**By understanding the gut microbiome, it can lead to preventive care for colorectal cancer**

Author: Rosalie Dohmen  
Major: Microbiology and Molecular Genetics  
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

**Key Words:**

Colorectal Cancer, Metagenomics, Adenoma, Carcinoma, Microbiome, Diet, Metagenomic Linkage Group

**Abstract**

**Colorectal cancer is the second most prevalent cancer in the world. Preventative measures can be taken, such as a colonoscopy, even though they are invasive. In this minireview, we are looking at a study that analyzes the gut microbiome of patients that are healthy, have advanced adenoma, or have carcinoma. Metagenomic sequencing is performed on fecal samples to analyze the bacteria present in the gut. Correlations and relationships are made between each of the samples. A significant difference in the bacterial composition is observed when all three groups are compared to one another. A major linkage between enriched bacterial samples from carcinoma patients and the likelihood of inflammation. This bacterial composition also show various differences in transportation and synthesis genes of amino acids being detected within the different stages of these cancers. Diet, obesity, and smoking can negatively affect the gut microbiome, leading to the formation of colorectal cancer. The goal was to analyze the genomic diversity within the guts of health, adenoma, and carcinoma patients to potentially generate a less invasive preventative method foratching colorectal cancer.**

**Introduction**

Colorectal cancer (CRC) is known to be one of the most common cancers in the world; to be exact, CRC is the second most common cancer when both male and female statistics are combined. In both sexes, the incident rate of this cancer was 10%, with a 9.4% mortality rate in 2020 (Sung et al., 2021). In 2022, the United States is expected to have approximately 151,030 new cases of CRC and 52,580 deaths (American Cancer Society, 2022).

An aspect of colorectal cancer that is well studied is the effect of diet.A highly westernized diet that is high in meat, and low in calcium, combined with a low intake of vegetables and fruits, has shown to be a risk factor for developing CRC (American Cancer Society, 2022). Overall, diet has shown to be an important aspect of maintaining a healthy colon and rectum. However, the relationship between the gut microbiome and colorectal cancer is not well studied. The gut microbiome contains a complex community of bacteria, protozoa, fungi, viruses, and bacteriophages that all live within the gut of the host. The relationship between the host and the microbiota is thought to be mostly symbiotic. It has been found that certain bacteria undergo important functions for the host. Some of these include nutrient (i.e. vitamins and drugs) metabolism, detoxifying chemicals and deterring pathogens from colonizing within the gut (Chen, 2018).

Over time, genetic changes accumulate in the host, potentially leading to cancer. In terms of CRC, there is a loss of the tumor suppressor gene, adenomatous polyposis coli (APC), as well as mutations that lead to the inactivation of various other genes, mainly being KRAS, PIK3CA, and TP53 (Brenner et al., 2014; Vogelstein & Kinzler, 2004). In the United States, there are preventative measures taken to diagnose and treat CRC at its early stages. These measures include sigmoidoscopy and a colonoscopy that also include a polypectomy (American Cancer Society, 2022). Preventative treatment of CRC tumors by the measures stated above, however, can be intensive and invasive.

In this micro review, we will explore how the gut microbiome can identify signs of early CRC by analyzing fecal samples. This will lead to analyzing relationships between the gut microbiome and CRC, eventually to better understand how to prevent this disease as well as ways to better treat it, and a lower mortality rate.

**Recent Progress**

*Trends in healthy colorectal adenoma and carcinoma patients to identify possible markers of cancer.* In a recent study, metagenomic shotgun sequencing was completed on 156 fecal samples from healthy controls, patients with advanced CRC adenomas, or carcinomas. The researchers used the term metagenomic linkage group (MLG) to describe their data. This term is defined as “a group of genetic material in a metagenome that is probably physically linked as a unit rather than being independently distributed” (Qin et al., 2012). They identified that 58.9% of the gene markers were elevated in carcinoma patients when compared to healthy and individuals with adenomas. There was a total of 24.3% higher abundance of genes in the carcinoma patients compared to the other groups. This finding supports the claim that those markers are specific for colorectal cancer. Another 4.1% of the total genes showed significantly reduced in the individuals with carcinoma compared to the other two groups. In the carcinoma, 2.0% of the genes were significantly less abundant, with intermediate levels in the patients with advanced carcinomas compared to healthy individuals (Feng et al., 2015).

*Healthy gut commensals are underrepresented in patients with advanced adenoma and carcinoma*. In the same study as described above, known commensals of the gut like *Bifidobacterium animalis* and *Streptococcus thermophilus* have decreased numbers in the fecal samples from the patients with adenoma or carcinoma tumors compared to healthy individuals. To investigate this further, in healthy patients, the organism from the genera *Ruminococcus, Bifidobacterium,* and *Streptococcus* were shown to be overrepresented in the fecal samples. On the other hand, in the sample from the patients with carcinoma *Bacteroides, Alistipes, Escherichia,* *Parvimonas, Bilophila,* and *Fusobacterium* were the genera that showed to be overrepresented (Feng et al., 2015). An imbalance in these gut bacteria can also be a cause of other gut diseases, such as, ulcerative colitis and Crohn’s disease, two different types of inflammatory bowel diseases (Zhang et al., 2015).

*High intake of red meat shows a correlation with an overrepresented community of bacteria that possibly causes CRC.* Bacteria that were highly represented in the fecal samples of carcinoma patients were noted to produce short-chain fatty acids. These short-chain fatty acids are an important energy source for the epithelial cells of the colon. These bacteria are able to produce these fatty acids by amino acid fermentation and/or bile acid metabolism. These bacteria also show a positive relationship with high consumption of red meat and a negative relationship with fruit and vegetable consumption. What this research group also found was that this pathway mentioned above can be a common way for tumors to originate within the colon/rectum. The bacteria that were correlated with the consumption of red meat showed to be less abundant in individuals that consumed more fruits and vegetables.

*Other risk factors that affect the gut microbiome can lead to enhanced chances of developing CRC.* A protein that oversees storing intracellular iron, known as ferritin, shows to be negatively correlated with the MLGs of individuals with carcinoma.Iron is an important mineral that many pathogenic bacteria utilize for their growth. They are able to uptake the iron from the host and can increase the uptake when the host consumes a lot of red meat. Interestingly, hemoglobin also has been showed to negatively correlate with MLG within the carcinoma patients.

Another risk factor that is the cause of many cancers is smoking. Smoking showed to correspond with the enrichment of *Bacteroides dorei* and *Bacteroides vulgates*. As mentioned earlier, *Bacteroides* correlated strongly with the fecal samples from patients with carcinoma.

This research also found that the waist to hip ratio shows a negative correlation between *Clostridium* and *Streptococcus thermophilus*. On the other hand, this ratio seems to have a positive correlation between *Bacteroides sp.* in the carcinoma-enriched samples. BMI was another risk factor that correlates negatively with the MLGs from carcinoma enriched samples (Feng et al., 2015). These results support the claim that individuals with central obesity have a higher risk of developing CRC than individuals with general obesity (Ma et al., 2013).

*Bacterial functions showed increased levels in samples from individuals with advanced adenomas and carcinomas.* Modules for transport, synthesizing, and metabolic mechanisms were analyzed using the KEGG orthology (KO).Proteins used for the transportion of amino acids such as lysine, histidine, and arginine were found to have higher levels of these modules in the carcinoma compared to the adenoma samples. The modules that synthesize lysine, histidine, cysteine, tryptophan, methionine, and leucine appeared to be enriched in the healthy individuals compared to the patients with adenomas or in the patients with adenoma when those samples were compared with the carcinomas. Overall, this finding shows that the samples from patients with adenoma and carcinoma have increased utilization of host or dietary amino acids.

The cancerous samples also have an increased capacity to metabolize the glycans that the host produces. Some of these include mucin and glycosaminoglycans. These conclusions were drawn from observing the increased levels of the KO modules that saw the higher abundance of the degradation of sulphate, keratan sulphate, dermatan, and heparin sulphate. taurine, nitrate and sulfonate transport system showed elevated levels in the adenomas when compared to the health control. This suggests that there are changes in bile acid metabolism.

Methanogenesis also showed to be elevated in the adenomas or carcinomas. Interestingly, three important functions found in the MLG markers, keratan sulphate degradation, iron transport systems and lipopolysaccharide biosynthesis, adjacent to other house-keeping mechanisms revealed to be a classifier for the adenoma or carcinoma samples. These results concluded that individuals that intake a low amount of fruit and vegetables but a high amount of meat are more likely to increase their chances of CRC (Feng et al., 2015).

*The gut microbiome can control the response to various cancer therapies*. The genera *Alistipes* and *Ruminococcus* showed a positive correlation with the productions of TNF after Il-10R/CpG oligonucleotide immunotherapy in mice (Iida et al., 2013). The monoassociation of *Parabacteroides distasonis* appeared to negatively affect the immunogenic chemotherapy by the use of doxorubicin in mice (Viaud et al., 2013). *P. distasonis* and *P. merdae* in the MLGs were more prominent in the carcinoma samples when compared to the advanced adenoma. Overall, this shows that the gut bacteria in humans with CRC can either hinder or facilitate the immune or chemo therapies and should be investigated further to give individuals the most useful treatment (Feng et al., 2015).

**Discussion**

The goal of this minireview was to observe the association of the gut microbiome and CRC. The main study used to observe this connection showed that there were significant differences in the microbiome when the control group was compared to the adenoma and carcinoma group. The main purpose of this study was to determine new and less invasive methods to detect CRC at earlier stages. Which in turn should lead to fewer incidences and lower mortality rates.

Diet is an important consideration when discussing the gut microbiome. One’s diet is feeding their own body, but it is also feeding the microorganisms that live in the gut. It is important to keep the good and bad bacteria in check with one another. One main finding of this study was that a diet that featured large amounts of red meat consumption, and a low intake of vegetables and fruits enhanced the growth of bacteria that are more likely to cause inflammation. This can lead to not just CRC but various other cancers, chronic irritation and infection. However, inflammation is a critical component of tumor progression (Coussens & Werb, 2002).

*B. dorei, B. vulgatus* and *E.coli* are enriched in the carcinoma samples when compared to the healthy samples. This is of interest because these three bacterial species are also known to have a correlation with the levels of CRP, which is a known marker for acute inflammation. This links the unhealthy gut-microbes with colitis-associated and adenoma-linked CRC. The bacteria that were associated with the cancerous samples showed a higher rate of bile acid metablosim as well as elevated levels of methoanogeneis. An unhealthy microbiome could not only increase the risk of developing CRC, but it could also affect the treatment options. Certain gut microbiota had a positive correlation with the production of TNF during immunotherapy treatment. Other bacteria showed a negative correlation with different types of immunotherapies.

In conclusion, it is crucial to maintian a well-rounded diet, active lifetstyle and avoid tabacco products to prevent CRC from developing.

**References**

American Cancer Soceity. (2022). Cancer Facts & Figures 2022. *Atlanta: American Cancer Society*.

Brenner, H., Kloor, M., & Pox, C. P. (2014, 2014/04/26/). Colorectal cancer. *The Lancet, 383*(9927), 1490-1502. <https://doi.org/https://doi.org/10.1016/S0140-6736(13)61649-9>

Chen, G. Y. (2018, //01.05.2018). The Role of the Gut Microbiome in Colorectal Cancer. *Clin Colon Rectal Surg, 31*(03), 192-198.

Coussens, L. M., & Werb, Z. (2002). Inflammation and cancer. *Nature, 420*(6917), 860-867. <https://doi.org/10.1038/nature01322>

Feng, Q., Liang, S., Jia, H., Stadlmayr, A., Tang, L., Lan, Z., Zhang, D., Xia, H., Xu, X., Jie, Z., Su, L., Li, X., Li, X., Li, J., Xiao, L., Huber-Schönauer, U., Niederseer, D., Xu, X., Al-Aama, J. Y., Yang, H., Wang, J., Kristiansen, K., Arumugam, M., Tilg, H., Datz, C., & Wang, J. (2015, 2015/03/11). Gut microbiome development along the colorectal adenoma–carcinoma sequence. *Nature Communications, 6*(1), 6528. <https://doi.org/10.1038/ncomms7528>

Iida, N., Dzutsev, A., Stewart, C. A., Smith, L., Bouladoux, N., Weingarten, R. A., Molina, D. A., Salcedo, R., Back, T., Cramer, S., Dai, R.-M., Kiu, H., Cardone, M., Naik, S., Patri, A. K., Wang, E., Marincola, F. M., Frank, K. M., Belkaid, Y., Trinchieri, G., & Goldszmid, R. S. (2013). Commensal Bacteria Control Cancer Response to Therapy by Modulating the Tumor Microenvironment. *Science, 342*(6161), 967-970. <https://doi.org/doi:10.1126/science.1240527>

Ma, Y., Yang, Y., Wang, F., Zhang, P., Shi, C., Zou, Y., & Qin, H. (2013). Obesity and Risk of Colorectal Cancer: A Systematic Review of Prospective Studies. *PLOS ONE, 8*(1), e53916. <https://doi.org/10.1371/journal.pone.0053916>

Qin, J., Li, Y., Cai, Z., Li, S., Zhu, J., Zhang, F., Liang, S., Zhang, W., Guan, Y., Shen, D., Peng, Y., Zhang, D., Jie, Z., Wu, W., Qin, Y., Xue, W., Li, J., Han, L., Lu, D., Wu, P., Dai, Y., Sun, X., Li, Z., Tang, A., Zhong, S., Li, X., Chen, W., Xu, R., Wang, M., Feng, Q., Gong, M., Yu, J., Zhang, Y., Zhang, M., Hansen, T., Sanchez, G., Raes, J., Falony, G., Okuda, S., Almeida, M., LeChatelier, E., Renault, P., Pons, N., Batto, J.-M., Zhang, Z., Chen, H., Yang, R., Zheng, W., Li, S., Yang, H., Wang, J., Ehrlich, S. D., Nielsen, R., Pedersen, O., Kristiansen, K., & Wang, J. (2012, 2012/10/01). A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature, 490*(7418), 55-60. <https://doi.org/10.1038/nature11450>

Society, A. C. (2022). Cancer Facts & Figures 2022. *Atlanta: American Cancer Society*.

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians, 71*(3), 209-249. <https://doi.org/https://doi.org/10.3322/caac.21660>

Viaud, S., Saccheri, F., Mignot, G., Yamazaki, T., Daillère, R., Hannani, D., Enot, D. P., Pfirschke, C., Engblom, C., Pittet, M. J., Schlitzer, A., Ginhoux, F., Apetoh, L., Chachaty, E., Woerther, P.-L., Eberl, G., Bérard, M., Ecobichon, C., Clermont, D., Bizet, C., Gaboriau-Routhiau, V., Cerf-Bensussan, N., Opolon, P., Yessaad, N., Vivier, E., Ryffel, B., Elson, C. O., Doré, J., Kroemer, G., Lepage, P., Boneca, I. G., Ghiringhelli, F., & Zitvogel, L. (2013). The Intestinal Microbiota Modulates the Anticancer Immune Effects of Cyclophosphamide. *Science, 342*(6161), 971-976. <https://doi.org/doi:10.1126/science.1240537>

Vogelstein, B., & Kinzler, K. W. (2004, 2004/08/01). Cancer genes and the pathways they control. *Nature Medicine, 10*(8), 789-799. <https://doi.org/10.1038/nm1087>

Zhang, Y.-J., Li, S., Gan, R.-Y., Zhou, T., Xu, D.-P., & Li, H.-B. (2015). Impacts of gut bacteria on human health and diseases. *International journal of molecular sciences, 16*(4), 7493-7519. <https://doi.org/10.3390/ijms16047493>