Review article:

Relationship Between Cancer and Microbiota

Arzuhan Çetindağ Çiltaş[1], Feride Taşkın Yılmaz[2]

Abstract

Microbiota might be considered as an environmental factor which we are always exposed to at high doses lifelong. It also includes bacteria and other organisms (fungus, protozoa, virus and etc.) existing and living in our gastrointestinal tract and other anatomic regions (mouth, skin, vagina). After it has been indicated that microbiota is related with human health and many diseases such as cancer, studies in this field have gained speed and in view of the fact that microbiota should be assessed as a new organ in our body has emerged. Microbiota protects tissues from antigens and pathogens by strengthening mucosal barrier. Cancer and inflammatory disorders increase when the barrier is destroyed. When the barrier is destroyed, microbes might affect immune reactions in growing tumor microenvironments more by forming proinflammatory or immunosuppressant programs. Microbiota which accompanies intestinal and epithelial surface of human body affects starting and growing of the cancer and impact of cancer treatment on tumor cells by intervening systemic metabolism, immune system and inflammations. Many factors including environmental conditions such as host genetics and diet regulate microbiota diversity and ultimately regulate carcinogenesis and cancer treatment. In this review, we planned to emphasize importance of the relation between microbiota and cancer which has been an important subject of scientific researches in recent years.

Keywords: Cancer, microbiota, carcinogenesis.

International Journal of Human and Health Sciences Vol. 04 No. 04 October'20 Page : 251-256
DOI: http://dx.doi.org/10.31344/ijhhs.v4i4.209

Introduction

Cancer is the second leading cause of death all around the world[1]. Cancer is a multifactorial disease. Cancer formation is the result of random intracellular deposits of spontaneous mutations during DNA replication; both of them might significantly affect cancer risk with exposure to environment and lifestyle habits[2]. For instance, exposure to transmissible agents, UV radiation and toxic substances, individual diet and lifestyle increase cancer risk. However the risk depends on dose, duration and combination of this type of damages when essentially combined with individual genetic background[3]. Genetic mutations and changes are essential for proliferation of cancer cells and their robustness in the tissue which they originate[4].

Approximately 16% of the cancers in the world are related with transmissible agents or chronic infections and this rate is 22.9% in less developed countries while it is 7.4% in more developed countries. Cancer incidence all around the world has been also increasing with prolongation of human life. World Health Organization shows that cancer incidence will increase by 70% in the next twenty years and this will increase global cancer epidemic[5]. Colorectal cancer is the third most common cause of cancer mortality among all cancers and studies have shown that intestinal microbiota plays a role in the development of colorectal cancer although no single causal microorganism is indicated[6].

Treatment of tumors has drawn attention a lot in recent years; however, the number of people with

1. Lecturer. Sivas Cumhuriyet University, School of Susehri Health High, Sivas, Turkey.
2. Associate Prof. Sivas Cumhuriyet University, School of Susehri Health High, Sivas, Turkey.

Correspondence to: Feride Taşkın Yılmaz, RN, PhD, Associate Prof. Department of Internal Diseases Nursing, School of Susehri Health High, Sivas Cumhuriyet University, Sivas, Turkey. E-mail: feride_taskin@hotmail.com

neoplastic syndrome has been still increasing. Thus, researchers are trying to tackle with this process looking for innovative treatments and prophylaxis. Although cancer risk indisputably depends on genetic factors, immunologic condition of the organism plays an important role in close relation with essentially probiotic bacteria in digestive tract and commensal bacteria flora[7].

The relation between cancer and microbes is complex. Although cancer is generally considered to be a disease of genetic and environmental factors, microorganisms occur in 20% of human malignancies[8].

Microbes in mucosa area might be a part of tumor microenvironment of digestive system malignancies in the air and intertumoral microbes might affect cancer growth and spread in many ways. Intestinal microbiota also functions in detoxification of diet components, decrease of inflammation and protecting balance in growth and proliferation of host cell[9].

Possibility of micro based cancer therapeutics has been drawing attention for more than 100 years from Coley toxins (one of the oldest cancer bacteriotherapy types) to designer microbes of synthetic biology and microbiota transplant periods nowadays. For this reason, questioning the roles of microbe and microbiota in cancer requires a holistic perspective[10].

In this review, we planned to emphasize importance of the relation between microbiota and cancer which has been an important subject of scientific researches in recent years.

Microbiota

This ecological community of microorganisms (bacteria, fungi, protozoa) which do not have any harmful effects on human body and are often beneficial is defined as "microbiota" and total genome of the microorganisms living in this environment is defined as "microbiome". In fact, these expressions indicate microorganisms in and out of the human body that benefit the human body (mutualist) or live without harming it (commensalits). There are nearly 100 trillion cells in our body and 10 times more of these cells are useful bacteria. In recent years, lots of evidence has been shown to be the key determinants of commensal bacteria colonizing body surfaces, health or pathological conditions including cancer. Intestinal microbiota is the most studied subject among human symbiotic microbial populations and it is also very effective in host homeostasis[11].

Microbiota might be considered as an environmental factor which we are always exposed to at high doses lifelong and it also includes bacteria and other organisms (fungus, protozoa, virus and etc.) existing and living in our gastrointestinal tract and other anatomic regions (mouth, skin, vagina). Most of these microbes are common bacteria which is difficult to make acculturation. These microorganisms help many physiological activities such as digestion, metabolism, epithelial homeostasis and growth of lymphoid tissues related to the intestines, they can also metabolize bile acids and xenobiotics, they can synthesize vitamin B and K, their antigens and metabolic products can stimulate cytokine production against potential pathogens[11]. After it has been indicated that microbiota is related with human health and many diseases such as cancer, studies in this field have gained speed and the view of the fact that microbiota should be assessed as a new organ in our body has emerged[12]. Diversity of the microbiota differs depending on many etiologic factors defined as age, geographical differences, diet habits, antibiotics, pH, micronutrients, secretions (acid, bile, mucus and enzymes) and these changes are related with many chronic diseases including diabetes mellitus, cardiovascular diseases and cancer. Approximately 1-2 kg of a 60-70 kg person consists of bacteria. Approximately 90% of these microorganisms and 80% of immune system cells are located in our intestine[13].

Human intestinal microbiota has the highest number of bacteria compared to other parts of the body. There are up to 10^{14} bacteria in gastrointestinal tract and a few archae, eukaryote and virus[14]. Combination of intestinal microbiome changes with age of the host and it is placenta starting colonization of fetus in uterus, amniotic fluid, umbilical cord blood and meconium origin. Placental microbiota might affect formation, growth and also survival of fetus and various postnatal pathologies. Premature birth might lead to long term results for the growth of immune-

mediated diseases (bronchial asthma, atopic dermatitis)[15,16]. There is a vertical microbiome transmission at birth, newborns are exposed to vaginal microbes among the most common ones we have mentioned: *Lactobacillus* and *Prevotellaspp*; after that, breast milk or formula milk affects colonization process in the newborn[17]. For this reason, delivery method affects the microbiota which the baby will have. *Bifidobacterium* and *Bacteroides* types are less common in the ones with caesarean section. Microbiome combination is very dynamic in the first three years of life and human microbiome which differs in every person relatively reaches stability at 2-3 ages and changes of the microbiota at genus and species level continue dynamically over the years[18].

Cancer and Microbiota

Microbiota protects tissues from antigens and pathogens by strengthening mucosal barrier. Mucosal surface barriers allow host-microbial symbiosis, they are always susceptible to environmental damage and they need to repair mucosal barrier quickly in order to provide homeostasis again. Danger resistance of the host or microbiota might turn tissues into malignancy. Cancer and inflammatory disorders increase when the barrier is destroyed. When the barrier is destroyed, microbes might affect immune reactions in growing tumor microenvironments more by forming proinflammatory or immunosuppressant programs. Although microbiota provides such a significant support for host immune system, growing of obesity, diabetes mellitus, inflammatory diseases, allergy and cancer accelerates in case of dysbiosis as a result of abnormal changes in the ecosystem. The number of these diseases increased in 2013[19,20] (Table 1).

Table-1. Diseases associated with dysbiosis (First findings in 2011)

Atopy and asthma
Celiac disease
Colon cancer
Type 1 DM
Type 2 DM
HIV infection
Inflammatory Bowel disease
Irritable Bowel syndrome
Gastroenteritis
Necrotizing Enterocolitis
Obesity
Rheumatoid arthritis

Pathogenic microorganisms are defined as determinant in nearly 15% of all cancers. The infection which the only bacteria *Helicobacter pylori* among many microorganisms including oncogenic viruses causes the risk of stomach cancer[21]. Besides, recent studies have shown that pathogens also affect various diseases as well as commensal microbiota. When the environment of human intestinal microbiota is destroyed, some common microbiota types such as *clostridium difficile* and *vancomycin resistant Enterococci* (VRE) become pathogenic. Microbiota which accompanies intestinal and epithelial surface of human body affects starting and growing of the cancer and impact of cancer treatment on tumor cells by intervening systemic metabolism, immune system and inflammations. Many factors including environmental conditions such as host genetics and diet regulate microbiota diversity and ultimately regulate carcinogenesis and cancer treatment[22].

Carcinogenesis defines all stages of a healthy body cell turning into a cancer cell after genetic and epigenetic changes. Initiation of genetic damage is an active process still not fully illuminated, in which tumor suppressor genes and proto-oncogens play active role, whose aetiopathogenesis where organism eventually encounters with cancer cells after transition to irreversible stage following a series of genetic and molecular changes has many factors. The role of microbiota in carcinogenesis is divided into 3 broad categories: (i) Translocation: Disruption of the relation between microbiome and the host leads to bacterial translocation and inflammation, (ii) Genotoxic effect: Bacterial genotoxins such as colibactin cause damage to DNA of the organs such as digestive system having direct contact with microbiome after entering the host's cells and (iii) Metabolic effect: While acetaldehyde, nitrosamine and other carcinogens are active, hormones such as oestrogen and testosterone and metabolism of

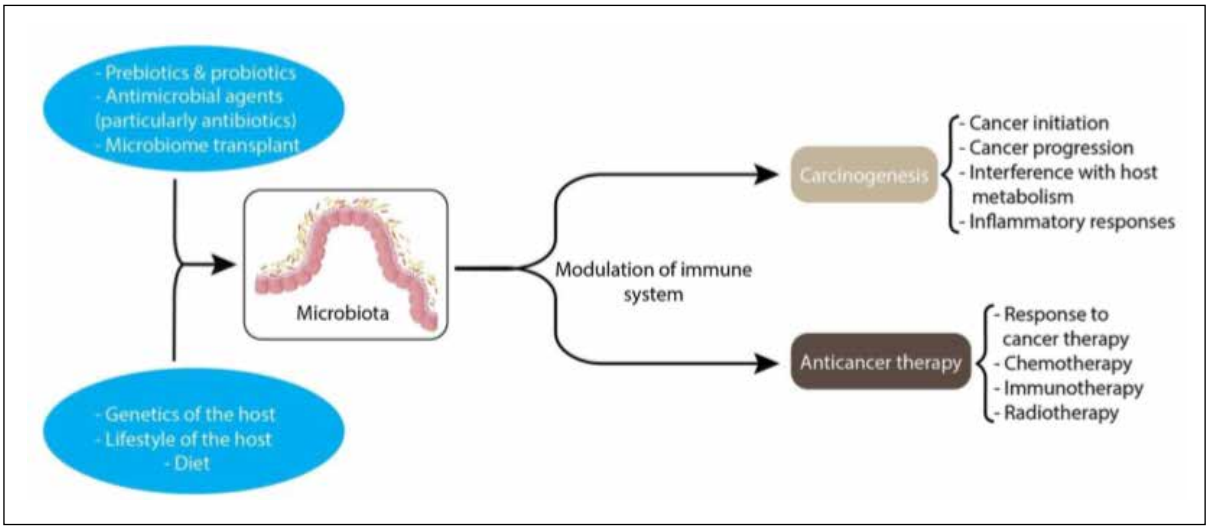

Figure 1: Microbiota and carcinogenesis

bile acids, energizing metabolism are destroyed[10] (Figure 1).

Among all pathologies associated with intestinal microbiome, tumorigenesis is one of the most studied. This relation exists both in local gastro-intestinal cancer and other distal tumors. Metabolomic and metagenomic studies emphasize dual role of gastro-intestinal microbiome in preventing cancer and tumorgenesis and cancer preventive treatment. In fact, intestinal microbiome might be tumor suppressor or oncogenic[23]. Although this link has been studied for long time, it is only partially illuminated. Existing information emphasizes complexity and bidirectionality of the link between microbiome and cancer. Cancer growth might change microbioma and in parallel with this, microbiome changes might affect progression of the cancer[24].

Direct contact of microbiota with hemopoietic cells after destruction of dysbiosis and intestinal barrier starts inflammatory process in carcinogenesis. Short chain fatty acids produced by fermentation by microbiota regulate mucosal immunity and mucosal functions through G- protein. It has been shown that IL- 18 mediates mucosal protective mechanisms and it has been found in a study that colon cancer develops with chemical stimulation as a result of disruption of microbiota in mice without IL-18 production[25]. In another study, bacterial endotoxines also trigger carcinogenesis in animal models whose IL-18 and IL-22 expression is inhibited. The role of many microbial factors especially *enterococcus faecalis*, *enterotoxigenic bakterio desfrajilis*, *entero pathogenic E.coli*, *fusobakteriumspp* and *streptococcus gallolitukus* in carcinogenesis has been defined. *Odaribacter* and *akkermanya* colonization increased in microbiota in animal models with colon tumor and it has been associated with colorectal cancer growth[26]. Besides, it has been also proved that intestinal microbio plays an important role in cancer progress by affecting genomic stability of the host cells by using different signals/pathways and modulating inflammation[27].

Probiotic bacteria might both increase and reduce the production of anti-inflammatory cytokines playing an important role in prevention of carcinogenesis. Besides, they might activate fagocytes in order to eliminate early stage cancer cells. There are many cohort studies indicating the relation between intake of dairy products and colon and colorectal cancer[7].

Dysbiosis in intestinal microbiota plays a key role in starting of many cancer types except colorectal cancer. Experimental results obtained from the studies on intestinal microbiota changes show that it plays role in growth of other organ cancers (stomach, breast and lung)[28].

It is useful to address important points between microbiome and cancer:

1. Even if it cannot be completely explained, it is possible that microbiota might lead to some cancers. It has been shown in experimental studies that *Lactobacillus acidophilus* prevents colorectal cancer, inhibits colitis and polyposis, increases tumor suppressor

gene in cell lines by reducing inflammation. It is known that *Bifidobacteriumbre* and *Lactobacillus rhamnosus* suppress pro-inflammatory cytokines and reduce DNA methylation of the host. Studies on probiotics seem promising.

2. It is known that microbiota affects response to chemotherapy and modulate possible side effects in individuals with cancer. Microbiota has both local and systemic effect on effectiveness and toxicity of cancer treatment. However, studies up to now have been done on rats and ideal microbiota combination has not been provided yet. There is not enough data about benefit of fecal transplantation for this purpose. Similarly, effectiveness of microbiota manipulation in terms of preventing recurrences or metastasis has not been illuminated yet[22,29].

Conclusion

Consequently, in recent studies, it has been shown that microbiota has an effect especially on preventing digestive system cancers. Intestinal microbiota is now considered as a separate organ and even it is also called second brain of the body. In line with all this information, it seems that microbiota is and will be an important objective to prevent cancer and provide effectiveness of cancer treatment. Besides, which probiotic bacteria, in which doses and ways should be given in individual treatments is one of the most up to date and hot topics. Further studies are required in order to use microbiota to treat and prevent cancer.

Source of funding : None declared

Conflict of Interest : None declared

References:

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: A systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2015;388:1459–1544.
2. Tomasetti C, Vogelstein B. Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. Science. 2015;347:78–81.
3. Anand P, Kunnumakkara AB, Kunnumakara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, Sung B, Aggarwal BB. Cancer is a preventable disease that requires major lifestyle changes. Pharm Res. 2008;25: 2097–2116.
4. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA, Kinzler KW. Cancer genome landscapes. Science. 2013;339:1546–1558.
5. Vyshenska D, Lam KC, Shulzhenko N, Morgun A. Interplay between viruses and bacterial microbiota in cancer development. Semin Immunol. 2017;32:14-24.
6. Walsh CJ, Guinane CM, O'Toole PW, Cotter PD. Beneficial modulation of the gut microbiota. FEBS Lett. 2014;588(22): 4120-4130.
7. Górska A, Przystupski D, Niemczura MJ, Kulbacka J. Probiotic Bacteria: A Promising Tool in Cancer Prevention and Therapy. Current Microbiology. 2019;76(8):939-949.
8. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, Plummer M. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012;13:607– 615.
9. Sears CL, Garrett WS. Microbes, microbiota and colon cancer. Cell Host Microbe. 2015;15:317–328.
10. Garret WS. Cancer and the microbiota. Science. 2015;348:80-86.
11. Çetin R, Güven GB, Tunçbilek V, Develi S, Aykutluğ Ö, Korkmaz A. Mikroorganizmalar ve insan vücudu ile olan etkileşimleri. TAF Prev Med Bull. 2015;14(3):272-278.
12. Sherwood L, Willey J, Woolverton C. Prescott's Microbiology. 9Th Edition. New York: Mc Graw Hill, 2013.
13. Fuentealba C, Figuerola F, Estévez AM, Bastías JM, Muñoz O. Bioaccessibility of lignans from fl axseed (Linum usitatissimum L.) determined by singleβbatch in vitro simulation of the digestive process. Journal of the science of food and agriculture. 2014;94(9):1729-1738.
14. Sandek A, Bauditz J, Swidsinski A, Buhner S, Weber-Eibel J, von Haehling S, Schroedl W, Karhausen T, Doehner W, Rauchhaus M, Poole-Wilson P, Volk HD, Lochs H, Anker SD. Altered intestinal function in patients with chronic heart failure. Journal of the American College of Cardiology. 2007;50(16):1561-1569.
15. Sekirov I, Russell SL, Antunes LC, Finlay BB. Gut microbiota in health and disease. Physiol Rev. 2010;90:859–904.
16. Goedicke-Fritz S, Härtel C, Krasteva-Christ G, Kopp MV, Meyer S, Zemlin M. Preterm Birth affects the risk of developing immune-mediated diseases. Front Immunol. 2017;8: 1266.
17. Pelzer E, Gomez-Arango LF, Barrett HL, Nitert MD. Review: maternal health and the placental microbiome. Placenta. 2017;54:30–37.
18. Kundu P, Blacher E, Elinav E, Pettersson S. Our gut microbiome: the evolving inner self. Cell. 2017;171:1481–1493.
19. Salman T, Varol U, Yıldız İ, Küçükzeybek Y, Alacacıoğlu A. Mikrobiyota ve kanser. Acta Oncologica Turcica. 2015;48(2):73-78.
20. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, et al.: International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. Nature. 2001; 409:860–921.
21. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. Nature. 2007;449(7164):804-810.
22. Roy S, Trinchieri G. Microbiota: a key orchestrator of cancer therapy. Nat Rev Cancer. 2017;17(5):271–285.
23. Gagnaire A, Nadel B, Raoult D, Neefjes J, Gorvel JP. Collateral damage: Insights into bacterial mechanisms that predispose host cells to cancer. Nat Rev Microbiol. 2017;15:109–128.
24. Zitvogel L, Daillère R, Roberti MP, Routy B, Kroemer G. Anticancer effects of the microbiome and its products. Nat. Rev. Microbiol. 2017;15:465–478.
25. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly M, Glickman JN, Garrett WS. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science. 2013;341(6145):569-573.
26. Mira-Pascual L, Cabrera-Rubio R, Ocon S, Costales P, Parra A, Suarez A, Moris F, Rodrigo L, Mira A, Collado MC. Microbial mucosal colonic shifts associated with the development of colorectal cancer reveal the presence of different bacterial and archaeal biomarkers. J Gastroenterol. 2014;50(2):167-179.
27. Schwabe RF, Jobin C. The microbiome and cancer. Nat Rev Cancer. 2013;13:800–812.
28. Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. Nat Rev Microbiol. 2014;12:6.
29. Bhatt AP, Redinbo MR, Bultman SJ. The role of the microbiome in cancer development and therapy. CA Cancer. 2017;67(4):326-344.