes were obtained. However, the expression of two oncogenes studied was found to be decreased, whereas increased cytotoxic effects were also observed in lung cancer cells. In addition, protective mechanism of probiotics was supposed to be linked with immunomodulation.

1. Introduction

Worldwide, Lung cancer is the most common cause of cancer deaths (1.8 million), estimated to be responsible for nearly one in five deaths (Chen, Zheng, Zeng, & Zhang, 2015). It has been found to be the leading cause of cancer death among males and the second leading cause of death in females globally (Torre et al., 2015), and is responsible for 19.4% of all cancer deaths (Chen et al., 2015). Based on their morphological features of cancer cells, there are two major types of lung cancer: small cell lung cancer (SCLC; 18%), which grows more quickly and shows metastasis (more likely to spread) to other organs of the body, and non-small cell lung cancer (NSCLC; 78%), which develops and spreads slowly, and is further classified into three types, namely squamous cell carcinoma (25%), adenocarcinoma (40%), and large cell lung cancer (10%). With regard to other histological types of lung cancer, the incidence of squamous cell carcinoma and small cell carcinoma has been decreasing, while that of adenocarcinoma has been increasing in both men and women (Toyoda, Nakayama, Ioka, & Tsukuma, 2008). According to many studies, genetic factors (Lu et al., 2013), smoking, pollution from transport (Vineis et al., 2006), toxic heavy metal consumption, exposure to radon gas (in mines or homes) (Zhang et al., 2012), respiratory diseases, alcohol intake (Druesne-Pecollo et al., 2014) and exposure to asbestos, silica dust, and several elements (Islami, Torre, & Jemal, 2015) are responsible for the incidence of lung cancer. However, smoking has been found to be the major cause and accounts for 80–90% of all lung cancer cases (Alberg, Brock, Ford, Samet, & Spivack, 2013; Kim, Lee, et al., 2014; Kim, Kim, et al., 2014).

Over the past few decades, patients with early-stage lung cancer have shown significant improvements in their health. However, in spite of many therapeutic advances, it has been reported that the overall 5-year survival rate is confined to 15% for men and 21% for women (American Cancer Society, 2017).

Therefore, innovative strategies are required to prevent and treat lung cancer (Viktorsson, Lewensohn, & Zhivotovsky, 2014). The American Institute for Cancer Research and the World Cancer Research Fund have assessed that the food, nutrition, physical activity, and body composition play a central part in the prevention of cancer (WCRF/AICR, 2007).

It has been found that the gastrointestinal tract is a habitat for trillions of microbes, which are essential for maintaining immune homeostasis in the gut microenvironment (Lee, Kim, Han, Eom, & Paik, 2014; Serban, 2014). According to the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), probiotics are defined as live microorganisms, which when administered in adequate amounts, confer a health benefit on the host

* Corresponding author.
E-mail address: ypark@gachon.ac.kr (Y.-S. Park).

https://doi.org/10.1016/j.jff.2017.11.050
Received 17 October 2017; Received in revised form 29 November 2017; Accepted 29 November 2017

(FAO/WHO, 2001; Fijan, 2014). However, huge variations have been recorded in the health benefits of different strains of probiotics. Gut microbiota provides potential nutritional and health benefits, such as nutrient utilization, resistance against infections, manipulation of intestinal microbial communities, maturation of the immune system, and regulation of host metabolism (Brestoff & Artis, 2013; Hooper, Littman, & Macpherson, 2012). The composition of microorganisms present in the gut is highly variable to external influences such as age, diet, stress, illness, medications, and lifestyle (Sommer & Bäckhed, 2013). Moreover, it has been reported that changes in the gut microbiota may lead to many disorders, including obesity, asthma, inflammatory bowel disease, psychiatric problems, and cancers also (Yu & Li, 2016).

Worldwide, cancer incidence and mortality rates have increased over the past decade; therefore, the protective role of probiotics against various cancers has fascinated the scientific community. Several epidemiological pieces of evidence have been reported about the use of probiotics in the prevention and treatment of different types of cancer (Kumar et al., 2010). The possible pleiotropic health effects of probiotics in eliciting anti-microbial and anti-tumor effects (Kumar et al., 2010) include delaying tumor growth, improving host immunity (innate and adaptive), getting free of various mutagens by competitive binding and degradation, decreasing the side effects of chemotherapy by metabolic activity improvement, direct inhibition of foodborne pathogens by competition, and also help in the reduction of post-operative complications (Liu et al., 2017; Patel & Denning, 2013; Raman et al., 2013) and heavy metal sequestration. Nevertheless, many other useful modes of action of probiotics are still unknown. In a previous review, the possible strategies of probiotics for the prevention or treatment of various cancer cell types, i.e., colon & rectum, breast, blood, cervical, prostate & bladder, skin & esophagus, liver & gall bladder, and head & neck have been described (Dasari, Kathera, Janardhan, Kumar, & Viswanath, 2016). Nowadays, much attention is given to the use of probiotics in the treatment of lung cancer. However, very little literature is available about the link between probiotics and lung cancer. Considering the importance of probiotics, this review discusses our current understanding of (1) the direct effects of probiotics in lung cancer treatment, (2) the indirect possible roles of the impact of probiotics on respiratory diseases and their possible mechanisms of action in the lung cancerous cells (Fig. 1).

2. Direct impact of probiotics in treatment of lung cancer

It is essential to understand the composition of lung microbiota in both states of health and disease. For the accurate diagnosis and treatment of lung cancer, identification of novel therapeutic targets in the lung microbiome is crucial (Hooper et al., 2012). It is important to realize whether the microbe is directly involved in pathogenesis, or after disease occurrence, there is a reduction in the healthy microbial pool of the person. Though the evidences suggesting the role of probiotics in the prevention of lung cancer are still limited, still, some studies are showing the promising role of probiotics. A study has suggested that the well-balanced intestinal microflora play protective role in the treatment of cancer (Iida et al., 2013). In a recently reviewed literature, it has been proposed that with the help of metagenomics, metatranscriptomics and culturomics platforms, comparison of microbial composition in cancer patients and healthy volunteers is becoming practical. The data generated together can indicate which bacterial genera or species could be beneficial to patients (Zitvogel, Daillère, Roberti, Routy, & Kroemer, 2017). Therefore, cancer treatment with microbiome or their products has the potential to treat tumours. However, it has also been stated that the microbial agents could also negatively affect cancer prognosis through the production of potentially oncogenic toxins and metabolites by bacteria. Thus, future treatments would rely on the use of combination of microbiome and its products with immunotherapeutics and more conventional approaches to target directly the malignant cells (Zitvogel et al., 2017).

The coming section was describing the role of probiotics in treatment of patients with lung cancer, lung cancer-bearing mouse and few *in vitro* studies of lung cancer cell lines with other cancerous cells. Following this, a couple of studies describing the effect of probiotics on the lung metastasis, check point inhibitors, homeostasis, and elevated efficacy of anti-tumor drugs has been described. Finally, the approach of recombinant probiotic bacteria, i.e., *Bifidobacterium infantis* as a possible therapeutic agent against lung cancer has been described (Table 1).

Although there are not articles that showed the direct effect of probiotics against lung cancer in humans, one research described previously has used 30 lung cancer patients to check the possibilities of improvement in the gut bacteria of the patients receiving chemotherapy by using probiotic bacterial strains. One group (n = 21) which was given combined treatment of probiotic strain based on *Bacillus subtilis* together with chemotherapy course resulted in improvement in the intestinal microflora and decreased rate of intestinal dyspepsia was observed. Patients of the control group (n = 9) have only received chemotherapy, showed constipation and decrease quantity of *Lactobacillus*, *Bifidobacterium* and *Bacteroides* and an increase was observed in different pathogenic bacterial strains (Mlu et al., 2013). Using this (probiotic medicines + chemotherapy) in lung cancer patients is encouraging to decrease the frequency of gastrointestinal complaints and prevent deterioration of the gut microflora.

Lewis lung cancer (LLC)-bearing mice (C57BL/6J) were used as tumor models in one *in vivo* study depicting the use of probiotics. The lung cancer cells were subjected to three different treatments (Table 1) and divided into the following groups: cisplatin group, cisplatin/ABX (an antibiotic cocktail of vancomycin, ampicillin, and neomycin, which disturbs intestinal microflora homeostasis) group, and cisplatin/*Lactobacillus acidophilus* (probiotics) group. Results showed positive effects with decreased tumor size and better survival rates. In cisplatin and cisplatin/ABX groups, shorter survival rates were observed, as compared to cisplatin/*L. acidophilus* group, which showed longer survival rates in mice. In addition, the effect of the probiotic strain on two oncogenes (*Vegfa* and *Ras*) and two tumor suppressor genes (*Cdkn1b* and *Bax)* was also evaluated using western blotting. Decreased expression levels of *Vegfa* and *Ras*, and increased expression levels of *Cdkn1b* and *Bax* genes were observed. Additionally, this study showed an increased anti-tumor response in *Lactobacillus*-co-treated mice with upregulated interferon (IFN)-γ, Gzmb, and Prf1 mRNA expression (Gui, Lu, Zhang, Xu, & Yang, 2015). IFN-λ plays an important protective role against cancers, mediated by probiotics. As far as we know, this was the sole study reported for individual lung cancer tumor model and use of probiotic bacterial strain.

The other two studies included in this were performed *in vitro* on various cancerous cell lines including the lung cancer, and the direct effects of various probiotic strains were analyzed for various clinical studies (Table 1). A probiotic strain, *Lactococcus lactis* KC24 was used, and its anti-cancer effect on various cancer cell lines, including lung carcinoma (SK-MES-1), breast carcinoma (AGS and MCF-7), and colon carcinoma (HT-29 and LoVo) was determined. Results showed that all the cancer cells with 10^6 CFU/well of *L. lactis* KC24 resulted in strong inhibition of proliferation using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Proliferation of SK-MES-1, AGS, MCF-7, HT-29, LoVo, and cells was inhibited by 86.53%, 90.12%, 91.89%, 68.30%, and 67.27% respectively (Lee et al., 2015).

In the same year, another study demonstrated that the probiotic strain, *L. lactis* NK34, exhibits anti-cancer and anti-inflammatory activity against various cancer cell lines, like SK-MES-1 (human lung carcinoma cell line; KCLB 30058), DLD-1 (human colon adenocarcinoma cell line; KCLB 30058), HT-29 (human colon adenocarcinoma cell line; KCLB 30038), LoVo (human colon adenocarcinoma cell line; KCLB 10229), AGS (human stomach adenocarcinoma cell line; KCLB 21739), and MCF-7 (human breast adenocarcinoma cell line; KCLB 30022). Cytotoxicity of the NK34 strain was observed in normal as well cancer