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Author
Yang, Hengyi Scarlett

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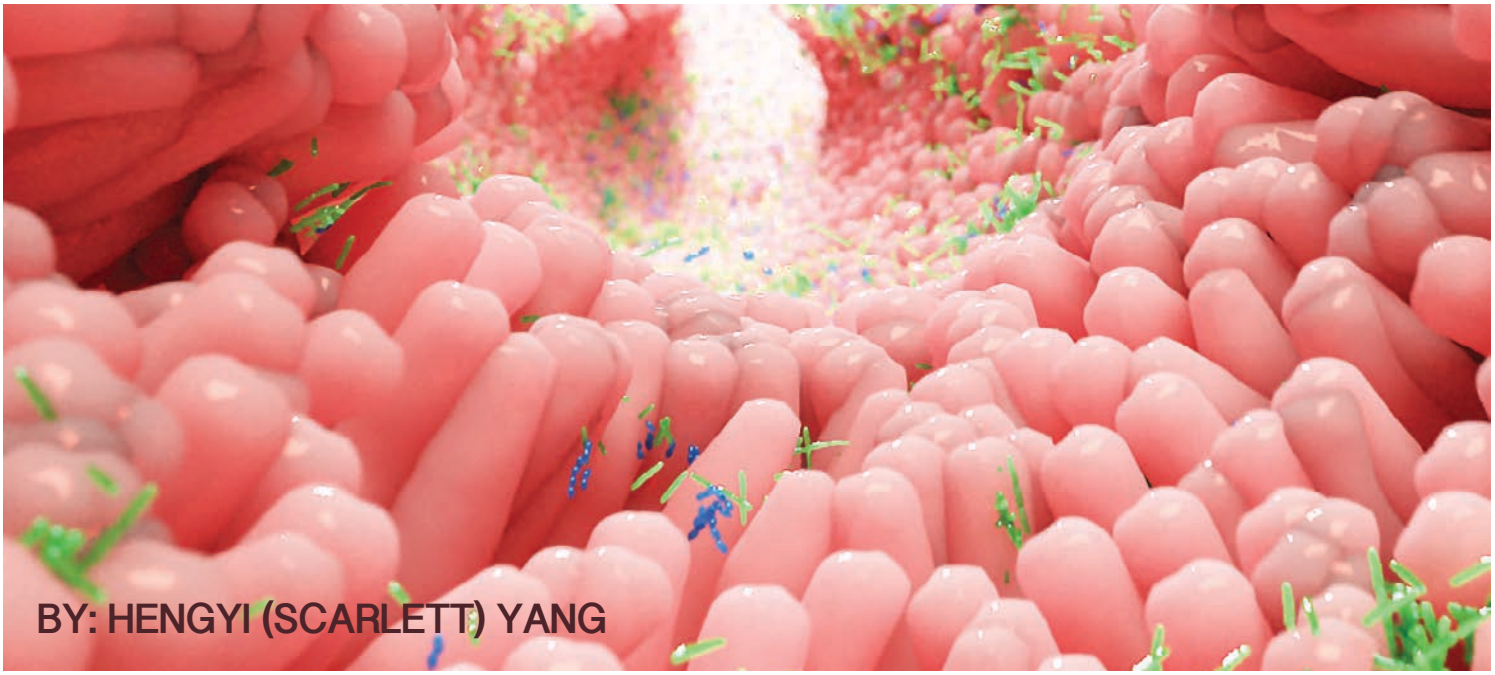

BY: HENGYI (SCARLETT) YANG

Gut Check: How the Microbiome And Diet Are Changing Cancer Treatment

In 2021, Onjalai Brown received a life-changing diagnosis: she had an aggressive type of stage two breast cancer known as ductal carcinoma. After surgical removal of the tumor, Brown started 20 rounds of chemotherapy, a common cancer treatment that uses powerful drugs to kill off remaining cancer cells or slow their growth. One of the chemotherapy drugs she received was doxorubicin, also known as the "Red Devil," which intercalates DNA to block cancer cell replication. This name was fitting, considering the drug's red color and notorious side effects such as nausea, bone pain, extreme fatigue, and nerve damage. Brown also experienced hair loss and depigmentation in her fingernails and toenails. Moreover, the chemotherapy compromised her immune system, intensifying her symptoms and sending her to the emergency room multiple times due to serious infections. These physical side effects, compounded with mental and financial stress, led Brown to develop severe depression and suicidal thoughts.[1]

Onjalai Brown's experience with chemotherapy is all too common: Chemotherapy's side effects can become so life-threatening that doctors have to dilute the strength of the therapy or even terminate the treatment course entirely, allowing the cancer to grow unchecked.[2,3]

"Chemotherapy's side effects can become so life-threatening that doctors have to dilute the strength of the therapy or even terminate the treatment course entirely, allowing the cancer to grow unchecked."

THE TWO FACES OF CHEMOTHERAPY

Since its first clinical use in 1942, chemotherapy has saved millions of lives and remains one of the most efficacious life-saving cancer treatments.[4,5] Most conventional chemotherapy drugs kill rapidly dividing cells by disrupting cell division and DNA synthesis. Cancer cells are therefore ideal targets, as they divide much faster and more frequently than normal cells.

Unfortunately, chemo drugs are imperfect. They cannot differentiate between cancer cells and healthy cells that are constantly dividing, such as those in the hair follicles, bone marrow, skin, and the lining of the digestive system. The non-specific targeting of chemo drugs results in the previously discussed side effects like hair loss, immune-weakening bone marrow suppression, and painful skin rashes (Figure 1).[6]

THE BATTLE IN THE GUT

The digestive system is particularly affected by chemotherapy. One condition that stands out is gastrointestinal (GI) mucositis, an inflammation of the membranes that line the GI tract, which causes nausea, vomiting, constipation, diarrhea, and cramps. Chemo-induced vomiting affects up to 80% of patients receiving systemic chemotherapy, with diarrhea occurring at a similarly high rate.[7] Some of the affected individuals require hospitalization, dose delays or reduction, or treatment discontinuation.[8] So, why does chemotherapy affect the gut so badly?

The gut cells divide and proliferate rapidly. In fact, the gut lining renews approximately every five days, which makes the gut lining particularly vulnerable to chemotherapy.[9,10] However, the high turnover rate of gut cells

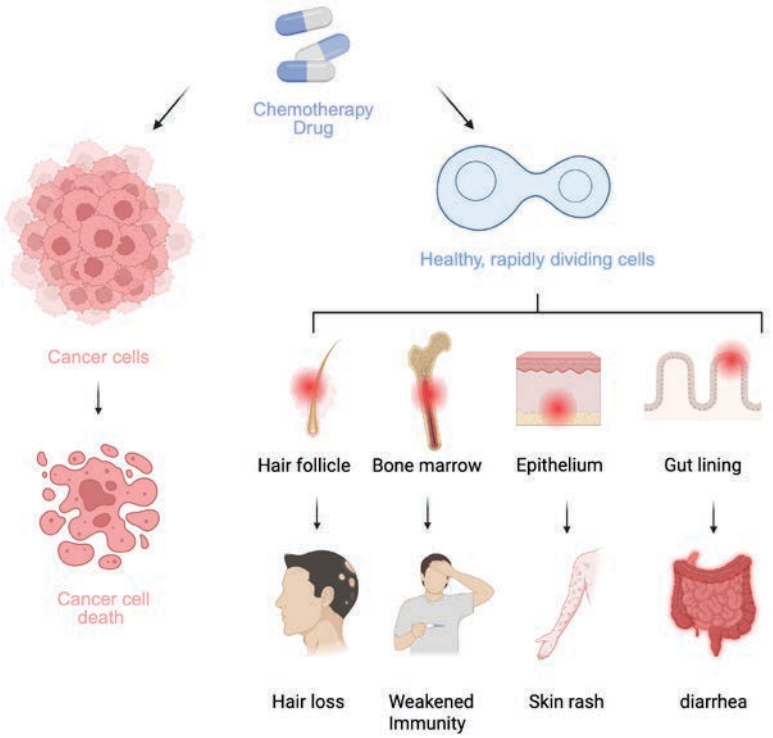

Figure 1. The two faces of chemotherapy. While chemotherapy induces cancer cell death (left), it also damages healthy, rapidly dividing cells (right), including those in hair follicles, bone marrow, epithelial tissues, and the gut lining. Respective side effects include hair loss, a weakened immune system, skin rash, and GI mucositis (one symptom of which is diarrhea).

does not explain why some patients can tolerate chemotherapy well while others suffer from serious GI side effects.

The rationale for differing GI responses could be explained by the microbial community residing inside the gut. The human GI tract houses over 100 trillion microorganisms from all three domains of life: bacteria, archaea, and eukaryota.[11] Collectively, these microbes form the gut microbiome. The composition of the microbiome strongly influences human health and disease, with established roles in conditions ranging from obesity to inflammatory bowel disease (IBD). With regards to cancer therapy, chemotherapy toxicity poses a great threat to this delicate microbial ecosystem.

Normally, the diversity and abundance of organisms is elegantly balanced within the microbiome community. However, chemotherapy drugs disrupt this equilibrium, driving the microbiome from its normal state ("eubiosis") into a disrupted state ("dysbiosis"). One study conducted by Dr. Montassier and his colleagues in 2014 followed 15 genera (groups of closely related species) of the gut microbiota in patients undergoing chemotherapy. They analyzed the microbial genetic sequences in stool samples before and after chemotherapy, finding lower overall gut microbiome diversity after chemotherapy. Moreover, the composition of the microbial community was shifted: the proportion of beneficial microbes like *Faecalibacterium* significantly decreased, while potentially harmful species like *Escherichia* experienced a proportional increase (Figure 2).[12,13] Other studies examining different types of chemotherapy drugs and gut microbes have confirmed that all chemotherapy drugs alter microbial composition to some extent.[8,14]

After chemotherapy disrupts the microbiome's composition, functional changes follow. One crucial role of gut microbes is to provide "colonization resistance": they defend against invading pathogens such as Salmonella, which can cause diarrhea, stomachache, and fever. They do this by competing with pathogens for resources, producing antimicrobial compounds, and boosting the host immune response. Chemotherapy-induced loss of microbial genetic diversity weakens this line of defense. It also reduces the abundance of anti-inflammatory species like *Faecalibacterium*, which normally dampen unnecessary inflammation by interacting with the immune system and secreting anti-inflammatory molecules. Together, the loss of diversity and the depletion of key microbial species create a gut environment that is more susceptible to chemotherapy-induced mucositis (Figure 3).[15,16]

Apart from killing many anti-inflammatory microbes, chemotherapy also depletes microbiota that produce butyrate, an important fatty acid that strengthens and nourishes the gut epithelial barrier. This alteration

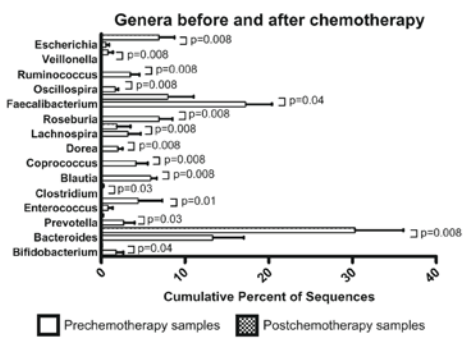

Figure 2. Chemotherapy alters the gut microbiome. Cumulative percentage of genera sequences detected in the pre-chemotherapy and post-chemotherapy samples.[11]

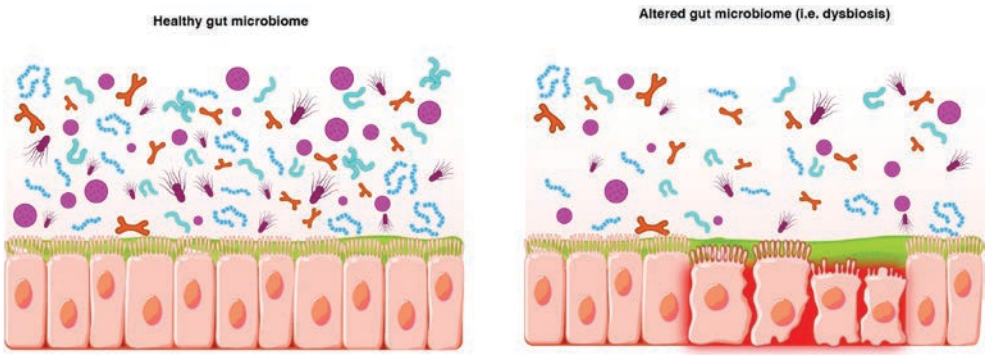

Figure 3. Dysbiosis is defined by microbiome alterations. Altered microbial composition can yield reduction in species diversity and/or changes in the relative abundances of "healthy" relative to "less healthy" microbes.[13]

causes the intestinal wall to become more permeable, thus allowing gut bacteria to pass through this weakened lining and into the body's internal environment. This process is known as bacterial "translocation" and can cause tissues in the GI tract and distant organs to become diseased with translocated bacteria. Thus, chemotherapy-related bacterial translocation may worsen GI and systemic inflammation.[17,18]

THE DIET-GUT CONNECTION

By understanding how chemotherapy influences the gut microbiota, scientists can develop tools that restore a balanced gut environment to mitigate chemotherapy-induced side effects. Interestingly, one of the most powerful solutions to dysbiosis may lie in a patient's diet.

As food passes through the GI tract, it directly interacts with intestinal cells and the gut microbiome. This intimate, symbiotic interaction positions diet as a powerful means of modulating GI health. Dietary interventions are more flexible, safe, and non-invasive compared to pharmaceutical drugs in treating chemotherapy side effects.

"This intimate, symbiotic interaction positions diet as a powerful means of modulating GI health."

Capitalizing on the diet-gut connection, scientists have come up with several nutritional strategies to reduce chemotherapy's side effects. These include administering prebiotics (compounds that promote the growth of certain bacteria), probiotics (live, beneficial bacteria), and other dietary supplements. The common goal of these interventions is to protect the patient and their microbiota from the damaging effects of chemotherapy.

In particular, providing fuel (prebiotics) for beneficial gut microbes is proven to replenish the microbial community. Prebiotics are dietary compounds that can be digested by bacterial cells but not by human cells. Many prebiotic-containing foods are plant-based and high in fiber, including fruits, vegetables, and whole grains.[19] The metabolic breakdown of prebiotics, or "fermentation," provides nutrients for beneficial gut microbes to thrive and grow. Prebiotics select for good microbes, counteracting the imbalance in microbial composition from chemotherapy.[20,21,22] Animal and human studies have shown that the administration of prebiotics altered the gut microbiome by increasing concentrations of beneficial Bifidobacteria and Lactobacilli.[10,23] Protecting the gut microbiota with prebiotics may help to alleviate chemotherapy-induced diarrhea and related symptoms.

Bacterial fermentation of prebiotics also produces a range of metabolites that confer other positive health effects. One such by-product is short-chain fatty acids (SCFAs), which are generated through the fermentation of fibers. SCFAs provide energy for intestinal lining cells to grow and repair, thus helping to maintain gut barrier integrity and reduce translocation-induced inflammation (Figure 4).[24]

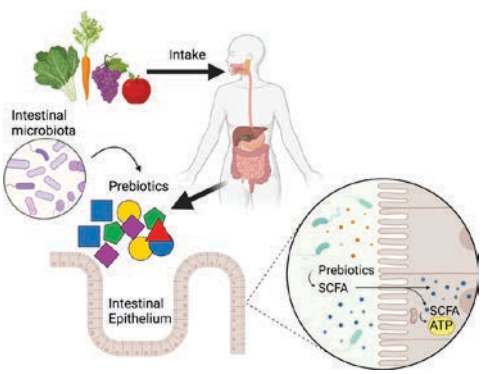

Figure 4. Dietary prebiotics increase bacterial short-chain fatty acid production. Food containing prebiotic oligosaccharides reach the colon, where microbiota convert these prebiotics into short-chain fatty acids (SCFA), which in turn strengthen intestinal cells.[23]

Prebiotics function synergistically with probiotics, live microorganisms that are consumed in capsules or fermented foods like yogurt. Unlike prebiotics, which feed existing beneficial microbiota, probiotics directly introduce live beneficial species into the gut. By working together, prebiotics and probiotics can re-establish a desirable microbial composition, enhancing resistance against pathogens while bolstering the effects of a healthy gut. Probiotic bacteria, including *Lactobacillus plantarum*, *Lactobacillus acidophilus*, and *Lactobacillus rhamnosus* GG, are shown to alleviate chemotherapy-induced diarrhea in animal and human studies.[10, 25]

In addition to prebiotics and probiotics, dietary supplements containing amino acids and vitamins can protect against chemotherapy-induced dysbiosis.[8] In particular, the amino acid glutamine significantly improves chemotherapy-related GI mucositis. Glutamine works by sustaining the increased expression of tight junction proteins, which maintain intestinal lining integrity.[26] Similarly, vitamin K2 is proven to mitigate chemotherapy side effects in mouse models, though the underlying mechanism is still being investigated.[27]

CONCLUSION

In summary, dietary modifications and supplementation with prebiotics, probiotics, and other adjuncts have the potential to mediate chemotherapy-induced damage to the gut and gut microbiome, thus relieving treatment-related side effects. Perhaps in the future, more cancer patients can have a less painful chemotherapy experience with proper nutritional adjustments. The scientific community is striving to make it happen.

Yet, determining how diet influences gut microbial activity, composition, and function in cancer patients remains challenging. Outcomes depend on numerous factors, like baseline dysbiosis: For example, cancer patients starting off with severe levels of microbial imbalance may react differently to dietary interventions. Other variables include cancer type and stage, adherence to dietary recommendations, and overall patient health and health-related behaviors.28 Continued research is needed to bridge the gap between preclinical findings and clinical application. Perhaps in the future, cancer patients like Onjalai Brown will experience a more comfortable course of treatment, supported in part by strategies as simple as dietary adjustments.

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