ejpmr, 2019,6(4), 26-29

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

BACTERIA CAN BE ACT AS ANTICANCER THERAPEUTIC AGENTS

Indra Kanta Maitra*[1] and Samir Kumar Bandyopadhyay[2]

[1]B.P. Poddar Institute of Management & Technology, Kolkata, West Bengal, 700052, India.
[2]JIS University, Kolkata, West Bengal 700109, India.

***Corresponding Author: Indra Kanta Maitra**

B.P. Poddar Institute of Management & Technology, Kolkata, West Bengal, 700052, India.

Article Received on 23/01/2019 **Article Revised on 13/02/2019** **Article Accepted on 05/03/2019**

ABSTRACT

The use of bacteria has been recognized for more than a century for the treatment of cancer. For the treatment of tumors bacterial therapy is promising approach. In this paper a review is presented to show how some bacteria can act as anti-cancer agent.

KEYWORDS: Cancer, Bacteria, Detection, Therapy.

INTRODUCTION

Bacteria are small with a size of the order few micrometers in length. Bacteria has wide variety of shapes and sizes and it is called the morphology of the organism. The shapes of bacteria are rod-like and it is called the bacillus form. Other shape is in spherical shape and it is called coccus form. Bacteria can be classified as Gram negative and Gram positive based on wall layer.

The role of bacteria is well known for infections but there is a link between cancer and bacteria in both positive and negative ways. The link between bacteria and cancer was first observed few decades back.[3] They noticed tumour regression in cancer patients suffering from erysipelas infection caused by Streptococcus bacteria. The causal agent was identified as Streptococcus pyogenes. But it was not until the end of 19th century a bone sarcoma surgeon, intentionally used bacteria for cancer treatment. Mixture of heat-killed Streptococcus and Serratia marcescens are used to treat bone and soft tissue sarcoma patients. This combination was known as Coley's toxin.[4]

Author hypothesized that a toxic material in the microbe elicited host immune response, which destroyed the tumour cells. The reported result is positive while treating patients suffering from various malignancies and carcinomas with this concoction. The importance of bacillus Calmette- Guérin (BCG attenuated strain of Mycobacterium bovis) was ascertained for treating bladder cancer.[5]

It is believed that bacteria is the causal agent of cancer as evidenced by the example of gastric cancer caused by Helicobacter pylori.[1] Live bacteria or their products are also responsible for curing some of the deadliest forms of cancer.[2]

Chemotherapy is the forerunner of all therapeutic strategies employed for treating cancer. It has potential drawbacks. Normal cells are damaged by therapeutic drugs instead of only penetrating tumour cell. Thus, they impart limited efficacy in treating cancer. Bacteria offer multiple benefits over the conventional available drugs. Certain bacterial strains like Clostridium specifically proliferate well in tumour cells.[6] Certain auxotrophic strains are attracted to tumour cells for the metabolic nutrients available in the tumour environment. This allows infiltration of such bacteria in the malignant cells, which are inaccessible or unresponsive to chemotherapeutic agents. It is expected that they are excellent candidates for delivery of anticancer agents due to metabolic nature. This includes production of cytotoxins (bacterial toxins), enzymes that make prodrugs active and immune modulating agents (cytokines, antigens). Certain tumour anti-proliferating components and genes to the tumour tissue by them. It helps tumour regression. The preferential specificity and proliferation of certain bacteria in tumour tissues can be used in combination with chemotherapeutic drugs to enhance their efficacy. Nevertheless, antibiotics can be used to control bacteria when they are no longer required in the tumour. It helps to control the use of bacteria. This paper reviews how bacteria can have promising nature for acting as anti-cancer agents.

Literature Review

The use of bacteria in the treatment of cancer has been recognized over a century.[1-2] It has the potential for novel treatment. However, the usage of bacteria to target tumours has limitations due to potential biosafety and other deleterious effects. It includes intrinsic bacterial

toxicity, lowered targeting efficiency, genetic instability, and complicated interactions with other therapies.[3-7] In 1813 it was observed that it is possible for spontaneous tumour regression from concurrent clostridial infection.[8-9] German physician Busch in 1868 cured the first patient of cancer using bacteria.[2,10] In 1890 a New York physician, found that several patients with inoperable tumours exhibited tumour regression subsequent to being inoculated with Streptococcus pyogenes.

In 1935, researcher observed tumour regression in advanced cancer during therapy using sterile filtrates from Clostridium histolyticum; the author attributed these results to the production of enzymes.[11-12] The deliberate injection of Clostridium was published in 1947.[13] This field was stopped due to certain drawbacks.[14] It was reported in 1976 that researchers made successful treatment of bladder cancer with bacillus Calmette-Guérin (BCG), that this field began to increase rapidly.[15] Some bacteria, such as Clostridium, Bifidobacterium, Salmonella, Mycobacterium, Bacillus and Listeria, are investigated to specifically act as antitumor agents, and colonize hypoxic and necrotic regions. These are present in solid tumours while normally absent in other parts of the body.

Bacteria as Anticancer Therapeutic Agents

Cancer occurs when tumour cells grow, invade, and spread into the surrounding normal tissues uncontrollably; this process is called metastasis. Although treatment of cancer can involve several modalities such as resection, radiotherapy, and chemotherapy, other strategies have developed with the aim of improving cancer therapies. Experimental cancer treatments are medical therapies, including photodynamic therapy, Human Alpha lactalbumin made Lethal to Tumour Cells, gene therapy, telomerase therapy, hyperthermia therapy, dichloroacetate (DCA), non-invasive RF cancer treatment, complementary and alternative therapy, diet therapy, insulin potentiating therapy, and bacterial treatment, which have been considered as alternative treatments to replace conventional methods; yet, due to lack of evidence, efficacy, feasibility, availability, specificity, and selectivity, the prevalent use of these therapies in cancer therapy has become controversial. Some microorganisms have been shown to selectively replicate in tumour cells such as many viruses, like vaccinia virus, Newcastle disease virus, reovirus, and adenovirus with an E1a deletion, carries altered genes to cancer cells, find target cells in body, and destroy them. and yet, sometimes body procures neutralizing antibody against these microorganisms which leads to deactivation of their efficacy. Some bacterial species are able to enter and then replicate within tumour cells, simultaneously carry and express multiple therapeutic proteins, and consequently be eliminated by antibiotics. Furthermore, in many infectious diseases and cancer, to deliver genes, live attenuated strains of bacteria should be applied, which have different advantages, including low-cost preparation, intensive immune stimulation, tolerance, safety, and the major point of antigen entry into the Major Histocompatibility Complex class I pathway for the induction of cytotoxic T cells. Therefore, the advent of advanced techniques, including bacterial drug delivery as bacterial vectors for genetic manipulation has created novel bioengineered microbes with great therapeutic efficacy in many therapeutic strategies including apoptosis induction, suicide gene therapy, immunotherapy, anti-angiogenesis therapy, and DNA vaccination.

Anaerobic bacteria can be exploited to proliferate in these hypoxic regions of the tumor and facilitate its destruction. Intense research focused upon the role of Clostridia spp. proved its potential of penetrating and colonizing tumor.

The resistance of chemotherapy for the exposed body cells enhanced capability to repair DNA defects in cellular machinery which intervenes apoptosis. Detoxification of drug and drug delivery services increase the production of enzymes due to exposed cells. These inherent complications of chemotherapy, which include drug resistive mechanism of cells caused by chemotherapy, have caused scientists to focus on examining the potential of using bacteria and their compounds for anti-cancer therapy.

Bacteria are carcinogens and tumour promoters.[4] The regulation of cell growth creates problem of cellular signal since bacteria produces toxins. Tumour promotes stains through inducing inflammation in the cells. Helicobacter pylori, stains, is associated with gastric cancer[5], Salmonella typhi bacteria which is associated with hepatobiliary carcinoma[6], Campylobacter Jejuni which is associated with small intestinal lymphomas[7], Chlamydia psittaci which is associated with ocular lymphomas[8], Mycobacterium tuberculosis which is associated with lung cancer[9], and Citrobacter rodentium, which is associated with human colorectal cancer.[10] In addition, the enzymes produced by bacteria are potential carcinogens, such as peptidyl arginine deaminase (PAD) enzymes that are found in oral bacteria and associated with pancreatic cancer.[11,12] The quorum sensing peptides down-regulate microRNA-222 and initiate angiogenesis which promotes neovascularization and results in tumour metastasis.[14]

Bacteria have shown great potential for cancer therapy. Invade and colonize solid tumours often results in neoplasm growth retardation, and in some instances, complete tumour clearance due to species in bacteria.[15] Tumour cells are destroyed by different strains of Clostridia, Bifidobacteria and Salmonella in colonizing the hypoxic area of the tumour. These are potential strains for selective tumour targeting therapy.[16–21]

Bacteria creates anti-tumour effects for cancer cell metabolism.[22-23] Salmonella bacteria through proper

administration can be flushed into the solid tumour through severe haemorrhaging area, the area which leads to necrotic regions in which bacteria proliferate[24], colonized the tumour and decreased the proliferation of the tumour. Reduction of oxygen and nutrient supply leads to the breaking down of blood vessels in the hemorrhagic area and causes the tumour cells in the center of the tumour to die from starvation and suffocation.[24] The tumour micro-environment may be conducive to bacterial survival and growth, as it may provide protection from the host immune system and nutrients.[25]

Bacteria mediated tumour therapy (BMTT) can only be achieved via the heat-inactivation method for controlling infection and the therapeutic benefit of bacteria.[26] Bacterial strains can be altered by genetic engineering.[27] It reduces bacteria side effects while increasing their therapeutic benefits. Bacillus Calmette–Guerin (BCG) vaccine for the treatment of human bladder cancer is arguably superior to intravesical chemotherapy for superficial disease.[28]

Tumour detecting bacteria provides a sensitive and minimally invasive method to detect tumour recurrence. It monitors treatment efficacy and identify the onset of metastatic disease.[29] Such genetic engineering approaches have paved the way for further development of promising bacteria-based cancer therapy.

CONCLUSIONS

Using bacteria for cancer therapy is used to treat solid tumors has been known for decades. Some attenuated species of bacteria capable of treating cancer have been recently identified and studied. This paper reviews the way bacteria can use as cancer therapy in future.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin., 2017; 67(1): 7–30.
2. Chen W, et al. Cancer statistics in China, 2015. CA Cancer J Clin., 2016; 66(2): 115–32.
3. Raguz S, Yague E. Resistance to chemotherapy: new treatments and novel insights into an old problem. Br J Cancer, 2008; 99(3): 387–91.
4. Lax AJ. Opinion: bacterial toxins and cancer–a case to answer? Nat Rev Microbiol, 2005; 3(4): 343–9.
5. Correa P, et al. Helicobacter pylori and gastric carcinoma. Serum antibody prevalence in populations with contrasting cancer risks. Cancer, 1990; 66(12): 2569–74.
6. Caygill CP, et al. The association between typhoid carriage, typhoid infection and subsequent cancer at a number of sites. Eur J Cancer Prev., 1995; 4(2): 187–93.
7. Mesnard B, et al. Immunoproliferative small intestinal disease associated with campylobacter jejuni. Dig Liver Dis., 2012; 44(9): 799–800.
8. Ferreri AJ, et al. Evidence for an association between chlamydia psittaci and ocular adnexal lymphomas. J Natl Cancer Inst., 2004; 96(8): 586–94.
9. Gupta PK, et al. Mycobacterium tuberculosis H37Rv infected THP-1 cells induce epithelial mesenchymal transition (EMT) in lung adenocarcinoma epithelial cell line (A549). Cell Immunol, 2016; 300: 33–40.
10. De Spiegeleer B, et al. The quorum sensing peptides PhrG, CSP and EDF promote angiogenesis and invasion of breast cancer cells in vitro. PLoS One., 2015.
11. Ogrendik M. Oral bacteria in pancreatic cancer: mutagenesis of the p53 tumour suppressor gene. Int J Clin Exp Pathol, 2015; 8(9): 11835–6.
12. Jacob JA. Study links periodontal disease Bacteria to pancreatic Cancer risk. JAMA, 2016; 315(24): 2653–4.
13. De Spiegeleer B, et al. The quorum sensing peptides PhrG, CSP and EDF promote angiogenesis and invasion of breast Cancer cells in vitro. PLoS One, 2015.
14. Wynendaele E, et al. Crosstalk between the microbiome and cancer cells by quorum sensing peptides. Peptides, 2015; 64(Supplement C): 40–8.
15. Leschner S, Weiss S. Salmonella-allies in the fight against cancer. J Mol Med (Berl)., 2010; 88(8): 763–73.
16. Wei MQ, et al. Facultative or obligate anaerobic bacteria have the potential for multimodality therapy of solid tumours. Eur J Cancer, 2007; 43(3): 490–6.
17. Chang J, et al. Pseudomonas aeruginosa preparation plus chemotherapy for advanced non-small-cell lung cancer: a randomized, multicenter, double blind phase III study. Med Oncol, 2015; 32(5): 139.
18. Hetz C, et al. Microcin E492, a channel-forming bacteriocin from Klebsiella pneumoniae, induces apoptosis in some human cell lines. Proc Natl Acad Sci U S A., 2002; 99(5): 2696–701.
19. Pawar V, et al. Murine solid tumours as a novel model to study bacterial biofilm formation in vivo. J Intern Med., 2014; 276(2): 130–9.
20. Ganai S, et al. In tumors Salmonella migrate away from vasculature toward the transition zone and induce apoptosis. Cancer Gene Ther., 2011; 18(7): 457–66.
21. Yan L, et al. Photodynamic treatment of tumor with Bacteria expressing Killer Red. PLoS One., 2015.
22. Danino T, et al. Measuring growth and gene expression dynamics of tumor targeted S. Typhimurium bacteria. J Vis Exp., 2013.
23. Forbes NS. Engineering the perfect (bacterial) cancer therapy. Nat Rev Cancer., 2010; 10(11): 785–94.
24. Leschner S, et al. Tumor invasion of Salmonella enterica serovar typhimurium is accompanied by strong hemorrhage promoted by TNF-alpha. PLoS One., 2009.
25. Nallar SC, Xu DQ, Kalvakolanu DV. Bacteria and genetically modified bacteria as cancer therapeutics: current advances and challenges. Cytokine, 2017; 89: 160–72.

26. Coley WB. The treatment of inoperable sarcoma by bacterial toxins (the mixed toxins of the Streptococcus erysipelas and the Bacillus prodigiosus). Proc R Soc Med., 1910; 3(Surg Sect): 1–48.
27. Felgner S, et al. Optimizing Salmonella enterica serovar typhimurium for bacteria-mediated tumor therapy. Gut Microbes, 2016; 7(2): 171–7.
28. Alexandroff AB, et al. Recent advances in bacillus Calmette-Guerin immunotherapy in bladder cancer. Immunotherapy, 2010; 2(4): 551–60.
29. Panteli JT, et al. Genetically modified bacteria as a tool to detect microscopic solid tumor masses with triggered release of a recombinant biomarker. Integr Biol (Camb), 2015; 7(4): 423–34.