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Creating markets & marketing strategies

Newsletter

August 15, 2015

Dear Regina,

Welcome to BioMarketing Insight's monthly newsletter.

We have a new mobile friendly newsletter. Love to receive your feedback.

Last month I covered Your Microbiome: What Is It and Why Is It Getting So Much Attention? Part 1 of a two part series. If you missed last month's article, click here to read it. This month's newsletter will cover part two, Our Microbiome and Its Relationship to Different Diseases.

Read on to learn more about this topic and other current news. The next newsletter will be published on September 15th.

We encourage you to share this newsletter with your colleagues by using the social media icons at the top, or by simply forwarding this newsletter or click on the link at the bottom of this newsletter. Should you or your colleagues want to join my mailing list, click on the icon below or scan the QR code.

Please email me, Regina Au, if you have any questions, comments, or suggestions.

Sincerely,
Regina Au
New Product Planning/
Strategic Marketing Consultant
BioMarketing Insight

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Stem Cell Research: Under Investigation

I am pleased to announce that my article "Stem Cell Research: Under Investigation has been published in the July 2015 issue of European Biopharmaceutical Review (EBR). To read an electronic version, click here and go to page 30.

ebr
European Biopharmaceutical Review

From Genetic Engineering to Genome

Engineering: What Impact Has it Made on Science and Society?

I am pleased to announce that my article "From Genetic Engineering to Genome Engineering: What Impact Has it Made on Science and Society?" was published in May 2015 in the Advanced Biology, Biotechnology and Genetics Journal. To read an electronic version, click here.

Guest Lecturer at MIT

I was a guest lecturer at the Martin Trust Center for Entrepreneurship at MIT in July. I spoke on "How to Develop a Successful Product: Where Do You Start?" from a commercial perspective to 14 MIT entrepreneurial companies.

Our Microbiome and Its Relationship to Different Diseases

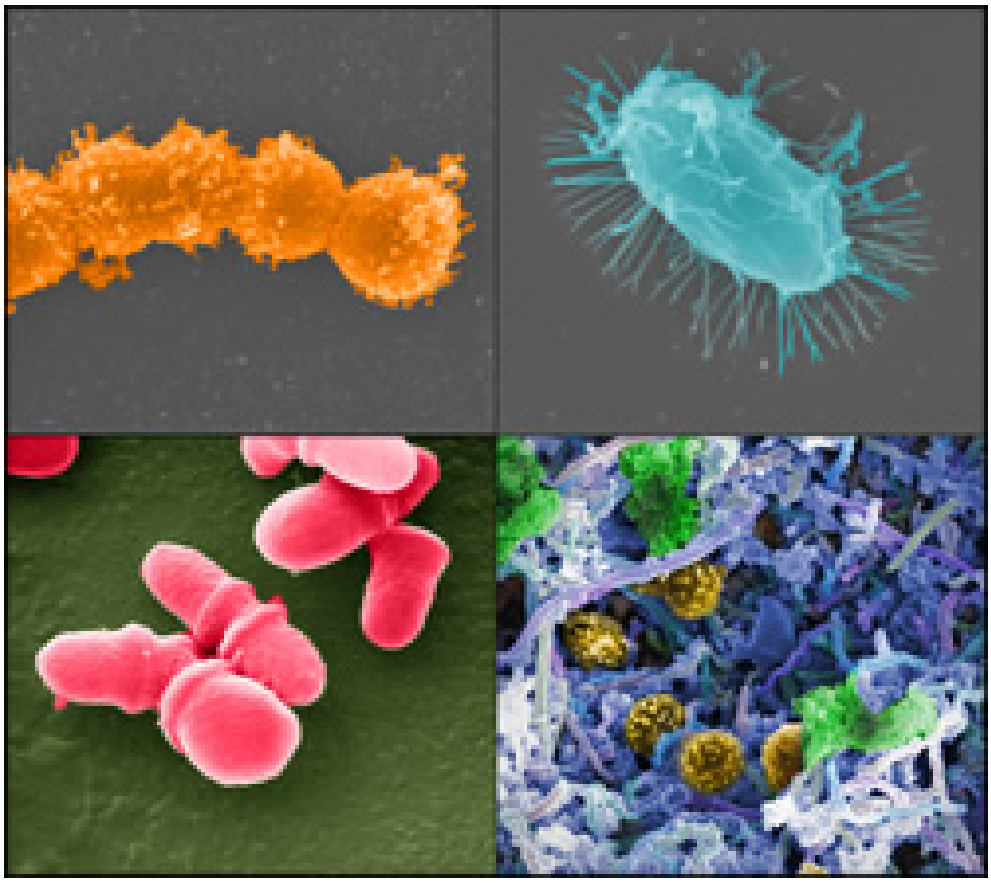

Figure 1. Mixed microbial species from human body. From A. Earl (Broad Institute/MIT, 2012).

1. Microbiome in the GI tract and the production of serotonin

GI inflammation is activated by immune cells from both the innate and adaptive immune system. In addition, inflammation is associated with alterations in the number of enterochromaffin (EC) cells that reside in the GI mucosa. Ninety percent of the body's serotonin production comes from these EC cells in the GI tract. Serotonin is important for maintaining GI motility and restoring hemostasis after inflammation. Changes in the number of EC cells and serotonin levels are associated with a number of GI disorders, such as inflammatory bowel disease, colitis, enteric infection-induced inflammation in the gut, and inflammatory bowel syndrome.

Elaine Hsiao, PhD, from California Institute of Technology and her team demonstrated that gut microbes do regulate serotonin biosynthesis. In their study they found that when mice were germ-free, their EC cells produced 60% less serotonin than those mice with gut bacteria. When bacteria was introduced to the germ-free mice, production was increased. Their findings suggest that EC cells depend on microbes for serotonin

production. They also found that about 20 species of spore-forming bacteria were responsible for elevating serotonin levels when added to germ-free mice.

Highlights from the study by Hsaio and her team:

- Gut microbes regulate levels of 5-HT in the colon and blood
- Spore-forming bacteria modulate metabolites that promote colon 5-HT biosynthesis
- Microbiota-dependent changes in 5-HT impact GI motility and hemostasis
- Altering the microbiota could improve 5-HT-related disease symptoms

2) Production of Serotonin and the Central Nervous System (CNS)

In the brain, serotonin acts as a neurotransmitter to relay messages from one area of the brain to the other. While the brain produces serotonin, 90% of serotonin is produced in the GI tract for gut sensory and function and the rest is circulated as peripheral serotonin to areas such as the cardiovascular and endocrine systems and muscles. Scientists believe that low serotonin levels may lead to CNS disorders such as depression, obsessive-compulsive disorder, anxiety, panic, and even excess anger resulting from either a lack of receptor sites able to receive the serotonin; inability of serotonin to reach the receptor sites; or a shortage in tryptophan to make serotonin. It is also believed that serotonin is important for the regeneration of brain cells throughout our lifetime. One theory of the etiology of depression is the suppression of new brain cells and that stress is the most important precipitator of depression.

The term "gut-brain axis" or "second brain" was coined when the link, or communication, between the nervous systems and the digestive system was recognized. Therefore, what affects the brain, affects the gut and visa versa. Hsiao et al showed that microbes are needed for EC cells to produce normal amounts of serotonin and a number of studies have suggested that these gut microbiome can have an impact on the brain and behaviors such as anxiety and depression.

In the experimental autoimmune encephalomyelitis (EAE), an animal model of human multiple sclerosis study, it was found that when certain

bacteria in the gut are altered this can lead to proinflammatory conditions in distal effector immune sites, and may lead to autoimmunity disease, in this case multiple sclerosis (MS). Whereas certain commensal bacteria in the right balance can be protective against inflammation in the CNS.

3) Microbiome in obesity and other metabolic diseases.

In previous studies, it's been shown that a change in diet can alter the gut microbiome. In some animal studies, it was shown that obese mice or mice fed a high-fat diet had a decrease in Bacteroidetes and increase in Firmicutes. In a single day, a change from a low-fat to a high-fat, high-sugar diet exhibited a change in microbiome that resulted in metabolic change, and an increase in adiposity and the same trait was evident with a microbiome transplant to other mice. The microbiome controls many different facets of the host metabolism, including Tlr5 activation (e.g., through bacterial flagellin) on epithelial or myeloid cells, that ultimately regulates appetite, weight gain, and insulin sensitivity and also regulates Fiaf release from intestinal epithelial cells, which acts as an inhibitor of Lpl and thereby regulates peripheral fat storage, both of unknown mechanism.

It is hypothesized that our microbiota also affects Ampk, a key enzyme that controls cellular energy like a fuel gauge. It signals to the liver and skeletal muscle and affects the skeletal muscle and liver fatty acid oxidation pathways. The exact mechanism is not clear. How the microbiome affects the host metabolism is very complex, as demonstrated here, but scientists are making strides in uncovering the physiology of the interactions between gut microbiome and other metabolic diseases.

4) Microbiome and its relationship to colorectal cancer

Ashlee Earl, PhD from the Broad Institute in Massachusetts and colleagues examined the role of the microbiome in patients with colorectal cancer (Figure 1). They characterized the composition of the microbiota in colorectal carcinoma using whole genome sequences from nine tumor/normal pairs. They found four species within the Fusobacterium genus; Fusobacterium nucleatum, Fusobacterium necrophorum, Fusobacterium mortiferum, and Fusobacterium perfoetens with F. Nucleatum being the most dominant phylotype identified within cancers.

The Fusobacterium species can elicit host proinflammatory response and invade epithelial cells. The absence of Bacteroidetes and Firmicutes phyla, most prominently Clostridia, in tumors was also noted. This suggested that the dominance of Fusobacterium and the dampening of Bacteroidetes and Firmicutes sets the stage for tumorgenesis by eliciting a proinflammatory response in a subset of patients and may explains why some patients get colorectal cancer and others don't. Another hypothesis is that Fusobacterium accumulates in the tumor environment, but is not involved with the development of tumors. More research is needed to confirm either hypothesis.

Others have noted that Fusobacterium species may be associated with inflammatory bowel diseases (IBD), including both ulcerative colitis and Crohn's disease and IBD is one of the three highest risk factors for developing colorectal cancer. Likewise, more research is needed to verify a causal relationship.

Closing Thoughts

Scientists have discovered that our microbiome is vital for survival with respect to our GI development, digestion of foods and intake of nutrients, regulating our immune system (innate and adaptive responses), acting as a protective barrier against pathobionts, gut hemostasis and regulating host fat storage. Gut microbes also produce beneficial compounds, such as vitamins and anti-inflammatories, properties that our genome cannot produce, and they affect how well our immune system works. One of the factors that can alter our gut microbiome is our diet. Depending on the type of diet we consume, it can lead to either a favorable alteration, or to dysbiosis that could contribute to a number of serious diseases, including gastrointestinal disease and systemic diseases.

EC cells depend on microbes for serotonin production, and changes to the number of EC cells due to inflammation and lower levels of serotonin have

been associated with IBD. Fusobacterium has been associated with IBD, one of the three highest risk factors for colorectal cancer. The study by Earl showed that in colorectal cancer, there is a dominance of Fusobacterium and the dampening of Bacteroidetes and Firmicutes, a dysbiosis of the microbiome and suggesting that it plays an important role in both IBS and colorectal cancer.

This study reinforces the HMP finding that the function of the microbes is more important than the type of species suggesting the importance in the change to the bacterial phyla composition and not the individual species. While F. Nucleatum was the dominate specie of the Fusobacterium genus for IBS and colorectal cancer, it's the dominance in conjunction with the dampening of Bacteroidetes and Firmicutes that played a role in colorectal cancer. The next important question will be, does restoring the Bacteroidetes and Firmicutes phyla as oppose to specific species within the genus return the host to a healthy state and eliminate one important risk factor for developing cancer?

The complexity of how the microbiome is involved with our metabolic system and its effects on our immune, cardiovascular and endocrine systems and muscles is daunting. Joshua Lederberg's foresight was accurate back in 2001, when he coined the term microbiome and recommended that it be included in the human genome because of its influence on human physiology.

These findings confirm the belief that treating patients in a holistic or multi-disciplinary approach, rather than a pure specialty approach will likely lead to better outcomes. For example, many believe that when treating CNS disorders such as depression and anxiety, one needs to treat the brain and gut simultaneously, since they are linked. As noted earlier, it has been demonstrated that patients with depression typically have low serotonin levels and treating those patients with Selective Serotonin Reuptake Inhibitors (SSRIs) is believed to increase serotonin levels by diverting serotonin away from the gut and into the brain. Serotonin is important for GI motility and hemostasis, particularly after inflammation. It has been shown that changes in the number of EC cells and serotonin levels are associated with GI disorders and could explain why SSRI users experience nausea, stomach upset, constipation, diarrhea, and fluctuations in appetite.

A study published in the New England Journal of Medicine examined two durations (until afebrile, WBC normal, consumer 50% of calories by mouth vs. 4 day course) of antibiotic therapy for complicated abdominal infections at leading academic institutions. The results of the trial showed that there was no difference in outcome between the standard treatment protocol and the short course of therapy and may encourage healthcare professionals to reconsider the standard practice of continuing antibiotic treatment until all physiological signs are normal. It can be theorized that a shorter course of therapy may alter the microbiome to a lesser degree and decrease the potential for negative consequences that may occur with a longer course of therapy.

Diet plays an important role in shaping the composition of the gut microbiome and this should be the first place to start, particularly since diet is linked to obesity which is then linked to Type 2 diabetes, cardiovascular disease and even cancer. To avoid gut dysbiosis, other non-pharmacological measures should be recommended as well such as exercise, which increases serotonin levels and works to alleviate depression. Life style, sleep, stress, exercise and environment each play equally important roles in our health. Unfortunately our Western life style is highly stressful and we have an appetite for instant gratification, which is reflected in our diet and other behaviors. For this reason, there is a new breed of physicians on the horizon who practice Functional Medicine that takes all these factors into consideration when treating a patient.

Pharma/biotech companies would do well to include microbiome hemostasis as part of the drug discovery process. Some companies have developed a microbiome platform, most notably Second Genome, a company that is translating novel disease insight from its platform and is targeting new disease pathways for therapeutic treatments. Other companies, such as Synthetic Biologic Inc., are developing drugs to be co-administered during antibiotic treatments, including one that protects the microbiome to help to alleviate diarrhea, a side effect of antibiotic usage that occurs as a result of dysbiosis to the microbiome. To date, there are approximately 40 companies worldwide that are working in the microbiome field and the US has the most companies doing research in this area.

The field of gut microbiome research is in its infancy and it will continue to gain traction in the years to come. By understanding how our microbiome interacts with our physiology and its correlation to diseases, we will understand diseases better, deliver better patients care and develop drugs that treat the etiology, rather than the symptoms.

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