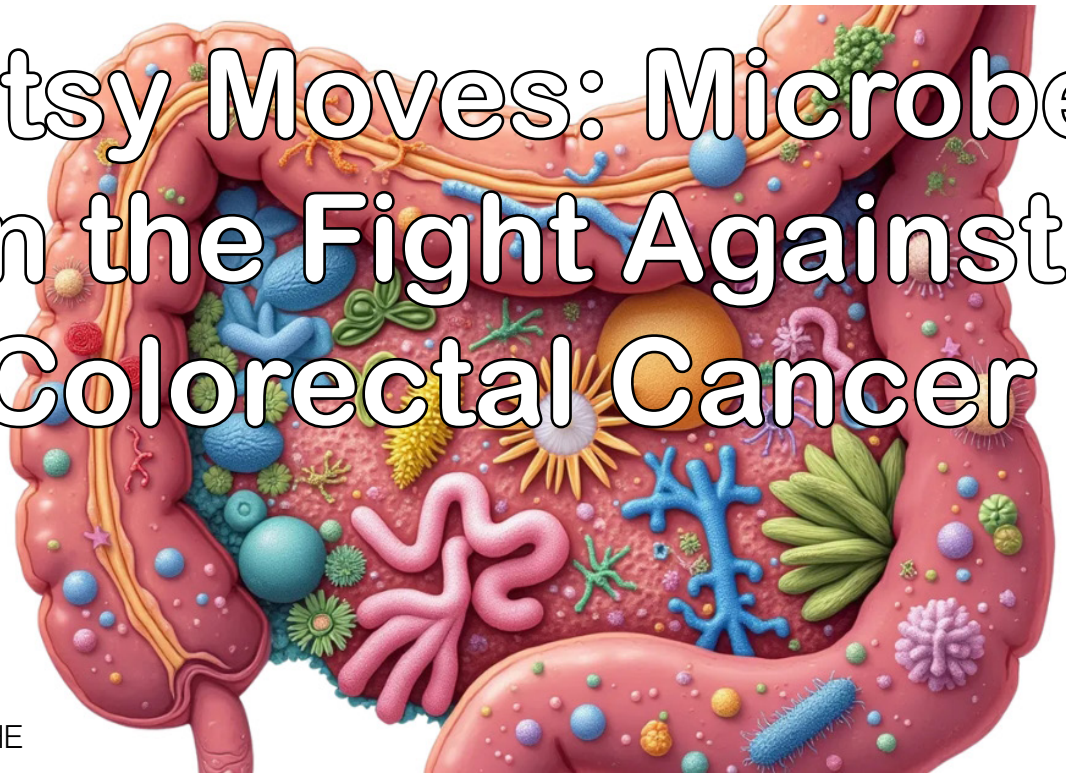
Gutsy Moves: Microbes in the Fight Against Colorectal Cancer



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A BACTERIAL ECOSYSTEM THAT LIVES WITHIN YOU: INTRO TO THE GUT MICROBIOME

Right now, there are upwards of 100 trillion microbial cells living in your gut.[1] For reference, the average human body contains only 30 trillion human cells, meaning gut bacteria outnumber your own cells roughly three to one.[2] While that may sound alarming, these tiny microbes are essential for human survival and play a crucial role in digestion, immunity, and overall health.

The gut microbiome is a collective phrase for the trillions of bacteria and microorganisms that reside in our digestive tracts.[3] Although the microbiome is too small to see, the nearly 4000 species of microorganisms that comprise it form a small ecosystem subject to the same laws as macro-ecosystems: diversity, symbiosis, and competition.[4]

The bacteria of the microbiome are sorted into three categories: beneficial, opportunistic (also known as neutral), and pathogenic—with each influencing gut health in different ways (see figure 1).[5]

The specific composition of a person's microbiome is determined by their environment and lifestyle—especially the food they eat. In individuals with poor diets, pathogenic bacteria proliferate, leading to chronic gut inflammation. This phenomenon is termed *dysbiosis*. Scientists have recently found a strong connection between gut dysbiosis and a person's risks of both developing and surviving colorectal cancer.

GUT BACTERIA AND COLORECTAL CANCER RISK

In 2024, the Colorectal Cancer Alliance released a report that unveiled many concerning statistics. For one, the incidence of colorectal cancer (CRC) has consistently risen by "1% [to] 2% each year in people under the age of 55… an alarming trend since the mid-1990s."[6] In fact, CRC is now the leading cause of death in men under the age of 50 and the second leading cause

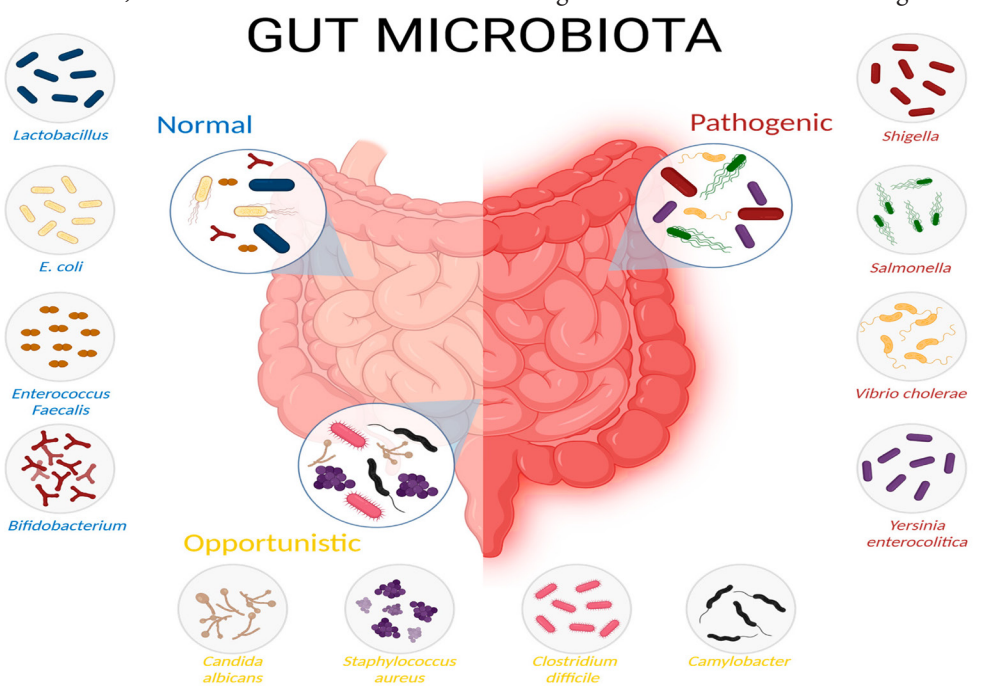

Figure 1: Gut bacteria are extremely diverse, spanning a wide range of roles and functions. Microbiota can either be beneficial/normal, opportunistic, or pathogenic. Beneficial bacteria support digestion, immune function, and overall gut health; opportunistic or neutral bacteria are normally harmless unless they overgrow; pathogenic bacteria disrupt gut health and lead to various gastrointestinal diseases.

"Scientists have recently found a strong connection between gut dysbiosis and a person's risks of both developing and surviving colorectal cancer."

of death in women in the same age category. Over half of these diagnoses are attributable to potentially modifiable risk factors, such as diet, physical inactivity, and other lifestyle choices (smoking, drinking, etc). The increase in CRC rates is most pronounced in high-income, Western countries, like the US, UK, and Australia.[7]

Specifically regarding diet, there are a plethora of reasons why an individual's nutritional profile affects their rates of CRC. For one, a Western diet (high in fat and sugar, low in fiber) contributes to obesity, which in turn leads to chronic inflammation and a surplus of growth factors that directly influence cancerous cell growth.[8] However, new research has turned to the microbiome for an *additional* explanation as to why diet influences CRC.

An unhealthy diet high in ultra-processed food promotes the growth of pro-inflammatory bacteria like the *Fusobacterium nucleatum* and *Bacteroides* species.[9] These strains of pathogenic bacteria thrive in fiber-poor, sugar-rich environments. When the supply of complex carbs is low, they turn to digesting fats and proteins instead (which most beneficial bacteria are unable to do). Additionally, processed foods tend to lower the natural pH of the human stomach, creating an environment uninhabitable for many beneficial bacteria while allowing these harmful, inflammatory bacteria to thrive.

As diet trends perpetuate, there has been a lot of media buzz surrounding "inflammatory foods" and "inflammatory bacteria."[10] But what exactly are inflammatory bacteria and how do they influence cancer rates?

THE APEX PREDATORS OF THE MICROBIOME: INFLAMMATORY BACTERIA

Bacteria are considered "inflammatory" if they activate their host's immune system. Bacteria can trigger an immune response by releasing toxic metabolites, physically harming cell membranes, or possessing foreign organelles (cell organs) that are flagged by the immune system.[11]

In relation to colorectal cancer, inflammatory bacteria like *Bacteroides* release two highly reactive types of molecules—Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS)—which directly damage DNA in colon cells, causing breaks in DNA and mutations in various genes. These mutations can lead to an overexpression of oncogenes (which promote cell overgrowth) and the repression of tumor suppressor genes (which combat cell overgrowth).[11]

In addition, these inflammatory bacteria can impair functional cells and tissues by physically breaking them down. When cells are damaged, a biochemical chain reaction begins, leading to the release of cytokines. These cytokines stimulate rapid cell division in order to repair and replace damaged cells; however, when this cell division becomes uncontrolled, there is an increased risk of overgrowth and cancer.[11]

Poor diets create acidic, metabolically dysregulated gut environments (known as dysbiosis), which allow inflammatory gut bacteria to proliferate. These bacteria then promote DNA mutations and cell overgrowth within the stomach and colon. In extreme cases, these compounded factors can lead to colorectal cancer.

With these risks in mind, maintaining a healthy gut microbiome may lower an individual's risk of getting CRC. But does gut health also benefit patients who *already have* CRC?

AN UNSEEMING CONNECTION: THE GUT AND IMMUNOTHERAPY

In 2021, the National Cancer Institute (NCI) conducted a study with the goal of understanding the role of gut bacteria in cancer therapy outcomes.[12] "Patient 4" was a 63-year old cancer patient with advanced cancer that was unresponsive to aggressive immunotherapy treatments. Researchers on the study began to question whether it was the cancer itself or some other biological factor that stifled his immune response. After conducting a comparative analysis of the gut microbiota of cancer patients who *did* respond well to the immunotherapy against Patient 4's, the researchers decided to conduct a Fecal Microbiota Transplant (FMT) on Patient 4 by using bacteria-rich stool from one of the immuno-responsive patients.

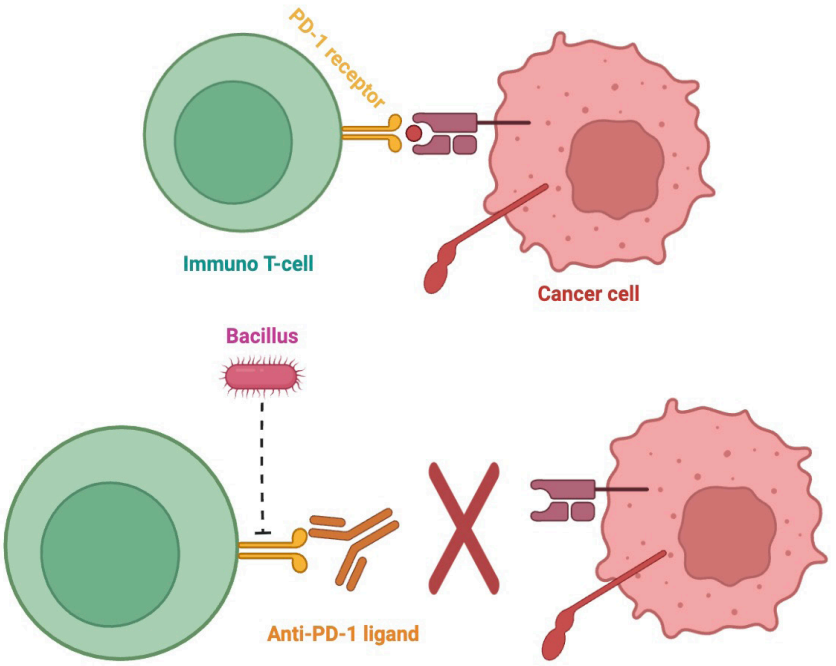

Figure 2: (Top) Interaction between cancer cell and PD-1 receptor on T-cell that prevents T-cell from properly identifying and killing cancerous cell. (Bottom) Bacterial-stabilized interaction between anti-PD-1 ligand and PD-1 receptor that inhibits cancer cell binding.

Following the FMT, Patient 4's gut microbiome composition started to resemble that of the donor. There was a systemic change in the composition of the patient's microbiome and a huge increase in the concentration of "beneficial" bacteria. Patient 4 then began the same immunotherapy treatment that had earlier failed. The results? A significant reduction in tumor size. Since this breakthrough, FMT has assisted numerous other CRC patients experiencing immunocompromisation from dysbiosis.[13]

A PRIMER ON THE IMMUNE SYSTEM

The mechanism that enabled Fecal Microbiota Transplant to improve Patient 4's response to immunotherapy is tied to microbial modification of immune pathways.

When an immune cell seeks out pathogens, it looks for "checkpoint proteins" on the other cell's surface. If these checkpoint proteins are present, the immune system recognizes the cell as belonging to the host and consequently will not attack it. If, however, no checkpoint protein is present, the immune system flags the cell as foreign and attacks it with killer T-cells.

Cancer cells often evade this detection by mimicking normal cell signals. For example, a common checkpoint protein expressed by many cancerous cells is PD-L1; this protein binds to the PD-1 receptor on immune killer T-cells to evade attacks.[14]

Immunotherapy hijacks this oversight by infusing small checkpoint inhibitors, called *anti*-PD-L1s, into the cancer patient to block the interaction between PD-L1 and PD-1. By preventing the T-cell receptors from binding to PD-1 checkpoint proteins, T-cells can recognize and attack cancerous cells.[14]

BACTERIA'S ROLE IN IMMUNE REGULATION:

So what is the connection between immunotherapy and gut bacteria composition?

Healthy gut bacteria like *Bifidobacterium* and *Akkermansia muciniphila* enhance immunotherapy in several of ways.[5] For one, these bacteria interact with killer T-cells and prime their receptors. Because of this reaction, T-cell receptors are much more likely to bind to anti-PD-1 checkpoint inhibitors, thus making immunotherapy more effective.[15] Additionally, healthy gut bacteria reduce system colorectal inflammation—this in turn lessens immune system exhaustion, meaning more immuno-resources can be allocated to battling disease like colorectal cancer.[16]

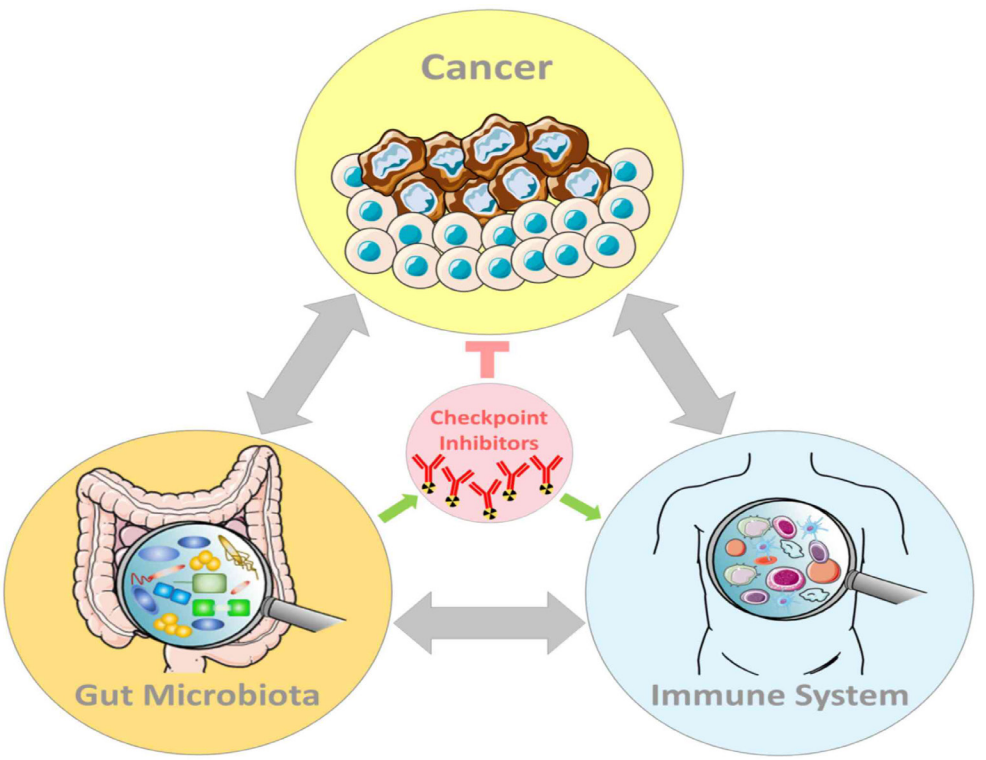

Figure 3: The dynamic relationship between the gut microbiome and the immune system influences the effectiveness of cancer immunotherapies. When inflammatory gut microbiota are abundant, immune stress prevents checkpoint inhibitors from effectively blocking the interaction between immune and cancer cells.

On the other hand, when inflammatory bacteria are present, the reactive oxygen species (ROS) and metabolic stress impairs T-cell receptors. This leads to the production of myeloid-derived suppressor cells (MDSCs). MDSCs deactivate T-cells, rendering tumors resistant to immune checkpoint inhibitors like anti-PD-1. In healthy individuals, MDSCs and T-cells exist in equilibrium; in fact, MDSCs are normally present in small amounts to prevent excessive T-cell activity—especially during periods of temporary inflammation. However, when this inflammation becomes chronic (like in individuals with dysbiosis), MDSC levels stay elevated and immune function becomes over-repressed.[16]

In the NCI study, Patient 4's initial lack of response to immunotherapy was not due to the cancer itself, but rather to chronic gut dysbiosis. The overgrowth of inflammatory bacteria hindered T-cell defense, and the most effective intervention was to re-regulate the microbiome by systemically introducing healthy bacteria through FMT.

CLOSING THOUGHTS: BIG THINGS COME IN SMALL PACKAGES

Promoting a healthy gut microbiome has proven benefits all throughout the oncological lifecycle, from cancer prevention to cancer therapy. Now, doctors and scientists alike must find ways to communicate the importance of maintaining a healthy gut microbiome—especially to the young adults who are falling victim to colorectal cancer. Most importantly, it does not take a Fecal Matter Transplant to improve microbial diversity; shifting eating habits towards more nutritious, fiber-rich, unprocessed foods can do wonders for gut health. Additionally, taking probiotics or eating live-culture yogurt may increase the proliferation of healthy bacteria in individuals with moderate dysbiosis.[17]

In the end, small lifestyle adjustments have the capacity to make impactful changes in an individual's health journey. The same principle applies to how a small colony of microorganisms is able to profoundly impact your immune function, metabolism, and overall well-being through powerful interactions with the gut.

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IMAGE REFERENCES

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