Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 4529 - 4533
Received 16 February 2021; Accepted 08 March 2021.

Interplay between Altered Gut Microbiota and Immune System May Amend the Face of Diagnosis and Therapeutic Regimens of Cancer

Harsha
University Institute of Sciences, Chandigarh University, District Mohali, Punjab, India
Email: harsha.e8137@cumail.in

AbstractEvery aspect of gut immune system is influenced by intestinal microbiome because it embraces the prevalent surface area of microbial interaction with immune system of the host which occurs in a dynamic equilibrium between tolerance and activation i.e. immune system provides protection against pathogenic microbes and the majority of the gut microbes are innocuous symbionts. Several immunological, metabolic and inflammatory pathways help in maintaining this subtle balance amid symbiosis and pathogenesis. Previous studies confirm that gut microbiota plays an important role in carcinogenesis and also has impact on efficiency and toxicity of anticancer therapy by immunomodulation, altered microbiota and xenometabolism. Mucosalassociated lymphoid tissue (MALT) lymphoma, hepatocellular carcinomas,pancreatic cancer etc. have been shown to be caused by the presence of pathogenic bacteria. This review updates the information regarding association among altered microbiota and carcinogenesis which can be exploited to augment our understanding about the disease progression, improve diagnosis .

Keywords:gut microbiome, carcinogenesis,diagnosis, therapeutics

INTRODUCTION

- Cancer and microbes both are in relationship. Although major causes of cancer are genetic factors and environment factors but microorganisms are also involved in human cancers.Mucosal sites have good amount of microbes that can initiate the tumor development of aerodigestive tract malignancies.There are three ways by which microbiota contribute to carcinogenesis(i) amending the balance of host cell proliferation and death (ii) leading immune system function, and (iii) influencing metabolism of host-produced factors.Lymphoma is cancer of immune cells,calledlymphocytes.Lymphocytesare responsible for clearing the microbial colonization because of activation of an immune system. The immunologically active cells are present in the mucosal-associated immune system and are receiving signals from other immune cells. Impairment can lead to inflammatory diseases like cancer. In case of lymphoma,lymphocytesgrow out of control.*Helicobacter pylori* is gram-negative bacteriaand shape of this bacteria is spiral, infects 50% of humans worldwide. H. pylori is responsible for increase risk of gastric lymphoma(Farinha & Gascoyne, 2005).At the same time, however, diet can regulate the microbial growth within gut, and this aids the idea that prebiotics andprobiotics can be used as effective strategies for prevention of cancer. Lactobacilli are beneficial microbes called probiotics. When sufficient amounts ofprobiotics administered in host body,these are directly responsible for health benefits. This review focus on relationship of microbiome and malignancy.(Yamamoto & Schiestl, 2014)

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Gut Microbiome

Gut microbiota is diverstyof microorganisms which are presnt in mammalian gastrointestinal tract. Microbes including bacteria, Archae and viruses are populated in human gut.Microbiome is alliedgenome of microbiomes in community and term microbiota refers to microbes in aggregate.The composition of microbial community isspecific for host, developing throughout host lifetime.In humans many microbes can interact with human organs such as mucosal surfaces. So microbes play very important role in human working including immunity. Additionally, they can be a responsible for many diseases, affecting both near and far organ systems.AsHuman GI tract is full of microbes, Many Gut microbespalys important role in carcinogenesis, and some are responsible for decreasing effects of cancer. Some microbes plays important role indiagnosis of carcinomas. The mechanisms by which microbiotaexpend its beneficial or destructive influences remain largely undefined, but include recognition of bacterial epitopes by both intestinal epithelial and mucosal immune cells.(Zuccaro et al., 2019)

Gut Microbiota and Host's Carcinogenesis

MALT Lymphoma

Bacteria and animal body both are in relationship and this relationship allows us to study about the diseases caused by microbiome changes. Mucosal-associated lymphoid tissue lymphomas are strongly associated due to the presence of *Helicobacter*.There are main three types of *Helicobacter* i)*H. felis,* ii)*H. pylori,* iii)*H. helmanii*.(Yamamoto & Schiestl, 2014)

Gut bacteria species can directly genesis for promotion of mutagens and oxidative stress which causes DNA damage and succeedingcancer. All immune cells and epithelial cells can be directly interact with immune cells and with epithelial cells. The interaction between bacteria and immune cells is major cause of increase production of reactive oxygen species,due to which oxidative stress increases. Oxidative stress can cause damage to DNA and carcinogenesis. Oxidative stress is increased by both bacteria *H. Pylori* and *C. Jejuni*.So bacteria may act as an antigen as it increases oxidative stress and then it activates proliferation of immune cells. (Yamamoto & Schiestl, 2014)*H. pylori* is responsible for lymphoma as it causes continousstimulation of presentation of antigens leading to B cell expansion. It is found that animals or animal's gut which is infected with *H pylori*can evolve lymphomas,whereas if *H pylori* is absent in animals then they did not have Lymphoma.

It has been reported that the p53 gene change isintricate in the progression of MALT lymphomas.It'srestricted inactivation is responsible for the progression of low grade MALT lymphomas.High grade MALT lymphomas development is due to complete inactivation of p53 gene. Gene p53 mutations is related to infection of *H. pylori* because *H. pylori* promotes degradation of p53 protein

Early phase of lymphomagenesis includes molecular event such as overexpression of Bcl-2 protein. Bcl-2 is an apoptosis suppressor gene which is responsible for the production of Bcl-2 protein.So due to overexpression of Bcl-2 protein rate of apoptosis decreases or this overexpression causes inhibition of apoptosis.Supression of apoptosis seems to be one of the major cause oflymphomagenesis.Proteinp53 expression is associated with the Bcl-2 expression. Mutations in p53 gene may be responsible for amendment of low to high grade

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lymphoma. Changes in gene p53 may serve as a probable marker of *H. pylori*-associated gastric carcinogenesis.(Xiao et al., 2000)
Campylobacter jejuni,*Borreliabergdorferi* and *Chlamidia*are types of other bacteria which may also play role in progression of lymphoma.(Yamamoto & Schiestl, 2014)

The Microbiome and Hepatocellular carcinomas

Hepatocellular carcinoma (HCC) is one of the major disease of liver. Increased levels of bacterial toxins in the blood causes damage of hepatocytes, thus causes progression of hepatocellular carcinomas. Increasein translocation of bacteria also play a role in the development of hepatocellular carcinomas. Hepatitis B virus (HBV) or hepatitis C virus infection is one of the major risk factor for hepatocellular carcinomas. Gut-liver axis plays important role in hepatocellular carcinomas. GIT is full of the combination of human microbial ecosystem and is the major site of bacteria in the body.
It is found that progression of hepatocellular carcinomasincreases with Viral hepatitis. Both HBV and HCV can assist the progression of liver scarring (fibrosis) and then causes the development of hepatocellular carcinomas. With the increasein permeability of intestine,overgrowth of bacteria or weakened clearance of products of microbes by Kupffer cells can accerelatethe gut microbial translocation. All the components of microbiotaare transported to the liver. After entry of gut microbiota in the liver,this results in stimulation of Toll-like receptors (TLRs) of liver. TLRs are the proteins.These proteins can recognize microbial moleculesi.eLPS(lipopolysaccharides).Inflammation inducedby LPS is responsible for major liver diseases, mainly hepatocellular carcinomasin patients with HBV or HCV infection.(Gupta et al., 2019)
There are some risk factors forprogression of hepatocellular carcinomas. Obesity and high fat both factors are considered as risk factors for the development of hepatocellular carcinomas. Early studies suggested that obesity starts because of the unusual growth of microbes in gut by affecting harvesting of energy from the diet. Microbial products which are formed in gut thentranslocatedto liver, and then they cause activation of TLRs and starts the progression of hepatocellular carcinomas.
Yoshimoto et al. treated mice with the carcinogen at the neonatal stage to induce a tumor model and demonstrated that gut microbiota were associated with obesity.Obesity can change the gut microbiomes.Due to this there is increases in the metabolites of microbes which causes DNA damage because of the production of reactive oxygen species.This causes promotion of HCC in liver by the production of tumor-promoting factors.

The Pancreatic Carcinogenesis and Microbiome

Alteration in the microbiome is one of the major risk factor for the cancer of pancreas. *Helicobacter pylori* is a type of gram-negative bacteria. It is identified that this bacteria havetendency to survive in the stomach.Due to which that is presence of bacteria is one of the major reason forgastric disease i.e gastritis and sometimes gastric cancer or peptic ulcer. *Helicobacter pylori* infection has also been linked with diseases which are nongastric such as cancer of pancreas.

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Progression of *Helicobacter pylori* infection starts with some other factors that are directly correlate with cancer of pancreas, such asalcohol intake, abnormal weight of body, smoking diet and abnormal sugar level in the blood.

These all are risk factors which are directly responsible for the pancreatic cancer.Here are some examples of microbes which shows changes due to these factors.

1.Smokingcan cause low amount of Firmicutes, Actinobacteria and increase in growth of Clostridium, Bacteroidetes, Proteobacteria.

2. Obesity can decrese growth rate of Bacteroides and increase in growth of Bacillaceae, Clostridiaceae.

3. Diabetes can decrease groth rate of Amuciniphila, butyrate producing bacteria.

These results suggest that the changes in these gut microbes can increase rate of pancreatic cancer(Archibugi et al., 2018).

Some microbes can be used as probiotics for the suprresion of cancer

Probiotics are living microorganisms. These are generally beneficial to the recipient . Probiotics may play important role in people with cancer.Some of the bacteria and products of bacteria may have a benefit for the cure of particular diseases. *Lactobacillus* and *Bifidobacterium*are strains which are used for the treatment of cancer(Redman et al., 2014).Lactic acid bacteria is one of the type of beneficial bacteria which can protect against cancer development. In rat intestines it is found that lactic acid bacteria(*Lactobacillus johnsonii)*have a beneficial effects on oxidative stress and inflammation. These bacteria can also improve mammalian immune system for the prevention of cancer in mouse tumor models (Yamamoto & Schiestl, 2014).

CONCLUSION

Microbiome affects lymphomagenesis. Lymphomas are cancer of lymphocytes,so there is great interest to study lymphoma becuase this type of cancer circulate via the gastro-intestinal tract and also through the rest of the body. Lymphomas,HCC and pancreatic cancer are associated with microbial infections.Themicrobiome provides a biomarker for the risk of progression of disease. So we can use these biomarkers for detection of type of disease.

The immense evidence isthat some microbes are important for the benefits of health like the *Lactobacilli*and some microbes can show negative effects. For example species of *Helicobacteraceae*are responsible for the number of diseases. It is very important to find the roles of microbes as these can cause health benefits orhealth loss .Finding of synergisms or antagonisms in between the bacteria and gut is also important . Then we can design new probiotics against the health detrimental bacteria.

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